German Guideline Program in Oncology (GGPO)

Evidence-based Guideline Thyroid Cancer

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Guideline (Long version)

Leading Scientific Societies:

- Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV) vertreten durch die Chirurgische Arbeitsgemeinschaft Endokrinologie (CAEK)
- Deutsche Gesellschaft für Endokrinologie (DGE)
- Deutsche Gesellschaft für Nuklearmedizin (DGN)

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Lead Professional Societies

Additional Participating Professional Societies

- Arbeitsgemeinschaft Bildgebung in der Onkologie der DKG (ABO)
- Arbeitsgemeinschaft für Psychoonkologie in der DKG (PSO)
- Arbeitsgemeinschaft Onkologische Rehabilitation und Sozialmedizin in der DKG (AGORS)
- Arbeitsgemeinschaft Palliativmedizin in der DKG (APM)
- Arbeitsgemeinschaft Radiologische Onkologie in der DKG (ARO)
- Bundesverband Schilddrüsenkrebs Ohne Schilddrüse leben
- Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV)
- Deutsche Gesellschaft für Endokrinologie (DGE)
- Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)
- Deutsche Gesellschaft für Humangenetik (GfH)
- Deutsche Gesellschaft für Innere Medizin (DGIM)
- Deutsche Gesellschaft für Kinderendokrinologie und - diabetologie (DGKED)
- Deutsche Gesellschaft für Medizinische Physik
- Deutsche Gesellschaft für Nuklearmedizin (DGN)
- Deutsche Gesellschaft für Palliativmedizin (DGP)
- Deutsche Gesellschaft für Pathologie (DGP)
- Deutsche Gesellschaft für Phoniatrie und Pädaudiologie (DGPP)
- Deutsche Gesellschaft für Radioonkologie (DEGRO)
- Deutsche Gesellschaft für Rehabilitationswissenschaften (DGRW)
- Deutsche Gesellschaft für Ultraschall in der Medizin (DEGUM)
- Deutsche Röntgengesellschaft (DRG)
- Fachverband für Strahlenschutz
- Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH)
- Schilddrüsen-Liga Deutschland

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1 Information about this Guideline

1.1 Editors

The German Guideline Program in Oncology (GGPO) of the Association of the Scientific Medical Societies in Germany (AWMF), the German Cancer Society (DKG), and the German Cancer Aid Foundation (DKH).

1.2 Leading Scientific Societies

Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV) vertreten durch die Chirurgische Arbeitsgemeinschaft Endokrinologie (CAEK)

Deutsche Gesellschaft für Endokrinologie (DGE)

Deutsche Gesellschaft für Endokrinologie
Hormone und Stoffwechsel

Deutsche Gesellschaft für Nuklearmedizin (DGN)

1.3 Funding of the Guideline

This guideline was funded by German Cancer Aid as part of the GGPO.

1.4 Contact

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1.5 How to cite

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056OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/schilddruesenkarzinom; Accessed [tt.mm.jjj]

1.6 Previous changes

Version 1.2 (September 2026):

- Correction in Chapter 5.8.2.3: Adjustment of the unit of measurement of thyroglobulin values
- Change in Chapter 8.3.4: Consensus-based Statement 8.20 was changed to Consensus-based Recommendation.

1.7 Special Comment

Medicine is subject to a continuous development process, so that all information, particularly in regard to diagnostic and therapeutic procedures, can only reflect the state of knowledge at the time of publication of the guideline. The utmost care has been taken with regard to the recommendations given for therapy and the selection and dosage of medications. Nevertheless, users are advised to consult the package inserts and specialist information provided by the manufacturers and, in case of doubt, to consult a specialist. In the general interest, any discrepancies should be reported to the GGPO editorial team.

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1.8 Objectives of the GGPO

The German Association of Scientific Medical Societies (AWMF), the German Cancer Society (DKG), and the German Cancer Aid (Deutsche Krebshilfe) have set themselves the goal of jointly promoting and supporting the development, updating and use of scientifically based and practicable guidelines in oncology with the German Guideline Program in Oncology (GGPO). This program is based on the medical-scientific findings of the specialist societies and the DKG, the consensus of medical experts, users and patients, as well as the AWMF guidelines and the technical support and funding provided by German Cancer Aid. In order to reflect the current state of medical knowledge and take medical progress into account, guidelines must be regularly reviewed and updated. The application of the AWMF guidelines should form the basis for the development of high-quality oncological guidelines. As guidelines are an

important tool for quality assurance and quality management in oncology, they should be incorporated into everyday care in a targeted and sustainable manner. Active implementation measures and evaluation programs are therefore an important part of the promotion of the oncology guideline program. The aim of the program is to create professional and, in the medium term, financially secure conditions for the development and provision of high-quality guidelines in Germany. These high-quality guidelines not only serve the structured transfer of knowledge, but can also be used to shape the structures of the healthcare system. Examples include evidence-based guidelines as a foundation for creating and updating disease management programs or the use of quality indicators extracted from guidelines as part of the certification of organ tumor centers.

1.9 Additional Documents relating to this Guideline

This long version of the guideline is currently available. A short version and a patient guideline (lay version of the guideline) are still being developed. All guideline documents are available on the following websites:

- AWMF (https://register.awmf.org/de/leitlinien/detail/031-056OL)
- German Guideline Program in Oncology (https://www.leitlinienprogramm-onkologie.de/leitlinien/schilddruesenkarzinom)
- Websites of the participating specialist societies (DGN, DGAV, DGE)

1.10 Composition of the Guideline Group

1.10.1 Guideline Coordination

Coordination (without voting rights):
Prof. Dr. Dr. Dr. h. c. Andreas Bockisch, Essen

Composition of the coordination group:

- Prof. Dr. Dr. Dr. h. c. Andreas Bockisch
- Prof. Dr. Thomas Lauenstein
- Prof. Dr. Kerstin Lorenz
- Harald Rimmele
- Prof. Dr. Matthias Schmidt
- Prof. Dr. Matthias Schott

Guidelines secretariat at the German Society of Nuclear Medicine

- Götz Jonas
- Tobias Fabiunke

1.10.2 Involved Professional Societies and Organisations

Table 1: Participating professional associations and organizations

Participating professional associations and organizations (alphabetical)	Representative(s)
Arbeitsgemeinschaft Bildgebung in der Onkologie der DKG (ABO)	Prof. Dr. James Nagarajah Prof. Dr. Thorsten Persigehl
Arbeitsgemeinschaft für Psychoonkologie in der DKG (PSO)	Dr. Matthias Büttner
Arbeitsgemeinschaft Onkologische Rehabilitation und Sozialmedizin in der DKG (AGORS)	Dr. Timm Dauelsberg Dipl.-Med. Gerhard Faber
Arbeitsgemeinschaft Palliativmedizin in der DKG (APM)	Prof. Dr. Markus Deckert Prof. Dr. Markus Meissner
Arbeitsgemeinschaft Radiologische Onkologie in der DKG (ARO)	Prof. Dr. Thomas Brunner Prof. Dr. Ursula Nestle
Bundesverband Schilddrüsenkrebs Ohne Schilddrüse leben	Harald Rimmele
Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV)	Prof. Dr. Cornelia Dotzenrath Prof. Dr. Thomas Musholt Prof. Dr. Christian Scheuba Prof. Dr. Theresia Weber
Deutsche Gesellschaft für Endokrinologie (DGE)	Prof. Dr. Joachim Feldkamp Prof. Dr. Karin Frank-Raue Prof. Dr. Dr. Dagmar Führer-Sakel Prof. Dr. Friedhelm Raue Prof. Dr. Christine Spitzweg
Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)	PD Dr. Wilfried Eberhardt
Deutsche Gesellschaft für Humangenetik (GfH)	Dr. Bernd Auber
Deutsche Gesellschaft für Innere Medizin (DGIM)	PD Dr. Wilfried Eberhardt
Deutsche Gesellschaft für Kinderendokrinologie und - diabetologie (DGKED)	Prof. Dr. Christian Denzer
Deutsche Gesellschaft für Medizinische Physik	Dr. Heribert Hänscheid

Participating professional associations and organizations (alphabetical)	Representative(s)
Deutsche Gesellschaft für Nuklearmedizin (DGN)	Prof. Dr. Wolfgang Burchert Prof. Dr. Rainer Görges Prof. Dr. Hubertus Hautzel Prof. Dr. Michael Kreißl Prof. Dr. James Nagarajah PD Dr. Simone Schenke
Deutsche Gesellschaft für Palliativmedizin (DGP)	Prof. Dr. Markus Deckert Prof. Dr. Markus Meissner
Deutsche Gesellschaft für Pathologie (DGP)	Prof. Dr. Kurt Werner Schmid PD Dr. Dr. Udo Siebolts
Deutsche Gesellschaft für Phoniatrie und Pädaudiologie (DGPP)	Prof. Dr. Michael Fuchs Prof. Dr. Annerose Keilmann
Deutsche Gesellschaft für Radioonkologie (DEGRO)	Prof. Dr. Thomas Brunner Prof. Dr. Ursula Nestle
Deutsche Gesellschaft für Rehabilitationswissenschaften (DGRW)	Dr. Timm Dauelsberg Dipl.-Med. Gerhard Faber
Deutsche Gesellschaft für Ultraschall in der Medizin (DEGUM)	Prof. Dr. Jörg Bojunga
Deutsche Röntgengesellschaft (DRG)	Prof. Dr. Thomas Lauenstein
Fachverband für Strahlenschutz	Prof. Dr. Christoph Reiners
Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH)	PD Dr. Antje Redlich
Schilddrüsen-Liga Deutschland	Prof. Dr. Michael Cordes

The German Society of Otorhinolaryngology, Head and Neck Surgery (DGHNOKHC) contributed intensively to the consultation phase and explicitly endorses the guideline.

1.10.3 Workgroups

Table 2: Working group

Workgroup	Composition of Workgroup
1. DTC and PDTC	**Prof. Dr. Dr. Dagmar Führer-Sakel, Prof. Dr. Thomas Musholt, Prof. Dr. Matthias Schmidt**
2. MTC	**Prof. Dr. Markus Luster, Prof. Dr. Friedhelm Raue, Prof. Dr. Christian Scheuba**
3. ATC	**Prof. Dr. Peter Bartenstein, Prof. Dr. Kerstin Lorenz, Dr. Vera Tiedje**
4. Overview: pathology/genetics	**Prof. Dr. Rainer Görges, PD Dr. Stefan Karger, Prof. Dr. Kerstin Lorenz**
5a Pre-/peritherapeutic initial diagnostics	**Prof. Dr. Joachim Feldkamp, Prof. Dr. Michael Kreißl, Dr. Jochen Schabram**
5b Diagnostics and differential therapeutic consequences in cases of suspected recurrence and suspected progression	**Prof. Dr. Joachim Feldkamp, Prof. Dr. Michael Kreißl, Prof. Dr. Norbert Niederle**
6a Initial surgical therapy	**Prof. Dr. Cornelia Dotzenrath, Prof. Dr. Martin Freesmeyer, Prof. Dr. Wolfram Karges**
6b Surgical therapy at recurrence or persistance	**Prof. Dr. Martin Freesmeyer, Prof. Dr. Wolfram Karges, Prof. Dr. Theresia Weber**
7. Follow-up care including substitution and suppressive medication	**Prof. Dr. Holger Amthauer, Prof. Dr. Matthias Schott, Prof. Dr. Dietmar Simon**
8. Drug therapy at recurrence or persistence	**Prof. Dr. Katharina Holzer, Prof. Dr. James Nagarajah, Prof. Dr. Christine Spitzweg**
Workgroup managers are marked in bold.	

1.10.4 Additional Parties without voting Power

Prof. Dr Andreas Müller (DGHNO-KHC) provided advice on respiratory tract and laryngeal issues, including associated functional disorders, in the context of the treatment of thyroid cancer.

The following professional societies/organizations have explicitly refrained from participating in the guideline:

- Deutsche Gesellschaft für Allgemein- und Familienmedizin e. V. (DEGAM)
  German Society for General Practice and Family Medicine
- Deutsche Gesellschaft für Pflegewissenschaft e. V. (DGP)
  German Society for Nursing Sciences

The following professional societies/organizations did not nominate any representatives in response to the request for participation in the guideline:

- Arbeitsgemeinschaft für Supportive Maßnahmen in der Onkologie (AGSMO) der Deutschen Krebsgesellschaft (DKG)
  Working Group for Supportive Measures in Oncology of the German Cancer Society
- Die Schmetterlinge e. V.

1.10.5 Patient Involvement

Representatives of the Bundesverband Schilddrüsenkrebs Ohne Schilddrüse leben *(Federal Thyroid Cancer Association Living without a thyroid)* - were directly involved in the development and coordination of the recommendations throughout the entire drafting process.

1.10.6 Methodological Support

Methodical support is provided by:

- Evidence-based Medicine | Cochrane Haematology (Prof. Dr. Nicole Skoetz)
- Office of the GGPO (Dr. Markus Follmann, Thomas Langer, Gregor Wenzel)
- Association of the Scientific Medical Societies in Germany AWMF - Institute for Medical Knowledge Management (Dr. Monika Nothacker)

1.11 Abbreviations Used

Table 3: Abbreviations

Abbreviation	Explanation
AG	Working group
AJCC	American Joint Committee on Cancer
AMES	Age, metastases, extent, size (risk classification system)
ARFI	Acoustic Radiation Force Impulse Imaging
ATA	American Thyroid Association
ATC	Anaplastic thyroid cancer
AUC	Area under the curve
AWMF	Association of the Scientific Medical Societies

Abbreviation	Explanation
ÄZQ	German Agency for Quality in Medicine (Ärztliches Zentrum für Qualität in der Medizin)
BTA	British Thyroid Association
CAEK	German Surgical Workgroup for Endocrinology (Chirurgische Arbeitsgemeinschaft Endokrinologie)
CCD	Color-coded duplex sonography
CCDS	Color-coded Doppler sonography
CEA	Carcinoembryonic antigen
CEUS	Contrast-enhanced ultrasound
CI	Confidence interval
CIONM	Continuous intraoperative neuromonitoring
CPS	Combined positive score
Ctn	Calcitonin
DHGTC	Differentiated high-grade thyroid cancer
DKG	German Cancer Society
DNA	Deoxyribonucleic acid
DSR	Desmoplastic stromal reaction
DTC	Differentiated thyroid cancer
EANM	European Association of Nuclear Medicine
EBRT	External beam radiotherapy
EC	Expert consensus
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Explanation
EMA	European Medicines Agency
ESES	European Society of Endocrine Surgeons
ESMO	European Society of Medical Oncology
FKDS	*see CCD*
FMTC	Familial medullary thyroid cancer
FNA	Fine-needle aspiration
FNAC	Fine-needle aspiration cytology
FND	Follicular nodular disease
FNMTC	Familial non-medullary thyroid cancer
FTC	Follicular thyroid carcinoma
HADS	Hospital Anxiety and Depression Scale
HR	Hazard ratio
IC	Immune cells
IMRT	Intensity modulated radiotherapy
IONM	Intraoperative neuromonitoring
LN	Lymph node(s)
MEN2	Multiple endocrine neoplasia, type 2
MIFTC	Minimally invasive follicular thyroid carcinoma
MKI	Multi-targeted tyrosin kinase inhibitors
MRI	Magnetic resonance imaging
MTC	Medullary thyroid cancer

Abbreviation	Explanation
NCDB	National Cancer Database (USA)
NIFTP	Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
NPV	Negative Predictive Value
NTCTCS	National Thyroid Cancer Therapy Cooperative Study Group
ORR	Overall response rate
OS	Overall survival
PDL	Programmed-death ligand
PERCIST	PET Response Criteria In Solid Tumors
PPV	Positive predictive value
PTC	Papillary thyroid carcinoma
PTC-CCV	Columnar cell variant of PTC
PTC-DSV	Diffuse sclerosing variant of papillary thyroid cancer
PTC-HV	Hobnail variant of PTC
PTC-OV	Oncocytic variant of PTC
PTC-SV	Solid variant of PTC
PTC-TCV	Tall-cell variant of PTC
PTMC	Papillary thyroid microcarcinoma
QI	Quality indicator
RECIST	Response Evaluation Criteria in Solid Tumors
RID	Radioactive iodine diagnostics
RIT	Radioactive iodine therapy

Abbreviation	Explanation
SGB	German Social Code
SSTR	Somatostatin receptor
SUV / SUVmax	Standardized uptake value / ...maximum
SWE	Shear-wave elastography
TDS	Tumor disposition syndrome
TgAb	Thyroglobulin antibodies
THW	Thyroid hormone withdrawal
TIRADS	Thyroid Imaging Reporting and Data Systeme
TKI	Tyrosine kinase inhibitor
TPS	Tumor proportion score
TSH	Thyroid-stimulating hormone
UICC	Union Internationale Contre le Cancer (eng.: Union for International Cancer Control)
WG	Working group
WHO	World Health Organization
WI-FTC	Widely invasive follicular thyroid carcinoma

2 Introduction

2.1 Scope and Purpose

2.1.1 Objective and Key Questions

The aim of the S3 guideline "Thyroid Cancer" is to provide physicians who deal with thyroid diseases and affected patients with an evidence-based and accepted decision-making aid for the diagnosis and treatment of thyroid cancer that is tailored to the care situation in Germany in order to offer curative and optimal treatment to as many patients as possible and to enable follow-up care with a high quality of life.

The creation of the S3 guideline "Thyroid Cancer" will summarize and evaluate the current evidence for the entire course of treatment of the disease.

The recommendations for action drawn up on this basis are intended to bring about a qualitative improvement in medical treatment as well as in the care of affected patients

2.1.2 Target Audience

The guideline is aimed at the members of the following medical specialties or professional groups as well as those working in the fields mentioned, including those in training who aspire to a corresponding medical specialty or professional title or activity (in alphabetical order):

- General medicine
- General and visceral surgery
- Endocrinology
- Hematology and medical oncology
- Human genetics
- Internal medicine
- Pediatric endocrinology and diabetology
- Medical physics
- Nuclear medicine
- Oncological rehabilitation and social medicine
- Pediatric oncology and hematology
- Palliative medicine
- Pathology
- Phoniatrics and pediatric audiology
- Psycho-oncology
- Radiology
- Radiologic oncology

The guideline also provides information on good medical practice for:

- Medical-scientific societies, professional associations,
- Patient representatives and self-help groups, as well as
- Quality assurance bodies and institutions at federal and state level, such as
    - the Federal Office for Radiation Protection (BfS),
    - the German Medical Association (BÄK),

- Medical bodies (in accordance with Section 128 of the Radiation Protection Ordinance)
- the National Association of Statutory Health Insurance Physicians (KBV),
- the Central Institute for Statutory Health Insurance Physician Care in Germany (ZI),
- the Federal Joint Committee (GBA),
- the Institute for Quality and Efficiency in Health Care (IQWIG),
- the Institute for Quality and Transparency in Health Care (IQTIG),
- the Robert Koch Institute (RKI) and
- the Society of Epidemiologic Cancer Registries in Germany (GEKID),

- Certification bodies (e.g. OnkoZert),
- Cost bearers.

2.1.3 Validity and Update Process

The S3 guideline is valid until the next update; the estimated period of validity is five years. Regular updates are planned; if urgent changes are required, these will be published separately. Comments and suggestions for the updating process are expressly welcome and can be addressed to the offices of the lead specialist societies.

2.2 Methodology

The methodological procedure for the preparation of the guideline is set out in the guideline report. This is freely available on the Internet, e.g. on the websites of the German Guideline Program in Oncology and the AWMF (see Chapter 1.9).

2.2.1 Levels of Evidence (LoE)

The evidence classification for questions addressed by Evidence-based Medicine | Cochrane Haematology (Prof. Dr. Nicole Skoetz) was carried out according to the scheme of the Oxford Centre for Evidence-based Medicine 2009 for intervention and prognostic studies (see table below). For nine recommendations, the endpoint-based assessment according to GRADE was used (see table "Scheme of evidence assessment according to GRADE"). Details can be found in the evidence report.

For drug-related questions that were processed by the GGPO Office, the quality of the evidence was assessed according to the GRADE methodology.

For drug-related questions that were dealt with in an evidence-based manner by the guideline group, the level of evidence was assessed according to the Oxford 2009 scheme following a critical evaluation of the study quality.

Level	Therapy/Prevention, Etiology/Harm	Prognosis	Diagnosis
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centers

Level	Therapy/Prevention, Etiology/Harm	Prognosis	Diagnosis
1b	Individual RCT (with narrow Confidence Interval"¡)	Individual inception cohort study with > 80% follow-up; CDR" validated in a single population	Validating** cohort study with good" " " reference standards; or CDR" tested within one clinical center
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts" "
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR" or validated on split-sample§§§ only	Exploratory** cohort study with good" " " reference standards; CDR" after derivation, or validated only on split-sample§§§ or databases
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research	
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies
3b	Individual case-control study		Non-consecutive study; or without consistently applied reference standards
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.

Level	Therapy/Prevention, Etiology/Harm	Prognosis	Diagnosis

" Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category).

"¡ See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.

§ Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.

§§ By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.

§§§ Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.

" " An "Absolute SpPin" is a diagnostic finding whose specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.

"¡"¡ Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.

" " " Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.

" " " " Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the same or more expensive.

** Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.

*** By poor quality prognostic cohort study we mean one in which sampling was biased in favor of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.

**** Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1 - 5 years chronic

Table 4: Evidence Grading Scheme based on GRADE

Grade	Description
⊕⊕⊕⊕	High quality of evidence according to GRADE = There is a lot of confidence that the true effect lies close to that of the estimated effect.
⊕⊕⊕⊖	Moderate quality of evidence according to GRADE = There is moderate confidence in the estimated effect: The true effect is likely to be close to the estimated effect, but there is a possibility that it is substantially different.
⊕⊕⊖⊖	Low quality of evidence according to GRADE = There is limited confidence in the estimated effect: The true effect might be substantially different from the estimated effect.
⊕⊖⊖⊖	Very low quality of evidence according to GRADE = There is very little confidence in the estimated effect: The true effect is likely to be substantially different from the estimated effect.

2.2.2 Grades of Recommendation (GoR)

The guideline development methodology of the German Guideline Program in Oncology is based on the processes for S3 guidelines defined in the AWMF guidelines (Version 2.1 of 05.09.2023).

With regard to the strength of the individual recommendations, a distinction is being made between three recommendation grades, which are also reflected in the specific wording of the recommendations (see table "Scheme of recommendation grading").

In principle, the evidence-based recommendations were based on the strength of the available evidence, i.e. a high level of evidence (e.g. meta-analyses/systematic reviews of RCTs or several methodologically high-quality RCTs), i.e. a high level of certainty regarding the results should generally also lead to a strong recommendation (recommendation grade A, "shall").

In addition, further criteria were taken into account when selecting the level of recommendation. The following criteria taken into account could lead to an upward or downward deviation in the strength of recommendation:

Consistency of the study results

Example: The effect estimates of the study results go in different directions and do not show a uniform trend.

Clinical relevance of the endpoints and effect sizes

Example: Although there are studies with results in one direction, the significance of the selected endpoints and/or effect sizes is not considered relevant.

Benefit-risk ratio

Example: The proven benefit of an intervention is offset by a relevant aspect of harm which speaks against an unrestricted recommendation.

Ethical obligations

Example: Downgrading: For ethical reasons, an intervention with proven benefits cannot be offered without restriction. Upgrading: Strong recommendation based on e.g. case-control studies, as an RCT is not feasible for ethical reasons.

Patient preferences

Example: An intervention with proven benefit is not strongly recommended because it is rejected by patients as burdensome or impractical.

Applicability, feasibility in care

Example: An intervention with proven positive effects cannot be recommended because it cannot be offered in the regional care system for structural reasons.

The recommendation grades were determined within the framework of structured consensus conferences moderated by AWMF-certified neutral persons. As part of these processes, the recommendations were formally agreed by the voting mandate holders (see "Authors of the guideline").

The neutral moderation was carried out by employees of the AWMF (Dr. Nothacker) and the Office of the German Guideline Program in Oncology (Dr. Follmann, Mr. Langer, Mr. Wenzel).

The recommendations and statements adopted in this way are presented in separate boxes in the guideline, indicating the level of recommendation and the strength of consensus. In the case of evidence-based recommendations or statements, the underlying evidence and its respective evidence class is also indicated.

The results of the respective votes (strength of consensus) are assigned to the recommendations according to the categories in the following table 6.

Table 5: Scheme of recommendation grading

Grade	Description
A	Strong recommendation for or against für a measure - expression used = shall/shall not
B	Recommendation for or against a measure - expression used = should/should not
0	Open recommendation (option) for a measure - expression used = can

Table 6: Consensus strength

Consensus strength	Percentage of Consensus
Strong consensus	> 95% approval from those eligible to vote
Consent	> 75-95% approval from those eligible to vote
Majority approval	> 50-75% approval from those eligible to vote
No majority approval	< 50% approval from those eligible to vote

2.2.3 Statements

Statements are statements or explanations of specific facts or issues without a direct call for action. They are adopted as part of a formal consensus procedure in line with the procedure for recommendations and can be based either on study results or on expert opinions.

2.2.4 Expert Consensus (EC)

Expert consensus refers to recommendations for which no systematic search for relevant literature has been carried out. As a rule, these recommendations address procedures of good clinical practice for which no scientific studies exist or can be expected. No symbols or letters were used for the grading of expert consensus; the strength of the recommendation is determined by the wording used (shall/should/can) according to the grading in table 6 (see above).

2.2.5 Independence and Disclosure of Possible Conflicts of Interest

This guideline was funded by the German Cancer Aid as part of the German Guideline Program in Oncology. This funding was used in particular for personnel costs (guideline secretariat, evidence research) and the consensus conferences. The guideline was developed in editorial independence from the funding organization.

During the guideline process, all members of the guideline group submitted a declaration of any existing conflicts of interest via the AWMF portal "Declaration of Interests Online".

Participants who did not submit a such declaration were excluded from the consensus processes. The submitted declarations of interest were evaluated by the guideline coordinator and the steering group; those of the guideline coordinator and steering group were in turn evaluated by members of the guideline group and the commissioned methodologists.

The consequences of the declarations of interest submitted were agreed by consensus in each case. Minor conflicts of interest did not lead to any restrictions on collaboration. In the case of moderate conflicts, participation in the preparation of the guideline text was only tolerated if the members with moderate conflicts of interest were in the minority. Furthermore, abstention from voting was required for the recommendations concerned.

The topic of conflicts of interest was discussed in the guideline group and also addressed in all consensus conferences. The affected members of the guideline group abstained from the votes in which they had a corresponding conflict of interest. Abstentions were documented in the minutes. The disclosed relationships and circumstances are presented in the guideline report.

3 Identification of the malignant thyroid nodule (primary diagnosis)

3.1 Epidemiology and prevalence of thyroid nodules and thyroid cancer

This chapter describes the epidemiology and prevalence of thyroid nodules in Germany and compares the figures with international data. In addition to the few published epidemiological studies, the data was mainly generated from the Robert Koch Institute's publication "Cancer in Germany".

3.1.1 Prevalence of thyroid nodules in Germany

The prevalence of thyroid nodules in Germany is high. In various broad-based studies from 2000 to 2006, prevalence rates ranging from 12.5% (for younger men) to over 80% (for older women) were reported, depending on region, age and gender [1], [2].

The most recent population study published on this topic from North East Germany [3] systematically compares the prevalence of goiter or thyroid nodules and iodine supply between the periods 1997-2001 and 2008-2012. The iodine supply deteriorated over time with values below the level considered sufficient by the WHO (100 µg/g creatinine) from 31% to 36% in men and from 46% to 54% in women. The frequency of goiter in men (thyroid volume > 25 ml) decreased significantly from 37% to 27%, while it remained the same in women (volume > 18 ml) at 34% and 33% respectively. The increase in the frequency of sonographically detectable nodules > 10 mm in diameter in men from 15 % to 24 % and in women from 23 % to 38 % was striking (both significant).

3.1.2 Thyroid cancer

Thyroid cancer is one of the rare forms of cancer. The latest figures from the regional German cancer registries are published in the 2018 report from the Robert Koch Institute's Center for Cancer Registry Data [4]. For the period 1999-2016, the number of people with a new diagnosis of thyroid cancer increased, while the mortality rate decreased for both women and men during this period. In 2017 and 2018, the number of new cases fell significantly. In 2018, 4,270 women and 1,930 men were newly diagnosed with thyroid cancer. This corresponds to a standardized incidence of 9.1 and 3.9 cases per 100,000 inhabitants respectively. The mean age at first diagnosis was 51 years for women and 56 years for men. The disease-related standardized mortality rate was 0.4 (per 100,000 inhabitants) for both men and women in 2017 and 2018. It was slightly higher for men in 2019 at 0.5. The average age at death for women was 80 years in 2019, for men 73 years).

The 5-year prevalence was 21,100 for women and 8,500 for men; the 10-year prevalence was 40,500 for women and 15,800 for men. The 25-year prevalence is 76,500 for women and 26,800 for men. The relative 5-year survival rate for all types of thyroid cancer was calculated at 91% for men and 95% for women. It should be noted that the survival rate is highly dependent on the type of thyroid cancer.

The prognostically favorable papillary microcarcinomas were predominantly diagnosed in younger people under the age of 60. The majority of thyroid carcinomas are detected at a very early tumor stage (UICC I) (88% in women, 75% in men).

This trend is also seen in many countries and is primarily attributed to expanded diagnostics and better examination methods [5][5], [6], [7], [8], [9]. A favorable T1 tumor stage was found in 62% of women and 52% of men. However, a more recent study [10] shows that there has also been an increase in higher stages and that improved diagnostics cannot be the sole explanation for the increase in prevalence.

The following distribution of histological subtypes of thyroid cancer was determined in 2015-2016 ([11]):

Table 7: Distribution of the histological subtypes of thyroid carcinoma

Histological type	Women	Men
Papillary carcinomas	78%	68%
Follicular carcinomas	11%	14%
Medullary carcinomas	4%	7%
Anaplastic carcinomas	2%	4%
Other entities	1%	2%
Unspecified/no further details	4%	5%

3.1.3 Comparison with other countries

In Denmark, an age-adjusted incidence of 4.5 cases per 100,000 inhabitants per year was registered in 2014 [12]. The annual percentage increase in the incidence of thyroid cancer was 2% in the years 1980-2006 and then accelerated sharply to 8.7% in women and from 1.3% to 8.9% in men.

In the United Kingdom, an average of 3,527 new cases of thyroid cancer were diagnosed between 2014-2016 in a population of around 65 million people, with 396 deaths caused by thyroid cancer in 2016, corresponding to a mortality rate of 11% [13]. A sharp increase in incidence of 155% was also observed in the United Kingdom compared to the early 1990s.

In the USA, the age-adjusted incidence of thyroid cancer rose from 5.7 to 13.8 per 100,000 inhabitants between 1992 and 2016, more than doubling during this period [8]. Since 2014, the incidence rate has been stable with a downward trend.
In the years 1999-2013, a disease-specific mortality rate of 0.44 per 100,000 inhabitants per year was recorded in the USA for both sexes [14].

With a significantly higher incidence rate of 28.28, the specific mortality rate in China (Zhejiang province) was just as high (0.44) as in the USA [15]. Both in the USA and in other countries, the increase in the incidence of thyroid cancer is almost exclusively

due to an increase in the number of prognostically favorable papillary microcarcinomas, while the number of anaplastic carcinomas with a poor prognosis is stagnating or even decreasing [14], [12], [16], [17], [18].

In the south of Spain, the incidence for women was higher at 12.8 (men 4.9). This means that thyroid cancer is already the 8th most common cancer in women in this region. If explicit screening for thyroid nodules is carried out, the incidence rate of thyroid cancer rises very sharply, reaching an incidence rate of 64.1 cases per 100,000 inhabitants (women 107.3, men: 21.1) in South Korea in the years 2008-1010. This increase largely concerned papillary microcarcinomas, with no change in thyroid cancer mortality [19].

In summary, the German data are roughly comparable with the international data. The incidence of thyroid cancer is in the middle of the range of comparable countries [20]. Only in some regions of the world (explicitly China) are the incidences significantly higher. As in almost all countries, the incidence of thyroid cancer is rising, whereby this increase is largely due to the increased proportion of people with papillary microcarcinomas. It should be noted that Germany has a higher prevalence of thyroid nodules in international comparison, which conversely leads to a lower probability of malignant genesis per detected nodule and requires good pre-selection for possible invasive measures for further clarification.

3.2 Risk factors for the development of thyroid cancer

This chapter describes the various risk factors for thyroid cancer and considers endogenous and exogenous risk factors.

3.2.1 Hereditary or genetic factors

A family history of thyroid cancer, especially in first-degree relatives, is a risk factor for the development of differentiated thyroid cancer. Several hereditary tumor disposition syndromes (TDS) are associated with an increased likelihood of thyroid cancer.

Approximately 20-25% of medullary thyroid carcinomas are hereditary and associated with activating, pathogenic germline variants in the RET protooncogene [21], [22]. Clinically, a distinction is made between familial medullary thyroid carcinoma (FMTC) without further clinical manifestations and multiple endocrine neoplasia (MEN) type II A or type II B. In RET-associated MTC, genotype-phenotype correlations are well established [23] and can contribute to clinical decision-making [24].

In contrast, the molecular genetic causes of familial non-medullary thyroid carcinomas are less well understood. Familial NMTC (FNMTC) account for only a small proportion of NMTC, approximately 3 - 9% [25] and can be divided into two groups. The first group shows an increased prevalence of NMTC in the following hereditary TDS: familial adenomatous polyposis coli (FAP) [26], PTEN hamartoma tumor syndromes (PHTS, e.g. Cowden syndrome) [27], Carney complex [28], Werner syndrome [29] and DICER-1 syndrome [25]. Furthermore, numerous gene mutations have been identified that may be associated with FNMTC [30].

In the group of non-syndromic familial NMTC cases, a distinction is made between familial PTC (fPTC) with or without oxyphilia, fPTC with renal cell carcinoma, and fPTC with multinodal goiter. In all familial NMTC forms, a clear association with pathogenic germline variants could only be established in a fraction (approx. 5%) [31], [32], [33], [34], [35].

Certain morphological findings in the pathological examination can provide indications of the underlying hereditary TDS [36].

3.2.2 Environmental factors/external factors

A long-known risk factor for the development of thyroid cancer is previous radiotherapy of the neck, but also of the mediastinum, head or whole body [37]. This is most frequently seen after previous radiotherapy. The lower the age at the time of radiation exposure, the higher the risk of developing thyroid cancer. In more recent studies, RET/PTC rearrangements were frequently found in papillary thyroid carcinomas after radiation exposure [37]. Previous radioiodine therapy is not considered a risk factor for the development of thyroid cancer. Although a single paper from 2019 reported a possible indication of a slight increase in risk after radioiodine therapy [38], the authors themselves pointed out methodological limitations that prevent a conclusive evaluation of the data. Other studies were unable to identify a link between thyroid cancer and previous radioiodine therapy [39].

3.2.3 Hormonal factors

There are several publications that show a weak influence of hormonal factors on the development of thyroid carcinoma: For papillary thyroid carcinoma, but not for follicular carcinoma, there is evidence for a discrete increase in incidence with increasing basal TSH levels [40]. Reproductive/gynecological factors may also have an - albeit weak - influence on the development of thyroid cancer [41], [42]: there appears to be a slightly higher risk with increasing duration of endogenous exposure to female sex hormones.

3.2.4 Immunological factors/immunosuppression

Patients with Hashimoto's thyroiditis have a slightly higher incidence of thyroid cancer than the general population. This was only seen for patients with euthyroidism or a low need for thyroid hormone replacement, not for late stages in patients with a high or very high need for replacement [43]. The extent to which this observation is due to the fact that patients with pre-existing thyroid disease may be subject to better thyroid diagnostics, which alone may lead to an increase in the detection of thyroid cancer in the patient group, remains unclear. One study found a higher probability of malignancy in punctured thyroid nodules in patients with Hashimotothyroiditis compared to patients without autoimmune thyroiditis (10.0% versus 6.4%; [44]).

After transplantation of a solid organ, a US study showed an increased risk of developing malignancies, including thyroid cancer. The risk was higher after kidney transplantation than after other organ transplants [45]. It is not yet clear what roles the usually long-term immunosuppression and the underlying disease that led to the organ transplant respectively play [46].

3.2.5 Iodine supply

In the past, a weak correlation between the improved or increased iodine supply of a population and an increasing incidence of papillary thyroid carcinoma could be demonstrated [47]. However, at least in Germany, no decrease in the incidence of follicular thyroid carcinoma was observed [10].

3.3 Clinical examination

3.1	Consensus-based Recommendation	2025
EK	A clinical examination should be carried out before a sonographical examination of the thyroid gland and neck.	
	Strong Consensus	

Depending on the symptoms and the clinical question, the clarification of changes in the thyroid gland or thyroid carcinoma includes clinical examinations. This includes inspection of the neck and palpation of the thyroid gland or thyroid lobe and the neck and nape region. A reclination of the head is helpful here. On palpation, look for increased consistency in the thyroid gland or thyroid lobe, the nature and displacement of nodules, swallowing displacement of the thyroid gland as well as redness and overheating of the skin and tenderness. Nodular palpation findings should be correlated with sonography and, if necessary, scintigraphy.

On palpation of the lymph node stations, the localization and nature of palpable lymph nodes (size, hardness, displacement) are documented.

3.4 Sonography (evidence and performance of sonography)

3.4.1 Sonographic individual criteria for malignancy assessment

3.2	Consensus-based Recommendation	2025
EK	Standardized B-mode sonography shall be used for risk stratification of thyroid nodules.	
	Strong Consensus	

Sonography is a widely used examination method among general practitioners and specialists. Thyroid nodules and thyroid carcinomas are often found during routine examinations. Sonographic screening for thyroid nodules is not useful as this leads to overdiagnosis [19], [48]. This chapter describes the importance of sonography in the diagnosis of thyroid cancer and provides information on how it is performed and the technical requirements for the examination. In addition to elastography, contrast-enhanced sonography, duplex sonography and lymph node sonography, standardized documentation is also addressed.

With B-mode sonography, various nodule characteristics such as singularity, composition (e.g. solid or cystic), echogenicity (reflex intensity of tissue), shape, edge characteristics and the presence of microcalcifications can be recorded and assessed in a standardized manner. In addition, the position of nodules within the thyroid gland is documented.

A standardized nomenclature with regard to echogenicity is particularly important. The following Table 8 is helpful for this purpose:

Table 8: Nomenclature of the echogenicity of thyroid nodules

Description of the nodule	DEGUM nomenclature	Synonyms
Nodule is more echogenic than healthy thyroid tissue	more echogenic	echogenic, hyperechogenic
Nodule is as echogenic as healthy thyroid tissue	echogenic, isoechogenic	isoechogenic
Nodule is less echogenic than healthy thyroid tissue	less echogenic	weaker echogenic
Nodule is less echogenic than the neck muscles (infrahyal, sternocleidomastoid muscle)	very weakly echogenic	strongly hypoechogenic
Node shows no echogenicity	anechoic	cystic

In a large meta-analysis by Remonti et al., who evaluated 52 retrospective observational studies with over 12,000 nodules (up to 2012), microcalcifications, greater depth than width growth of the nodule ("taller-than-wide" shape: larger diameter in the sagittal than in the transverse plane) and irregular nodule margins were associated with a higher risk of malignancy, although no single criterion led to a clinically relevant increase in diagnostic accuracy [49]. In a further meta-analysis specifically on the characteristics of medullary thyroid carcinomas, which included six studies up to 2013, calcifications and a "taller-than-wide" shape were associated with a higher probability of a malignant nodule, while a spongiform appearance of the nodules (multiple small cystic internal structures, spongy nodule structure) or cystic nodules were associated with a low probability [50]. The authors also came to the conclusion that none of the sonographic criteria, considered in isolation, represent a sufficient predictive factor for thyroid cancer. It must be critically noted that both meta-analyses demonstrated a high degree of heterogeneity in the study characteristics and results. Although fewer studies (n=6) or nodules (n=5,439) were included in the meta-analysis by Wolinski et al. than in the two previously cited meta-analyses, no significant heterogeneity or publication bias could be demonstrated for any of the individual criteria examined. The highest pooled PPV and the highest pooled specificity were calculated at 76% and 96% for the "taller-than-wide" shape, but the pooled sensitivity of 26% was the lowest of all criteria examined. For the other individual criteria, the values for the pooled PPV were between 23.5% and 42.3% [51]. In a further meta-analysis of 12 studies on young patients under 21 years of age, calcifications were associated with a higher probability of a malignant nodule, whereas cystic nodules were associated with benignity [52]. Here too, however, the view is shared that individual criteria are not sufficiently accurate predictors.

Table 9: B-mode individual criteria for the assessment of thyroid nodules

Criterion
1. solid or cystic
2. echogenicity (strongly echogenic, isoechogenic, weakly echogenic, strongly weakly echogenic, anechoic - see Table 8)
3. border (smooth incl. halo, lobulated, irregular, blurred)
4. calcifications (microcalcifications, macrocalcifications, marginal calcifications)
5. configuration (wider-than-tall, taller-than-wide)
6. specific characteristics (spongiform, conglomerate, cyst)
Additional documentation of the location within the thyroid gland

3.4.2 Use of standardized risk stratification systems in thyroid ultrasonography (TIRADS)

3.3	Evidence-based Recommendation	2025
GoR **B**	The probability of malignancy of thyroid nodules should be assessed using a TI-RADS classification system.	
LoE **2a**	[53], [54], [55]	
	Strong Consensus	

Thyroid Imaging Reporting and Data Systems (TIRADS) are available for standardized sonography of the thyroid gland, taking into account the number or combination of individual sonographic criteria. They enable risk stratification by classifying nodules into low, intermediate, and high malignancy risk (risk stratification systems). Various classification systems are currently still used worldwide [56], [57], [58], [59], [24], [60], [61].

In the systematic literature search on the diagnostic value of TIRADS classifications, a total of 3 meta-analyses were identified. One meta-analysis, which included 4 retrospective and 2 prospective studies with a total of almost 11,000 thyroid nodules, examined the classification system according to Kwak [55]. It showed a pooled sensitivity of 91% (88-94%) and specificity of 35% (31 to 39%) for the diagnosis of thyroid cancer. Another meta-analysis evaluated 12 studies on TIRADS classification systems that

included over 10,000 thyroid nodules [53]. The European study by Russ et al. [59] contributed almost half of the nodules examined. The sensitivity was determined to be 79% (77% - 81%), the specificity was 71% (70 - 72%). The authors point out that different standards in pathological assessment lead to heterogeneity in the results. In an earlier study by the same authors, the evaluation of older studies showed a pooled sensitivity of 72 - 78% and specificity of 68 - 70% [54]. The results of the studies included in the meta-analyses show considerable heterogeneity. What they all have in common, however, is that the findings are standardized and therefore objectively comprehensible and reproducible, which leads to a positive recommendation in the case of low confidence in the quality of the evidence, which is not least a consequence of the currently competing systems.

The various systems differ in their application and in some cases there are clear differences with regard to the recommendation for fine needle aspiration. In this respect, ACR TI-RADS appears to be superior to other systems [62], [63], [64], [65].

For Germany, a multicenter study comparing five TIRADS (Kwak-TIRADS, EU-TIRADS, ACR TI-RADS, K-TIRADS and ATA) was published by Seifert et al. in which non-autonomous thyroid nodules were prospectively classified [66]. The diagnostic accuracies of Kwak-TIRADS (79%), ACR TI-RADS (78%) and K-TIRADS (82%) were slightly superior to EU-TIRADS (70%). ATA classification showed good diagnostic accuracy (79%), but 11% of nodules could not be classified. Yoon et al. found a lack of classifiability of even 18% of nodules in the ATA system [67]. In summary, a preference for a TIRADS classification system cannot be stated at present.

The "International Thyroid Nodule Working Group", which is made up of radiologists, endocrinologists and surgeons from various organizations (including the American Thyroid Association, European Thyroid Association, Korean Society of Thyroid Radiology), began developing an internationally applicable "I-TIRADS" in 2018. Information and online calculators for TIRADS can be found at http://tiradscalculator.com, http://aace-thyroid.deontics.com and http://tirads.de. If sonographic follow-up checks of existing thyroid nodules are necessary, the existing risk stratification systems offer assistance with regard to follow-up. Corresponding follow-up intervals are stored there [61], [68].

3.4.3 Elastography of the thyroid gland

3.4	Evidence-based Recommendation	2025
GoR **B**	If available, elastography should be performed together with standardized B-mode ultrasonography for risk stratification of thyroid nodules.	
LoE **2a**	[69], [70]	
	Consensus	

Elastographic methods, which include qualitative strain elastography (SE) and quantitative shear wave elastography (SWE) and acoustic radiation force impulse (ARFI), are used to measure tissue hardness during sonography.

In their review, Nattabi et al. analyzed prospective and retrospective studies (n=14) that compared the results of shear wave elastography of 2,851 thyroid nodules, of which 1,092 were malignant and 1,759 benign, with the findings of fine needle aspiration cytology (FNAC) or histopathology of surgical specimens [69]. The overall sensitivity for the detection of malignant nodules was 66% (CI 64% - 69%) with a specificity of 78% (CI 76% - 80%).

Nell et al. analyzed prospective and retrospective studies (n=20) on the diagnostic performance of qualitative elastography compared to fine needle aspiration cytology (FNAC) or histology from surgical specimens [70]. They found a sensitivity of 85% (79% - 90%) with a specificity of 80% (73% - 86%).

Overall, the results are heterogeneous, which is not least due to the current lack of universal standardization of the method. Nevertheless, the use of elastography increases diagnostic certainty when the respective method is performed correctly and allows a high negative predictive value to make a malignancy unlikely, provided the lump is completely soft. Based on the results of the systematic reviews and their low reliability, a moderate recommendation for the use of elastography for risk stratification of thyroid nodules is derived and its use is recommended accordingly.

Knowledge of the underlying technical principles and limitations (presence of calcifications and cystic changes, location of the nodule) is essential [71], [72][72]. When comparing the elastographic methods, SWE proved to be less examiner-dependent than SE in most studies [71].

3.4.4 Duplex sonography of the thyroid gland

3.5	Consensus-based Recommendation	2025
EK	Color-coded duplex sonography (CCD) can be used to assess thyroid nodules. However, this is not useful for the assessment of thyroid nodules with regard to malignancy and is therefore unnecessary.	
	Strong Consensus	

The use of color-coded duplex sonography to assess the vascularization pattern of thyroid nodules is widespread in routine clinical practice, as almost all modern sonography devices support CCD for visualizing blood flow and the examination can therefore be completed quickly and easily. In contrast, however, the significance of the method in the dignity assessment of thyroid nodules is low [73]. Three meta-analyses identified in the primary search consistently showed a low sensitivity for the criterion of intranodular/central vascularization of 40%, 44%, and 46% [51], [74], [49]. The specificities varied between 61% [74] and 82% [51]. Overall, however, the study data are difficult to compare with each other, which is also reflected in significant heterogeneity, with the exception of the meta-analysis by Wolinski et al. [51].

In a retrospective study based on 1,083 nodules with 269 malignancies, it was shown that the description of the vascularization pattern of thyroid nodules has no added value to B-mode sonography in their dignity assessment [75]. This has been confirmed in more recent studies [76], [77]. However, CCD can be helpful in assessing the extent, limitation, and invasiveness of thyroid nodules [78].

Among the limitations of CCD are the strong dependence on the user and the sonography device used. There are no recommendations for standardized examination parameters such as flow rate amplification or frequency setting. With regard to the categorization of the vascularization pattern, various visual classification systems are described in the literature. The intensity and localization (peripheral versus intranodular) of the vascularization pattern are decisive [75], [79], [80]. In summary, according to the current literature, CCD alone cannot be used to assess the dignity of thyroid nodules, but it can be helpful for assessing the extent and borders of poorly delineated thyroid nodules in B-mode sonography.

3.4.5 Contrast-enhanced sonography (CEUS) of the thyroid gland

3.6	Evidence-based Recommendation	2025
GoR **B**	Contrast-enhanced ultrasonography (CEUS) should currently not be routinely performed as a complementary method to B-mode ultrasonography.	
LoE **2b**	[81]	
	Strong Consensus	

The current data on CEUS is summarized in the meta-analysis by Liu [81]. 33 studies (24 from China and 4 from Europe) with a total of 3,442 nodules were included, which compared the result of CEUS with cytology or histology. They showed a sensitivity of 88% (85-91%) and a specificity of 88% (83-91%) for the differentiation between malignant and benign thyroid nodules. Similar results (sensitivity 90% and specificity 86%) are shown in a meta-analysis by Ma et al. that includes 13 publications, including 7 Asian and 6 non-Asian studies [82]. The authors also carried out a subgroup analysis regarding the origin of the studies. The authors found significant heterogeneity in the Asian studies compared to the non-Asian studies. In addition, the sensitivity in the non-Asian subgroup was lower than in the Asian subgroup with the same specificity (77% vs. 92%) [81]. Limitations of the method are that there is currently no standardized examination algorithm for CEUS. In addition, the examination is quite expensive and only one node can be assessed at a time. The invasiveness of the examination must also be taken into account when using CEUS (additional information, consideration of contraindications, intravenous administration of contrast medium, follow-up observation of the patient). Despite the favorable results of the study by Liu et al., which is based predominantly on Chinese data, it currently appears too early for a conclusive evaluation, taking into account the above-mentioned aspects and the limited experience in Europe.

3.4.6 Lymph node sonography

3.7	Consensus-based Recommendation	2025
EK	In case of thyroid nodules with signs of malignancy, a systematic sonographic examination of the lymphatic drainage areas of the thyroid region shall be performed, if necessary repeatedly during the course of the disease.	
	Strong Consensus	

3.8	Consensus-based Recommendation	2025
EK	The sonographic examination of the lymphatic drainage areas of the thyroid region shall be performed and documented using a standardized protocol if malignancy is suspected.	
	Strong Consensus	

3.9	Consensus-based Recommendation	2025
EK	The abnormal lymph nodes should be classified as probably benign, indeterminate, or suspicious for malignancy using evaluated sonomorphological criteria.	
	Strong Consensus	

3.10	Consensus-based Statement	2025
EK	No recommendation can be made for or against the use of elastography to assess the dignity of lymph nodes in the lymph drainage areas of the thyroid region in thyroid nodules suspected of being malignant.	
	Consensus	

3.11	Consensus-based Recommendation	2025
EK	If a thyroid malignancy is suspected, color-coded Doppler sonography (CCDS) should be used to assess cervical lymph nodes.	
	Consensus	

3.12	Consensus-based Recommendation	2025
EK	Due to its very high specificity and therefore high positive predictive value for lymph node metastases, neck sonography shall be used preoperatively in cases of confirmed or suspected thyroid malignancy. However, with limited sensitivity, the examination cannot rule out lymphonodal metastasis preoperatively.	
	Strong Consensus	

Sonography is the method of choice for the detection and characterization of cervical lymph nodes [83], [84], [85].

Table 10: Important aspects of structured sonographic documentation of cervical lymph nodes

Important aspects
Completeness of coverage of all lymph node compartments in the neck area
Description of unclear or suspicious lymph nodes including their localization in relation to anatomical structures
Size of these lymph nodes in three dimensions
Shape (oval, round, polylobulated, blurred)
Presence or absence of a hilar sign
Echogenicity (weaker or stronger echogenicity, isoechogenicity)
Presence of cystic areas
Presence and localization of calcifications (micro- and macrocalcifications)
Doppler sonography features of vascularization (hilar, central, peripheral, diffuse, capsule penetrating)

Normal lymph nodes are oval, slightly less echogenic with a more echogenic hilus with a corresponding hilar vessel [86]. The hilus is not always detectable on B-image sonography, but can be visualized using color Doppler due to its vascularization. A hilus is found in about 90% of normal lymph nodes [84], [86], [87], [88]. Detection of the hilus almost always rules out malignancy [84], [86], [87], [88].

As the diameter in the long axis has only a low diagnostic value for the question of malignancy, the use of the short axis or the Steinkamp quotient (L/S, quotient of long to short axis in diameter) is recommended [89].

The preoperative detection of suspicious lymph nodes has prognostic value and can influence the surgical strategy [90], [91][91].

In metastatic PTC, up to 70% of lymph node metastases are found in the central and lateral lymph node compartment [92]. The specificity of sonography in detecting lymph node metastases of PTC is high and lies between 80% and 95%; Kim et al. found a specificity of 91% with a sensitivity of only 51% [93].

Typical sonographic signs of suspicious lymph nodes include microcalcifications, partly cystic parts, peripheral or diffusely increased vascularization with partly capsule-penetrating vessels, as well as a more echogenic appearance compared to normal lymph nodes, often comparable to the thyroid gland [84], [94]. The criteria are identical for preoperative and postoperative evaluation.

The size of cervical lymph node metastases from thyroid carcinoma can remain constant over several years [95]. A lack of growth in size is not a valid criterion for ruling out a lymph node metastasis. However, a growth in the size of lymph nodes of >3mm/year that is confirmed by several measurements is considered conspicuous [95].

The majority of lymph node metastases are found cervicocentrally (level III and IV or in level VI), usually unilaterally. Submandibular lymph node metastases are less common [96], [97]. However, the value of preoperative US differs for central and lateral lymph node metastases [85].

In studies, preoperative sonography showed lower sensitivity in the diagnosis of central cervical lymph node metastases and good diagnostic efficacy for lateral cervical lymph node metastases in PTC. Nineteen studies with 4,014 patients were included in a meta-analysis [98]. The pooled sensitivity, specificity, DOR and area under the curve (AUC) of sonography in detecting central LN metastases in PTC were 0.33 (95% confidence interval (95% CI): 0.31-0.35), 0.93 (95% CI: 0.92-0.94), 5.63 (95% CI: 3.50-9.04) and 0.69; for lateral LN metastases, these values were 0.70 (95% CI: 0.68-0.72), 0.84 (95% CI: 0.82-0.85), 18.7 (95% CI: 10.3-33.9) and 0.88, respectively. In this analysis, preoperative sonography showed low sensitivity in the diagnosis of central LN metastases and good diagnostic accuracy for lateral LN metastases in PTC. Another meta-analysis (Wu, L. M., 2012) included 13 studies with 1,020 patients and PTC [99]. The pooled sensitivity for sonography in the detection of LN metastases was 0.72 (95% CI, 0.46-0.88), the specificity was 0.98 (95% CI, 0.84-1.00) and the area under the curve (AUC) was 0.94 (95% CI, 0.92-0.0.96). The pooled sensitivity was 0.63 (95% CI, 0.47-0.76), the specificity 0.93 (95% CI, 0.73-0.99) and the AUC 0.81 (95% CI, 0.77-0.84). In the lesion-based analysis, the subgroup with lymph node involvement of the lateral compartment was found to have the highest sensitivity (0.72, 95% CI 0.68-0.75) and specificity (0.97, 95% CI 0.93-0.99) among the studies ($p < 0.05$). The authors conclude that preoperative ultrasonography is a good technique for preoperative lymph node staging of PTC and is helpful in detecting metastatic cervical LN in the lateral group.

Comparing ultrasonography with computed tomography, a meta-analysis including 10 studies with a total of 5,656 thyroid cancer patients showed that CT has a slightly higher sensitivity than US, while US has a higher specificity for the assessment of central, lateral and total cervical LN metastases [100].

Only "macroscopic" lymph node metastases can be detected preoperatively using US. However, the lack of detection of lymph node metastases of a PTC in the preoperative US is associated with a better prognosis for the patient [101].

Peripheral rather than hilar vascularization was described as the best single US criterion for malignancy of lymph nodes with a sensitivity of 86% and specificity of 82% [84]. However, peripheral vascularization is also found in up to 20% of benign lymph nodes [84], [86], [87], [88].

Table 11: B-mode criteria for differentiating normal, indeterminate and malignant lymph nodes

Normal lymph node	Indeterminate lymph node	Suspected malignancy (at least one of the following characteristics)

• hilus preserved
• oval shape and normal size
• absent or hilar vascularization
• no other suspicious signs
	• absence of a hilus and at least one of the following characteristics:
	  ○ round shape
	  ○ enlarged short axis
	  ○ increased central vascularization
		• microcalcifications.
		• partially cystic areas.
		• peripheral or diffusely increased vascularization
		• the lymph node tissue shows a stronger echogenicity comparable to that of the thyroid gland

The data on US elastography of cervical lymph nodes is limited compared to its use in thyroid nodes. For lymph nodes, some prospective studies, in particular with shear wave elastography (Azizi, G., et. al. 2016), showed an additional benefit of elastography in the characterization of cervical lymph nodes, especially for lymph nodes <1cm [102], [103], [104]. Eight studies with a sample size of 481 patients with 647 cervical lymph nodes were included in a meta-analysis [97]; shear wave elastography showed a sensitivity of 81 % (95 % CI: 72-88 %) and a specificity of 85 % (95 % CI: 70-93 %). The results of the meta-regression analysis showed that the prevalence of malignant lymph nodes was a significant factor influencing the heterogeneity of the study ($p < 0.01$). The data situation and the number of lymph nodes examined are therefore not yet sufficient for a conclusive assessment.

CCDS was used in several studies to assess cervical lymph nodes. Increased vascularization (peripheral and intranodular) indicates malignancy of the examined lymph node [78], [84], [105], [106].

3.5 Thyroid scintigraphy ([^{99m}Tc]pertechnetate, ^{123}I, evidence and performance of thyroid scintigraphy)

This chapter deals with thyroid scintigraphy, which can be used to assess the function of thyroid nodules.

3.13	Consensus-based Recommendation	2025
EK	As part of a planned dignity assessment of thyroid nodules ≥ 1 cm, a thyroid scintigraphy shall be performed in adults - regardless of the TSH value.	
	Consensus	

Thyroid scintigraphy (with iodine-123 (^{123}I) or with technetium-99m pertechnetate ([^{99m}Tc]$^{TcO4-}$) is the only imaging procedure with which the expression and activity of the sodium iodide symporter (NIS) can be visualized in vivo. For practical reasons, scintigraphy is generally performed with [^{99m}Tc]pertechnetate. For special questions such as the clarification of substernal or ectopic or dystopic thyroid nodules, ^{123}I is superior.

Scintigraphy is performed in accordance with the S1 guideline of the German Society of Nuclear Medicine (AWMF Reg. No. 031-011), as standard quantitatively with determination of the uptake. In the context of this guideline, only the aspect of determining the dignity of thyroid nodules is discussed.

In the thyroid scintigram, a distinction is made in comparison to extranodular thyroid tissue between hyperfunctional nodules with increased enhancement, hypofunctional nodules with reduced enhancement, and indifferent nodules that appear isointense.

3.14	Consensus-based Recommendation	2025
EK	In the case of scintigraphic findings of a hyperfunctional (autonomous) nodule, no further clarification of dignity (beyond sonography) shall be performed.	
	Strong Consensus	

The special clinical value of scintigraphy lies in the identification of autonomous adenomas as benign thyroid nodules. The scintigraphic findings of a hyperfunctional (autonomous) nodule cannot be predicted by any other method, including sonography [107] or ultrasound elastography [108], [109]. The majority of hyperfunctional nodules are detected by scintigraphy at the time of euthyroidism, as demonstrated by various studies [110], [111].
Scintigraphically enhanced nodules almost always correspond to focal autonomies [112], [113]. In a pathology-initiated review of 65 publications on thyroid malignancies presenting as hyperfunctioning nodules, only 10 withstood a critical review [114]. Malignancy of a hyperfunctioning thyroid nodule is therefore a rarity.

3.15	Consensus-based Recommendation	2025
EK	The scintigraphic findings of a hypofunctional nodule alone shall not be an indication for surgery.	
	Strong Consensus	

Thyroid scintigraphy contributes to the risk stratification of thyroid nodules by enabling the selection of hypofunctional nodules whose dignity shall be further clarified. Thyroid scintigraphy can increase the positive predictive value of fine needle cytology from 1.5% for unselected clarification [115]. The desired pre-test probability of at least 5-10% can be achieved by combining sonographic and scintigraphic criteria. For scintigraphically under-enriched nodules, the literature shows a wide range of malignancy prevalence from less than 3% in regions with iodine deficiency and 5.5% in regions without iodine deficiency [116], to 22% in a prospective study of 100 operated patients with a single thyroid nodule [117]. Thus, only in combination with other procedures (e.g. standardized sonography/ TIRADS, FNA, possibly US elastography) are predictive values achieved that provide a sufficiently reliable basis for a decision regarding the further procedure (e.g. surgery).

3.16	Consensus-based Recommendation	2025
EK	In the case of indifferent accumulation in thyroid nodules, a supplementary suppression scintigraphy can be performed.	
	Strong Consensus	

No reliable data is available on the negative or positive predictive value of scintigraphically indifferent nodules. Such findings may be due to nodules that actually have an enhancement behavior comparable to the perinodular tissue, as well as nodules that do not demarcate due to their small size or position. In the latter cases, suppression of the perinodular tissue can make the hyperfunctionality of a nodule visible and thus practically rule out malignancy.

3.6 Determination of laboratory values

Some laboratory values, especially for the thyroid-stimulating hormone, are frequently examined in medical practice. This chapter describes the importance of laboratory tests in assessing the dignity of thyroid nodules.

3.6.1 Thyroid-stimulating hormone (TSH)

3.17	Consensus-based Recommendation	2025
EK	A TSH determination shall be carried out every time a lump is investigated.	
	Strong Consensus	

In the case of thyroid nodules, low TSH values may indicate autonomic dysfunction [118], [119]. A TSH determination is therefore necessary in the investigation of thyroid nodules.
Some studies have found an association between higher TSH levels and the risk of a DTC occurring [120], [121], [122], [123], [124], [125], [126], [127], [128]. Huang et al. describe this only for men; in women, they found a higher risk with lower TSH values [126]. A correlation with the TSH level was also found for advanced tumor stages and aggressive tumor growth [129], [130], [131], [132]. One study describes the additional benefit of a TSH determination in cytologies of fine needle aspirates of thyroid nodules of undetermined significance [133]. In 127 Spanish patients with a Bethesda classification IV on fine needle aspiration, a higher rate of malignancy was found with higher TSH values [134]. Other authors could not find an association between higher preoperative TSH levels and tumor stage [122], [135], whereas one study described a lower risk of developing papillary thyroid carcinoma with lower TSH levels [136]. In a prospective collective, higher TSH levels in patients with histologically proven lymphocytic infiltration were not associated with a higher probability of carcinoma [137]. A German study shows an increased risk of carcinoma with both increased and decreased TSH values [138].
A meta-analysis with a total of 23,799 participants confirmed a slightly increased risk of DTC with higher TSH values [139]. However, the determination of a higher TSH value in an individual with nodules does not allow the prediction of malignancy.

3.6.2 Thyroglobulin

Thyroglobulin (Tg) is a well-validated tumor marker in the postoperative follow-up of patients with differentiated thyroid carcinoma [140]. In the preoperative diagnosis of thyroid nodules, thyroglobulin cannot reliably predict the presence of thyroid carcinoma [141]. The data on this is contradictory [142], [143], [144], [145], [146], [147]. There are no prospective studies that prove a sufficiently high significance of thyroglobulin determination in the preoperative clarification of thyroid nodules. Elevated thyroglobulin levels are also found in many patients with benign thyroid nodules, in goiters and in iodine deficiency [148], [149]. Comparatively high thyroglobulin levels are found more frequently in patients with lymphogenous metastatic tumors or radioiodine-refractory thyroid carcinomas [150], [151]. Some authors have calculated the ratio of TSH to thyroglobulin in order to improve the prediction of malignancy of thyroid nodules. Here too, only retrospective data is available [152], [153]. In individual cases, a thyroglobulin determination can be helpful in determining the further procedure, but a routine determination of thyroglobulin in the clarification of thyroid nodules is not useful.

3.18	Consensus-based Recommendation	2025
EK	A routine determination of thyroglobulin shall not be carried out as part of the clarification of thyroid nodules.	
	Strong Consensus	

3.6.3 Thyroglobulin antibodies (TgAb)

In a larger patient population, the preoperative determination of TgAb was identified as an independent risk factor for the presence of lymph node involvement and extranodal tumor spread [154]. Li et al. confirmed the association of a higher risk of papillary thyroid carcinoma with positive TgAb, but saw less extrathyroidal tumor spread in this population [155]. This was also seen in retrospective studies [127], [132], [156], [157], [158], [159], [160]. In two studies with fine needle aspirates, the suspicion or detection of thyroid carcinoma was higher in TgAb-positive patients than in TgAB-negative individuals [161], [162]. An individual prediction of the presence of differentiated thyroid carcinoma is not possible with a determination of thyroglobulin antibodies. Karatzas et al. found more cases with multifocality, capsular penetration, and lymph node metastases in nodules with cytology of unknown significance in FNA in TgAb-positive patients with PTC [163]. The presence of TgAb may therefore indicate a higher tumor stage in the presence of thyroid carcinoma and methodological problems in the postoperative determination of the tumor marker thyroglobulin [164].

3.6.4 TPO antibodies

Retrospectively, a large series of TPO-Ab-positive patients with diffuse lymphocytic infiltration of the thyroid gland showed more multifocal papillary carcinomas with a lower rate of extrathyroidal spread, but more tumors > 1 cm and more lymph node metastases. TPO-Ab-positivity without diffuse lymphatic infiltration showed no tendency towards increased tumor aggressiveness [165]. In a region with high to increased iodine supply, there was a higher rate of patients with papillary thyroid carcinomas with positive TPO-Ab [128]. With simultaneously elevated TPO and TgAb, Wu et al. showed a higher rate of papillary carcinomas [166]. A meta-analysis with over 64,000 patients shows an association between the presence of Hashimoto's thyroiditis and the occurrence of PTC. No information is provided on the level of TPO-Ab or the definition of Hashimoto's thyroiditis [167]. In the primary diagnosis of Hashimoto's thyroiditis with simultaneous detection of nodules, a significantly increased rate of papillary carcinomas was found in Italy. Extrathyroidal spread and lymph node metastasis were also associated with TPO positivity [168]. Song et al. showed that preoperative detectable TPO-Ab is associated with improved disease-free survival [169]. Further studies show an increased rate of PTC in patients with elevated TPO-Ab [170]. A meta-analysis with 18 included studies confirms these results [171].

3.6.5 Calcitonin

With regard to the determination of calcitonin in serum, please refer to Chapter **Fehler! Verweisquelle konnte nicht gefunden werden.** and Chapter 8.1.2.2.

3.7 Fine needle aspiration, incl. FNA of lymph nodes/punch biopsy

3.19	Consensus-based Recommendation	2025
EK	A fine needle aspiration of thyroid nodules (≥ 1 cm) shall only be performed after adequate pre-selection of suspicious nodules and if the puncture findings are included in the planning of the further procedure.	
	Strong Consensus	

3.20	Consensus-based Recommendation	2025
EK	Nodules < 1 cm should only be punctured if there are risk factors present, and with the aid of sonography and a puncture specialist who has expertise.	
	Strong Consensus	

3.21	Consensus-based Recommendation	2025
EK	Unselected fine needle aspiration of thyroid nodules shall not be performed.	
	Strong Consensus	

3.22	Consensus-based Recommendation	2025
EK	In the case of suspected C-cell carcinoma of the thyroid gland (e.g. suspicious findings in the calcitonin determination - see Chapter 8), fine needle aspiration should not be performed.	
	Consensus	

The following statements can be made about fine needle aspiration:

Fine-needle aspiration is a simple and safe procedure for obtaining cells from defined lesions ("nodules"), which can be used to make a diagnostic contribution to determining the biological nature and therefore dignity of these nodules.

Fine-needle aspiration cytology of the thyroid gland is referred to in international literature as fine-needle aspiration cytology "FNAC". If puncture is performed without aspiration, the term "FNC" is used.

The diagnosis of practically all thyroid neoplasms is based on special histological criteria and therefore cannot be made cytologically. The task of cytology is to identify lesions in which malignancy is likely or cannot be considered unlikely with the necessary certainty, and which are then subjected to surgery and subsequent histological clarification.
In contrast to the approach in other countries (especially in the USA/Canada), conspicuous nodules are more frequently diagnosed and operated on in the iodine deficiency region and thus subjected to histological dignity assessment; in this approach, the significance of FNAC must be assessed differently than, for example, in the ATA guidelines.

It is not possible to differentiate between adenomas and FTCs cytologically.

The establishment of the NIFTP made it necessary to redefine the morphological criteria for PTC. The criteria now include only histologically detectable aspects [172].
Whereas previously a PTC could be clearly diagnosed both cytologically and histologically on the basis of the characteristic nuclear features, the introduction of the NIFTP, for whose cytological prerequisites the detection of PTC-equivalent nuclear features is mandatory, means that further criteria - only detectable histologically - are necessary (invasion and/or clear papillae).

However, a fine-needle aspiration allows a good preselection of nodules that require histological clarification in the case of clinically and/or sonographically conspicuous nodules (seeChapter 3.4) with a size ≥ 1 cm after scintigraphic exclusion of focal autonomy. Smaller nodules (< 1 cm) are usually monitored sonographically, but they can also be punctured with sonographic guidance if the puncture specialist has the appropriate expertise and if there are particular risk factors [173], [174].

Puncturing nodes that do not meet this definition increases the number of unnecessary surgeries [115].
In cases where surgery would be indicated for various reasons even without the use of FNAC, FNAC can nevertheless provide decisive information for the preoperative management of the surgery (extent of the surgery, intraoperative frozen section, patient information).

The extent of surgical intervention in MTC is increasingly being made dependent on the detection of a desmoplastic stromal reaction (DSR) [175], [176], [177], [178], [179]. Thyroid fine needle aspiration can induce fibroblastic proliferation, which can mimic a tumor-induced DSR, and thus deprive corresponding surgical concepts based on intraoperative frozen section diagnostics of their foundation.

3.23	**Consensus-based Recommendation**	**2025**
EK	The fine-needle aspiration should be performed with sonographic guidance (this is mandatory for non-palpable nodules).	
	Strong Consensus	

3.24	Consensus-based Recommendation	2025
EK	Material can be obtained by aspiration puncture or non-aspiration puncture when puncturing solid nodules (parts).	
	Strong Consensus	

Sonographically guided puncture under control of the needle tip echo leads to greater accuracy and increases both the rate of diagnostic punctates and the diagnostic sensitivity [180], [181], [182].

Some studies have shown that small-lumen puncture needles (22 G to 25 G) produce a higher cell yield with a lower blood content than needles with a larger lumen [183], [184], [185], [186]. Ultimately, the choice of cannula thickness should be made in consultation with the cooperating pathology institution, taking into account the processing technique established there.

In the case of mixed cystic-solid nodules, sonographically guided material should be obtained from the solid parts to clarify the dignity (if necessary, repeat puncture after previous decompression puncture of larger cystic parts).

The puncture can be performed as a so-called aspiration puncture (possibly with the support of special suction pump systems) or non-aspiration puncture, in which the cytological material is obtained exclusively through the capillary action of the cannula [187], [188], [189], [190]. Non-aspiration puncture is particularly preferred for FNAC in children; otherwise, the studies cited did not show any clear superiority of either method.

Thicker cannulas are used for therapeutic puncture (reduction of cyst volume) of cystic thyroid lesions than for purely diagnostic FNAC; these cyst punctates should also be regularly subjected to cytological examination, as papillary carcinomas and metastases (e.g. of bronchial and renal carcinomas) may be cystically altered.

The cytologic material obtained by FNAC is usually spread directly onto slides. Depending on the staining method, the slides must then be air-dried or fixed accordingly. Alternatively, the puncture material can also be further processed using the thin-layer method [191], [192]. The material is transferred to a lysis reagent for (extensive) lysis of punctured erythrocytes (which is also used for transportation). After subsequent fixation, a defined number of cells are standardized and applied to a slide using special equipment. The mostly blood-free preparations can be microscopically assessed in a much less time-consuming manner. Disadvantages are the higher number of technically inadequate preparations and various specifics in the cytological assessment of the preparations.

With regard to hygiene requirements in Germany, the recommendations of the Commission for Hospital Hygiene and Infection Prevention (KRINKO) of the Robert Koch Institute (disinfection, sterile swab material, sterile gloves and sterile perforated cloth, sterile transducer cover if necessary) published in the Bundesgesundheitsblatt 2011 apply [193].

The intake of acetylsalicylic acid at a dose of 100 mg/die does not need to be paused [194]. A retrospective data analysis of 803 patients also showed no increased rate of bleeding complications with clopidrogel, coumarins, or newer oral anticoagulants (NOACs) such as rivaroxaban and ticagrelor [195]. The decision as to whether the puncture should be performed while the patient is still taking anticoagulants or after briefly discontinuing this medication (if necessary, a transient switch to heparin) requires an individual risk:benefit assessment. Relevant bleeding after thyroid fine needle puncture is the exception. Brief follow-up observation of the patient and, if necessary, a sonographic check after 15 - 30 minutes if bleeding is suspected further reduce the risk of complications.

3.7.1 Fine needle puncture of lymph nodes

In rare cases, sonographically assisted puncture of conspicuous lymph nodes (see Chapter 3.7.1) in the neck area can be the primary diagnosis of thyroid carcinoma, especially if the thyroid gland shows no conspicuous nodes or only very small lesions [196], [197]. Sensitivity is high, but varies between examiners and regions as well as needle sizes used. One meta-analysis lists published sensitivities between 52 and 100% [198]. The specificity is given as between 71.4 and 100% [198], [199], [200], [201], [202].

If a high-grade thyroid carcinoma is already suspected or has already been detected, a supplementary puncture of sonographically conspicuous lymph nodes may be useful if the result of the puncture changes the surgical procedure [203], [204]. Lymph node involvement indicates a higher tumor stage and can lead to an extended resection strategy.

In individual cases and if technically feasible, a molecular genetic analysis of the punctate can be performed. A BRAF mutation is of particular importance in the diagnosis of papillary thyroid carcinoma [205].

3.25	Consensus-based Recommendation	2025
EK	A fine-needle aspiration of sonographically and/or clinically abnormal lymph nodes should only be performed if this results in therapeutic consequences.	
	Consensus	

3.7.2 Thyroglobulin determination in the punctate washout

3.26	Consensus-based Recommendation	2025
EK	Thyroglobulin can be determined in the punctate washout of a fine needle aspirate of sonographically and/or clinically conspicuous lymph nodes.	
	Consensus	

The combination of FNAC and the measurement of thyroglobulin in fine needle washout can increase the accuracy of carcinoma prediction [199], [206], [207], [208], [209]. Tg determination in the fine needle aspirate of lymph nodes has a high sensitivity and specificity [210]. The preoperative Tg determination in the washout of a lymph node aspirate can also contribute to the decision on the type of surgical procedure [211]. The combination of cytology and Tg determination in the washout of the puncture achieves a sensitivity of 97% and a specificity of 93% [212].

3.7.3 Punch biopsy

3.27	Consensus-based Recommendation	2025
EK	A punch biopsy can be performed for non-diagnostic fine needle aspirations.	
	Consensus	

In the primary diagnosis of thyroid nodules, punch biopsies have no advantage over FNAC [196], [198].

If there are severe macrocalcifications or significant regressive changes in the nodules, a punch biopsy may offer an advantage over FNAC [213], [214]. This also applies in the case of non-diagnostic FNAC [214]. FNAC cannot reliably differentiate follicular adenomas from follicular carcinomas. In this case, a "follicular neoplasia" is diagnosed. In this case, only histological confirmation by surgery can provide clarification. As a rule, however, less than 20% of the nodules operated on in this way are malignant, meaning that the majority of surgeries would have been unnecessary in retrospect. The distinction between follicular adenoma and follicular carcinoma is essentially made by vascular invasion. This can be seen to some extent in specimens from a punch biopsy, so that some data indicate that punch biopsy is significantly superior to FNAC in the diagnosis of follicular carcinoma [215].

FNAC is usually not able to reliably diagnose anaplastic carcinoma. In the case of clinical and sonographic suspicion of anaplastic carcinoma, the primary punch biopsy is significantly more informative. This also applies to suspected lymphoma or suspected non-organ metastases [216].

3.8 Further imaging procedures

This chapter describes supplementary imaging procedures that go beyond the usual primary diagnosis of thyroid carcinoma. MIBI scintigraphy, skeletal scintigraphy, conventional X-ray examinations, computer tomography including PET/CT and magnetic resonance imaging examinations are discussed.

3.8.1 Scintigraphy with ^{99m}Tc-MIBI

3.28	Evidence-based Recommendation	2025
GoR **0**	If fine needle aspiration is indicated, imaging with ^{99m}Tc-MIBI can be used if fine needle aspiration is not possible, has been rejected by the patient, is not representative, or has remained without meaningful findings.	
LoE **2a**	[217], [218], [219]	
	Consensus	

3.29	Consensus-based Recommendation	2025
EK	Imaging with ^{99m}Tc-MIBI shall not be used for hyperfunctional and functionally indifferent thyroid nodules.	
	Strong Consensus	

3.30	Consensus-based Recommendation	2025
EK	Imaging with ^{99m}Tc-MIBI shall not be used as a "screening procedure" for risk stratification of thyroid incidentalomas.	
	Strong Consensus	

Imaging with ^{99m}Tc-MIBI is a non-invasive nuclear medicine molecular imaging procedure that is approved for cardiological ischemia and vitality diagnostics, for localization diagnostics of parathyroid adenomas in hyperparathyroidism and for the detection of breast cancer. It has been used clinically off-label for decades to assess the dignity of thyroid nodules. The off-label use must be explained.

Three meta-analyses were identified during the evidence search. The included studies examined the diagnostic accuracy of MIBI scintigraphy in comparison to cytologic or histologic findings.

In the meta-analysis by Wale et al. [219], the 10 included studies with a total of 712 patients consistently showed a high negative predictive value of 97% on average with a low PPV of 34%. Kim et al. [217] included 22 studies with 2,421 patients in their meta-analysis based on Medline and MBase and found a sensitivity of 87% (CI 76% - 93%) and a specificity of 78% (67% - 86%). Treglia et al. [218] also carried out a comprehensive literature search and included 21 publications in their meta-analysis. The overall evaluation resulted in a sensitivity of 85.1% (81.1 - 88.5%) and a specificity of

45.7% (42.7 - 48.7%). They point out that the specificity of the method is increased if MIBI scintigraphy is only used for scintigraphically hypofunctional nodules, which is good medical practice.
Fine-needle aspiration cytology is currently the gold standard if the punctate is conclusive. Due to the high sensitivity and the associated high negative predictive value, ^{99m}Tc-MIBI scintigraphy is an option. The low confidence in the evidence quality of the studies leads to the restrictions made in the recommendation.

3.8.2 PET in combination with CT or MRI

3.8.2.1 Incidental [^{18}F]FDG uptake in the thyroid gland in PET

3.31	Consensus-based Recommendation	2025
EK	In the case of an incidental focal FDG accumulation in the thyroid gland, further clarification should be carried out to exclude malignancy if the diagnosis of thyroid carcinoma would lead to therapeutic consequences.	
	Strong Consensus	

[^{18}F]FDG-PET is increasingly used in combination with CT and MRI in patients with suspected or known malignant or inflammatory diseases. A focally increased glucose metabolism in [^{18}F]FDG-PET in the thyroid gland is found incidentally in 1 to 2% of patients, a diffusely increased uptake in approx. 2% of patients [220], [221], [222], [223].

The focally increased [^{18}F]FDG uptake usually corresponds to a clinically palpable thyroid nodule (> 1cm), so that further sonographic clarification is recommended. It must be taken into account that these thyroid nodules are malignant in approx. 35% of cases (relative frequency depends on the prevalence of autonomous nodules); on average, malignant nodules show a significantly higher SUV_{max} than benign nodules (6.9 vs. 4.8; $p < 0.001$) [223]. Accordingly, further clarification is recommended, taking into account the underlying disease (reason for performing the PET/CT). In one retrospective study by Pattison et al., only one of a total of 180 deceased patients died of their incidentally diagnosed medullary thyroid carcinoma [224]. Incidental focal accumulations in the thyroid gland also occur in the much less frequently performed PET/CT examinations with DOTATOC, DOTATATE, and PSMA and must be recognized in the clinical context.

A diffusely increased glucose metabolism of the thyroid gland is usually the result of a benign change (inflammatory genesis). It does not require the exclusion of malignancy but may require further clinical evaluation for thyroiditis.

3.8.2.2 [^{18}F]FDG-PET for the assessment of nodules with inconclusive cytological findings

3.32	Consensus-based Recommendation	2025
EK	In thyroid nodules > 1.5 cm with sonographic malignancy criteria and hypofunctionality in thyroid scintigraphy, [^{18}F]FDG-PET (as PET/CT or PET/MRI) can be performed due to the high negative predictive value if a dignity classification is/was not possible using fine needle aspiration.	
	Strong Consensus	

The benefit of [^{18}F]FDG-PET/CT for the assessment of nodules with inconclusive cytologic findings has been the subject of three meta-analyses to date [225], [226], [227]. In this patient population, the ability of [^{18}F]FDG-PET/CT to differentiate between benign and malignant lesions can be described as moderate [227]. Overall, [^{18}F]FDG-PET showed a sensitivity of 89%, a specificity of 55%, a positive predictive value of 41%, and a high negative predictive value of 93% [226].

Especially in patients with nodules >1.5 cm who had inconclusive cytologic findings, a negative [^{18}F]FDG-PET scan led to improved diagnostic accuracy [225].

Vriens et al. conducted a cost-benefit analysis in Dutch patients scheduled for thyroid surgery due to inconclusive fine-needle biopsy cytology findings and demonstrated that the implementation of preoperative [^{18}F]FDG-PET/CT would have prevented up to 47% of surgical procedures retrospectively deemed unnecessary, led to a small increase in health-related quality of life, and may reduce costs compared to diagnostic surgery and molecular testing [228].

In a single prospective study, [^{18}F]FDG-PET showed no additional diagnostic benefit or improved risk classification compared to thyroid sonography in multivariate analysis [229]. However, other recent prospective studies again show added value in the inclusion of [^{18}F]FDG-PET in the diagnostic workup of cytologically indeterminate thyroid nodules [230], [231]. Even though the majority of the available literature supports the use of [^{18}F]FDG-PET/CT in this patient population, further prospective studies are necessary, as the currently available data provide partly controversial results regarding the added value of [^{18}F]FDG-PET/CT in differentiating between benign and malignant lesions in cytologically indeterminate thyroid nodules.

A comparison with MIBI imaging in terms of sensitivity and specificity as well as cost-effectiveness has not yet been carried out.

3.8.2.3 Preoperative sectional imaging using PET/CT

3.33	Consensus-based Recommendation	2025
EK	Regular preoperative [^{18}F]FDG-PET/CT should not be performed.	
	Strong Consensus	

3.34	Consensus-based Recommendation	2025
EK	A [^{18}F]FDG-PET (in combination with CT or MRI) can be performed preoperatively to diagnose spread in "high-risk" patients with an extensive tumor, high-grade lymph node metastases, clinically aggressive progression, suspected distant metastases, and tumors with indications of aggressiveness in the biopsy. The examination shall then be carried out promptly.	
	Strong Consensus	

3.35	Consensus-based Recommendation	2025
EK	A [^{18}F]FDG-PET (in combination with CT or MRI) should be performed promptly if anaplastic thyroid carcinoma is clinically suspected (see alsoChapter 9.1.4).	
	Strong Consensus	

The majority of differentiated thyroid carcinomas show relatively slow growth. Sometimes the tumor can also be [^{18}F]FDG-negative [222]. With regard to the local findings and the locoregional lymph nodes, [^{18}F]FDG-PET/CT only provides limited information compared to preoperative sonography [230], [232], [233], [234]. The method showed very low sensitivity (10%) and low NPV (50%) but high specificity (90%) for locoregional lymph node metastases in the study by Kim et al. [235]. Since only 4-7% of patients with differentiated thyroid carcinoma have distant metastases at initial presentation, routine, preoperative/perioperative use of [^{18}F]FDG-PET/CT imaging is generally not recommended [222], [236].

For the detection of distant metastases, [^{18}F]FDG-PET shows a high sensitivity of up to 85% and specificity of up to 95% in several studies [24]. Therefore, [^{18}F]FDG-PET/CT plays a role in the initial staging of patients who have a significant risk of distant metastasis or who are clinically suspected of having distant metastases [222].

In the study by Rosenbaum-Krumme et al., patients with extensive or metastatic, differentiated "high-risk" thyroid carcinoma who received [^{18}F]FDG PET/CT after initial radioiodine therapy were examined [237]. Of these, 29% had FDG-avid tumor lesions, 36% had iodine-avid lesions, and 8% had concordant FDG- and iodine-avid metastases. The [^{18}F]FDG-PET/CT examination performed led to a change in patient management in 21% of cases (especially in patients with stage pT3bN1 and distant metastases).

Promising results were also shown by [^{18}F]FDG-PET/CT studies in tumor subtypes considered more aggressive, such as Hürthle cell tumor or the large cell variant [238], [239], [240]. In the study by Pryma et al. [240], 44 patients with Hürthle cell carcinoma were examined, with [^{18}F]FDG-PET/CT showing a sensitivity of 96% and a specificity of 95% and the intensity of FDG uptake in the tumor lesions providing additional important prognostic information. Nascimento et al. [239] examined 38 patients with different aggressive subtypes, for example the large cell or diffuse sclerosing variant,

using [^{18}F]FDG-PET/CT. A total of 86 lesions were found in 20 patients in the PET/CT and the post-therapeutic whole-body scintigram. Here, 41% of the lesions could only be detected by [^{18}F]FDG-PET/CT.

[^{18}F]FDG-PET/CT can also be used for risk stratification. A retrospective evaluation by Robbins et al. [241] in 400 thyroid cancer patients showed that patients with a significantly increased [^{18}F]FDG uptake had a 7-fold higher risk of death compared to the patient group that had no [^{18}F]FDG-positive lesions. It can therefore be concluded that patients with non-[^{18}F]FDG-avid lesions tend to have a better outcome than those who have a significantly increased glucose metabolism.

In the preoperative setting, the value of [^{18}F]FDG-PET (in combination with CT or MRI) lies in sensitive whole-body staging (without the use of iodine-containing X-ray contrast medium) in high-risk constellations for distant metastasis. If distant metastases are detected, the intervention in the neck area would be less extensive in many cases. It also seems possible to make a statement about the prognosis.

With regard to the preoperative use of [^{18}F]FDG-PET in anaplastic thyroid carcinoma, please refer to Chapter 9.1.4

3.8.3 Skeletal scintigraphy, chest X-ray, CT or MRI

3.8.3.1 Skeletal scintigraphy

3.36	Consensus-based Recommendation	2025
EK	Skeletal scintigraphy can be performed as part of initial staging in cases of suspected osseous metastasis if [^{18}F]FDG-PET (in combination with CT or MRI) is not available.	
	Consensus	

There are no studies with large numbers of patients and no randomized studies. In recent years, studies with smaller case numbers have been published, mostly comparing planar bone scintigraphy, [^{18}F]FDG-PET, and [^{18}F]fluoride PET.

In several studies, planar bone scintigraphy showed a sensitivity of 64% to 85% for the detection of bone metastases in thyroid cancer [242], [243], [244], [245]. The specificity in these studies is given as 81 - 95 %. The use of SPECT technology has significantly increased the sensitivity of planar bone scintigraphy; up to 100% has been published here, although this must be critically questioned [244]. For other tumor entities such as prostate and breast cancer, it has been shown that the use of SPECT or SPECT-CT can significantly increase the sensitivity and specificity in the detection of bone metastases compared to planar bone scintigraphy alone [246].

In a study published in 2007 on 47 patients with thyroid cancer, planar bone scintigraphy showed a sensitivity of 78 % and a specificity of 91.4 % [245]. Another study in 2012 found a sensitivity of 79% and a specificity of 83% in 80 patients with thyroid cancer using the planar technique; SPECT was not used here [243].

Studies comparing [^{18}F]FDG-PET/CT with planar bone scintigraphy show different results. While in one study [^{18}F]FDG-PET/CT shows higher sensitivity and specificity compared to planar bone scintigraphy, another study only shows better specificity with the same sensitivity [243]. In a more recent study from 2014, the sensitivity of planar bone scintigraphy improved to a level above that of [^{18}F]FDG-PET/CT due to the additional use of the SPECT technique, although this was a small patient population of 11 patients [244]. Skeletal metastases of a differentiated thyroid carcinoma can present as "cold lesions". A two-phase acquisition technique with early images can increase the identification of skeletal metastases by identifying hyperemic marginal enhancement

3.8.3.2 Chest X-ray examination

3.37	Consensus-based Recommendation	2025
EK	X-ray examination of the thorax should not be used as initial routine staging for thyroid cancer.	
	Strong Consensus	

The benefit of performing a routine chest X-ray is limited and questionable [247].

3.8.3.3 Computed tomography (CT)

3.38	Consensus-based Recommendation	2025
EK	Computed tomography should not be performed as initial routine staging for thyroid cancer.	
	Strong Consensus	

3.39	Consensus-based Recommendation	2025
EK	Native computed tomography can be performed initially if lung metastasis is suspected.	
	Strong Consensus	

3.40	Consensus-based Recommendation	2025
EK	If a differentiated thyroid carcinoma has been ruled out, a contrast-enhanced CT should be performed for staging in the case of advanced tumors, with [^{18}F]FDG-PET if available in a timely manner. In exceptional cases, this may also apply to differentiated thyroid carcinoma.	
	Strong Consensus	

The value of preoperative computed tomography (CT) was investigated in 2019 in a prospective study of 111 patients with differentiated thyroid carcinoma (tumor diameter < 4 cm); a change in the surgical procedure was described here in 22.5% of cases due to the use of preoperative CT, but it should be noted that the most frequent change was the performance of a central lymph node dissection, which, however, is usually performed in Germany with previously confirmed carcinoma [248]. The rate of false-positive findings was 44% centrally.

The additional performance of a CT scan of the thorax can be useful for the assessment of advanced thyroid cancer, as it can be used to assess extrathyroidal spread, particularly posteriorly or mediastinally [249].

A study published in 2015 shows that the combined use of sonography and CT as part of preoperative imaging can have advantages over sonography alone [250].

It should be noted that contrast-enhanced CT makes radioiodine therapy impossible in the narrow time interval after surgery due to the high amount of iodine. From a clinical point of view, postponing radioiodine therapy (if clinically indicated) is possible in many cases, but this can lead to considerable psychological stress, especially in patients with postoperative tumor manifestations that can be detected macroscopically.

3.8.3.4 Magnetic resonance imaging (MRI)

3.41	Consensus-based Recommendation	2025
EK	Magnetic resonance imaging can be performed initially in the case of locally advanced cervical tumors or suspected metastasis.	
	Strong Consensus	

3.42	Consensus-based Recommendation	2025
EK	The administration of iodine-containing contrast media or other substances with a high iodine content should be avoided in cases of thyroid carcinoma.	
	Strong Consensus	

Magnetic resonance imaging (MRI) is often used for tumors in the head and neck region to assess tumor spread and, above all, to rule out infiltrative growth. However, a 2014 study on thyroid cancer patients showed a lower sensitivity in the assessment of extrathyroidal spread of the carcinoma compared to sonographic examinations [251].

3.9 Preoperative vocal fold diagnostics and laryngological diagnostics

3.43	Consensus-based Recommendation	2025
EK	Before any thyroid surgery, a laryngoscopic check of the respiratory mobility of the vocal folds shall be performed and subjective voice, breathing and swallowing complaints shall be recorded. A phoniatric voice examination should be performed in the event of functional limitations.	
	Strong Consensus	

4 Cytology/Pathology

4.1 Pathological classification of thyroid tumors

The WHO periodically updates the system of histological classification of thyroid tumors. The 4th edition [252] is still authoritative for this guideline; changes to the 5th edition were not adopted until 2022 [253] and therefore no studies or clinical experience with it are yet available. The following table compares the classification of the 4th edition with the 5th edition with regard to the most important points on thyroid carcinomas of the follicular epithelial cells.

Medullary thyroid carcinoma is dealt with separately in Chapter 8.

Table 12: Comparison of the 4th and 5th editions of the WHO classification of common thyroid neoplasms of the follicular epithelial cells

4th edition (2017)		5th edition (changes)
Follicular adenoma	Benign neoplasms	Follicular adenoma
		Follicular adenoma with papillary architecture
Oncocytic adenoma		Oncocytic adenoma
		Thyroid follicular nodular disease (FND)
Hyalinizing trabecular tumor (HTT)	Low-risk neoplasms	Hyalinizing trabecular tumor (HTT)
Follicular tumor of unknown malignant potential (FT-UMP)		Follicular tumor of unclear malignant potential (FT-UMP)
Well-differentiated tumor of unclear malignant potential (WDT-UMP)		Well-differentiated tumor of unclear malignant potential (WDT-UMP)
Non-invasive follicular neoplasia with PTC-equivalent nuclear features (NIFTP)		Non-invasive follicular neoplasia with PTC-equivalent nuclear features (NIFTP)
Follicular thyroid carcinoma (FTC)	Malignant neoplasms	Follicular thyroid carcinoma (FTC)
		Invasive encapsulated papillary thyroid carcinoma follicular variant (IEFVPTC)
Papillary thyroid carcinoma (PTC)		Papillary thyroid carcinoma (PTC)
Hürthle cell carcinoma		Oncocytic thyroid carcinoma (OTC)

4th edition (2017)		5th edition (changes)
		High-grade thyroid carcinoma of the follicular cells
		Differentiated high-grade thyroid carcinoma (DHGTC)
Poorly differentiated thyroid carcinoma (PDTC)		Poorly differentiated thyroid carcinoma (PDTC)
Anaplastic thyroid carcinoma (ATC)		Anaplastic thyroid carcinoma (ATC)

In the 4th edition of the WHO classification, the (vast majority of) epithelial tumors of the thyroid gland are divided into benign tumors, other encapsulated tumors with a follicular structure (all tumors in this group have an uncertain/very low malignant potential) and malignant tumors (carcinomas). In the 5th edition of the WHO classification, epithelial tumors of the follicular epithelial cells are consistently classified into the categories "benign", "low-risk" and "malignant" as a significant change. Further changes to the naming of tumors and the introduction of new entities are discussed in the text below where necessary. Non-epithelial tumors are rarities.

4.1	Consensus-based Recommendation	2025
EK	The histopathological classification of thyroid tumors shall be based on the current WHO classification.	
	Strong Consensus	

The histological type or subtype of a thyroid tumor influences the prognosis, the further therapeutic procedure (e.g. radioiodine therapy), and the design of tumor follow-up care.

Benign neoplasms

While only follicular adenoma and oncocytic adenoma (Hürthle cell adenoma) of the thyroid gland were listed in the 4th edition of the WHO classification, the 5th edition now introduces two further entities, follicular adenoma with papillary architecture and follicular nodular disease (FND).

Follicular adenoma with papillary architecture represents a benign, encapsulated neoplasm without PTC-like nuclei with a characteristic centripetal structure of pseudopapillae. These adenomas are often associated with autonomic hyperfunction.

One innovation is the classification of nodular goiter (struma colloides nodosa, SCN) as a true neoplasia. This takes into account the fact that many nodular goiters have true neoplastic parts in addition to inflammatory-reactive hyperplastic nodule

formation. These often do not show a complete capsule, but classic driver mutations of a neoplasia are detectable. The authors of the 5th edition of the WHO classification refer to this lesion as "thyroid follicular nodular disease, FND".

Low-risk neoplasms

In both the 4th and 5th editions of the WHO classification, thyroid neoplasms with unclear malignant potential, non-invasive follicular neoplasia with PTC-like nuclear features (NIFTP), and hyalinizing trabecular tumors (HTT) are classified in this group. NIFTP was newly introduced in the 4th edition in order to spare patients with a biologically indolent subgroup of the follicular variant of papillary carcinoma both overtreatment and a psychologically stressful cancer diagnosis; the establishment of NIFTP necessitated a redefinition of the diagnostic criteria for PTC and has implications for the evaluation of fine needle aspiration of the thyroid gland [254].

Malignant neoplasms

Follicular thyroid carcinoma (FTC)

The WHO classification distinguishes three clinically relevant subgroups of FTC:

- Minimally invasive FTC is an invasively growing encapsulated tumor whose diagnosis is based solely on evidence of one or more complete capsular ruptures. Vascular invasion must be explicitly excluded histologically in minimally invasive FTC, as vascular invasion represents a relevant negative prognostic marker in contrast to isolated capsular breakthroughs. A capsular rupture alone represents a very low prognostic risk factor [255], [256], [257], [258], [259], [172].
- Encapsulated angioinvasive FTC is diagnosed on the basis of vascular invasion detectable in the area of the tumor capsule or beyond the tumor capsule; capsular breakthroughs may occur. Vascular invasion must be reliably differentiated from the frequently occurring artificial spread of tumor components during surgery and further processing in pathology. Encapsulated angioinvasive FTCs are divided into 2 groups. Those with limited vascular invasion of < 4 vascular invasions and tumors with ≥ 4 vascular invasions. The number of ≥ 4 vascular invasions alone does not qualify for the diagnosis of a broadly invasive FTC.
- Broadly invasive FTC is defined by varying degrees of invasive growth of the tumor into adjacent non-neoplastic tissue ("normal" thyroid tissue and/or extrathyroidal soft tissue). Vascular invasions are often additionally detectable, but are generally not necessary for the diagnosis

Encapsulated FTCs must be differentiated from adenomas (vascular and capsular invasion), encapsulated (follicular) PTCs and NIFTP (core criteria), as well as encapsulated PDTCs (Turin criteria). Broadly invasive FTC must first and foremost be distinguished from PDTC and differentiated high-grade thyroid carcinoma (DHGTC).

There are currently no specific molecular markers for the diagnosis of FTC or for differentiation from adenomas (see also the section Chapter 3.7).

Papillary thyroid carcinoma (PTC)

Due to the introduction of NIFTP (non-invasive follicular neoplasia with PTC-equivalent core features) in the WHO classification in 2017, the definition of PTC had to be

changed. In addition to the characteristic nuclear features that are mandatory for PTC, invasion and/or well-developed papillae or other surrogate markers such as true psammoma corpuscles must now be present [254].

PTC are either unencapsulated and thus basically invasively growing, or encapsulated. Encapsulated PTCs require invasion in the capsular region (or beyond) and/or papillae for diagnosis; encapsulated PTCs with a completely or predominantly follicular structure are usually differentiated from NIFTP on the basis of invasion in the capsular region and/or immunohistochemical/molecular pathological evidence of a BRAF V600E mutation in addition to other surrogate markers such as true psammoma corpuscles.

Completely encapsulated PTC of the follicular subtype, which cannot be classified as NIFTP based on histomorphological criteria and do not have a BRAF V600E mutation, are classified according to the WHO classification (5th edition) as a separate entity in the sense of an infiltrative encapsulated follicular variant of PTC (IEFVPTC). According to current understanding, these tumors behave biologically more like FTC and are assigned to the group of RAS-like thyroid tumors in terms of molecular biology [253].

According to current understanding, PTC can be diagnosed molecularly on the basis of a BRAF V600E mutation, RET fusion or NTRK fusion (so-called diagnostic markers of PTC), whereby the absence of these mutations does not rule out PTC. These genetic alterations do not occur in adenomas or in FTC, but they can also be detected in poorly differentiated carcinoma (PDTC, also known as differentiated high-grade thyroid carcinoma DHGTC) and anaplastic carcinoma (ATC). Therefore, a morphological differentiation of PTC as a well-differentiated carcinoma from PDTC and DHGTC is mandatory, particularly in the case of a solid/trabecular growth pattern, necrosis and/or ≥3 mitoses/2mm² (PDTC) or classic architecture with ≥ 5 mitoses/2mm², Ki67 10-30 %, necrosis (DHGTC).

PTC subtypes

Numerous subtypes of PTC are listed in both the 4th and 5th editions of the WHO classification. It is advisable to list the subtypes with prognostic significance in the pathology report. The large cell variant, columnar cell variant, and hobnail variant are considered aggressive subtypes. These usually occur at an advanced age and are often associated with vascular invasion, increased mitotic activity, and an advanced pathological stage. A DHGTC should be considered in the differential diagnosis. The indication of an aggressive subtype (especially the hobnail variant) requires the exclusion of regressive processes in classic PTC, which can also show hobnail-like changes. The aggressive subtypes can also appear as clinically non-aggressive and encapsulated, especially in younger patients. In these cases, pathological signs such as extrathyroidal extension, lymphatic and venous infiltration and lymph node metastases are absent [253], [260].

Cases with aggressive clinical courses have also been described for the diffuse sclerosing and solid or trabecular subtypes. It remains to be seen whether a prognostic significance can be confirmed in future studies following the introduction of the PDTC and DHGTC entities as a possible differential diagnosis [253], [260].

Papillary thyroid microcarcinoma (PTMC) will no longer be listed as a subtype in the 5th edition of the WHO classification, as it is not a histomorphological subtype and will only be named as a PTC with a corresponding size indication (corresponds to TNM stage pT1a). PTC with a diameter ≤ 1 cm can also become clinically conspicuous

primarily with lymph node metastases [253], [260]. These tumors are therefore obviously biologically different from incidences of small PTC without prior clinical suspicion of malignancy. The prognostic significance of histological subtypes of PTC in TNM stage pT1a should therefore be critically questioned, especially in the case of incidental tumors.

Oncocytic thyroid carcinoma (OTC) / Hürthle cell carcinoma

Tumors with a proportion of >75% of oxyphilic differentiated cells are referred to as Hürthle cell neoplasms if their structure basically corresponds to an adenoma or an FTC. In the WHO classification (4th edition, 2017), Hürthle cell neoplasms are listed as a separate entity; until then, these tumors were classified as adenoma, oxyphilic variant, or FTC, oxyphilic variant. In the 5th edition of the WHO classification, the name was changed to oncocytic thyroid carcinoma.

Oncocytically differentiated PTC, PDTC, and MTC are still classified as oncocytic variants of the respective tumor type.

Oncocytic thyroid carcinoma / Hürthle cell carcinoma is differentiated from oncocytic adenomas / Hürthle cell adenomas based on the diagnostic criteria of the FTC; oncocytic carcinomas / Hürthle cell carcinomas are also subclassified into minimally invasive, encapsulated angioinvasive and broadly invasive. Broadly invasive oncocytic thyroid carcinomas / Hürthle cell carcinomas must be differentiated from the oncocytic variant of PDTC.

Poorly differentiated carcinoma (PDTC)

PDTC is morphologically and biologically located between the differentiated (FTC, PTC) and the ATC. The diagnostic criteria were defined in 2007 in the so-called Turin Proposal [261].

PDTC show a solid, trabecular and/or insular structure (so-called STI pattern), usually two or even all three patterns are found side by side in varying degrees. In addition, at least one of the three criteria necrosis, mitoses (≥3/2mm²), and convoluted nuclei must be detectable for the diagnosis of PDTC. In the majority of cases, there are also clear signs of invasion (vascular invasion, broadly invasive growth), but in individual cases the diagnosis is made solely on the basis of the STI pattern and the detection of tumor necrosis and/or mitoses (≥3/2mm²).

To date, no molecular genetic alterations specific to PDTC are known.

Differentiated high-grade thyroid carcinoma (DHGTC)

Despite the often clinically indolent course of differentiated thyroid carcinomas (PTC and FTC), some patients experience distant metastasis and recurrence and fail radioiodine therapy. In addition to molecular risk factors (see Chapter 3.2), histomorphological criteria for differentiated carcinomas with unfavorable disease progression have been identified in recent years and the 5th edition of the WHO classification has introduced the tumor entity of differentiated high-grade thyroid carcinoma (DHGTC). Due to the lack of insular, solid or trabecular architecture, these tumors could not be classified as poorly differentiated thyroid carcinomas (PDTC). Similar to PDTC and high-grade MTC, the division activity of the tumor cells is also an important criterion here. The detection of five or more mitoses per 2 mm² supports the diagnosis of a

DHGTC. An alternative/additional criterion is the detection of true tumor necrosis, which must be differentiated from focal ischemic necrosis.

Convoluted nuclei are an additional criterion for PDTC in accordance with the Turin criteria. In practice, however, these are a rather uncertain criterion due to the high interobserver variability. These nuclear changes play no role in the diagnosis of DHGTC [261].

Table 13: Comparison of the histomorphological criteria for the diagnosis of PDTC and DHGTC. Convoluted nuclei are an additional criterion for PDTC according to the Turin criteria. In practice, however, these are a rather uncertain criterion due to the high interobserver variability

		PDTC	DHGTC
1.	Architecture	solid / insular / trabecular	FTC- / PTC-like
	and		
2.	Necrosis	yes	yes
	and / or		
	mitoses	≥ 3 / 2mm²	≥ 5 / 2mm²

Anaplastic thyroid carcinoma (ATC)

Anaplastic thyroid carcinoma (ATC) - or previously undifferentiated thyroid carcinoma (UTC) - is rare compared to differentiated thyroid carcinomas, but contributes significantly to the mortality of thyroid carcinomas due to the often extremely poor prognosis. At the time of diagnosis, the tumor is often at an advanced stage due to its rapid growth. Microscopically, ATC is defined by a widespread absence of histomorphologic and immunohistochemical characteristics typical of thyroid carcinomas, so that it is primarily a diagnosis of exclusion based on the clinical-radiologic findings and the patient's medical history. In many cases, pan-cytokeratin and PAX8 positivity can be detected. Markers such as TTF1 and thyroglobulin are usually negative. ATC must always be differentiated immunohistochemically from angiosarcoma, lymphoma, and medullary thyroid carcinoma. The paucicellular variant of ATC can be difficult to differentiate from Riedel's goiter, particularly in biopsies, due to its clinical appearance and extreme paucity of cells. In some cases, more differentiated parts (FTC, PTC, PDTC, DHGTC) may be present in the ATC. Depending on the differentiation, numerous molecular aberrations can be detected in ATC. All the mutations typical of differentiated thyroid carcinomas can also occur. In special cases (e.g. BRAF V600E, RET fusion, NTRK fusion), this results in a treatment option using molecularly targeted therapeutics approved for ATC or the possibility of an individual treatment attempt. Depending on the clinical context, genome-wide parallel sequencing using a large gene panel and subsequent discussion in an interdisciplinary molecular tumor board is therefore advisable.

Frequency of the various entities

There is little recent, reliable data on the distribution of histological types of thyroid cancer in Germany. In a representative population study from Lower Franconia, in which the changes from 1981-2015 were analyzed in 5-year intervals [10], there was an increase in the incidence of thyroid cancer from 4.5 to 8.7/100,000/year in women and from 1.7 to 4.1/100.000/year in men, which is mainly attributable to papillary thyroid carcinomas, while the incidence of anaplastic thyroid carcinomas decreased with a largely constant proportion of follicular thyroid carcinomas. In the last analyzed 5-year interval 2011-2015, the incidence of papillary and follicular and anaplastic thyroid carcinomas was 7.60 and 1.06 and 0.08/100,000/year in women and 3.41 and 0.63 and 0.04 /100,000/year in men, respectively. A similar trend was also described in a population-based study from 25 countries [20].

As far as the TNM stage is concerned, the study from Lower Franconia showed a significant increase in T1 stages with a simultaneous decrease in T4 and M1 stages in the analyzed period from 1981 to 2015, but also a significant increase in T3 stages and lymph node involvement, which argues against overdiagnosis as the sole cause of the observed increase in the incidence of thyroid cancer [10].

4.2	Consensus-based Recommendation	2025
EK	The stage of thyroid malignancies shall be specified according to the currently valid TNM classification and the edition of the International Union Against Cancer (UICC). If the stage is also specified according to an older edition, the underlying edition must also be stated in the findings.	
	Strong Consensus	

The TNM classification and the staging based on it - including age - is the most commonly used criterion worldwide for risk stratification and estimating the prognosis of thyroid malignancies [262], [263], [264], [265], [266], [267], [268], [269], [270], [271], [272], [273]. The changes implemented in the 8th edition compared to the 7th edition lead to an overall "down-staging", which is intended to avoid unjustified overtreatment [274]. However, criticism of the 8th edition was also voiced [275], for example the fact that the minimal extrathyroidal tumor extension - with regard to the prognostic significance of which there is no consensus - is no longer included in the 8th edition; at the same time, supplementary proposals were made to compensate for the criticized deficits.

Compared to the previous editions, the current 8th edition of the TNM classification does not include the prognostic classification (higher grouping) of microscopic and thus initially organ capsule-exceeding growth. The reason for this is the often unclear capsule situation in the dorsal parts of the thyroid gland with a sometimes difficult to delimit organ capsule and retracting fatty/connective tissue parts with a high interindividual variation in the assessment by the individual pathologist [276].

The application of strict histomorphologic criteria for microscopic extrathyroidal spread has been shown to have a clear impact on the postoperative management of

patients [258]. The extranodal spread of local lymph node metastases is also described as a significant prognostic marker [277], [278], [279], which is why this should be indicated in the TNM classification as extracapsular extension (ece+) in the pN category.

In order to establish comparability with earlier TNM classifications, it may be useful to also report the older TNM classification (7th edition) in the findings. Alternatively, the TNM classification generally provides the option of specifying an extended classification for the respective organ system. For stages T1 to T3, this was published in a publication by Schmid and Wittekind et al. [280] in a proposal for extension, including the microscopic extrathyroidal and nodal extracapsular spread (N1a and b) (Table 14).

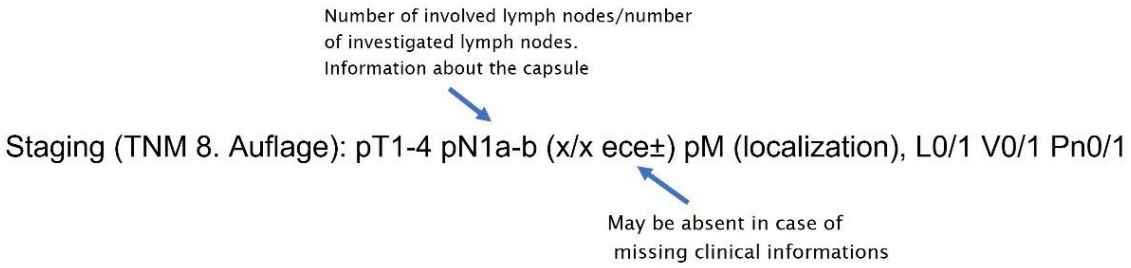


Figure 1: It is recommended that the TNM classification is always given in full according to this pattern.

General prognostic histomorphological markers such as infiltration of lymphatic (L) and blood vessels (V) as well as perineural sheaths (Pn) are often only seen in the area of the tumor in advanced tumors with extrathyroidal extension. Angioinvasive follicular thyroid carcinomas and some histomorphologic subtypes of PTC are exceptions. An immunohistochemical work-up to confirm infiltration of lymphatic vessels and/or veins can help in individual cases, but is generally not helpful, as the thyroid gland is highly vascularized and interpretation of the antibody staining is therefore difficult.

The synchronous detection of local lymph node metastases, even in material from central or lateral compartments that may have been sent in at the same time, is a sign of infiltration of the afferent/efferent lymphatic pathways and should therefore be classified as L1 (see TNM classification, Supplement).

Grading information is not provided for thyroid carcinoma, as it is included in the type diagnosis of the malignancy.

A statement on removal in healthy / not in healthy tissue of the primary tumor (R classification) is mandatory for thyroid resectates, lobectomies, and thyroidectomies. If the specimens are sent in fragmented, it is often not possible to determine the R classification. The R classification (R0/1/2) is not an integral part of the TNM classification but should be listed both in the text of the findings and in a structured manner in association with the TNM formula.

Table 14: TNM classification of thyroid carcinomas according to the 8th edition of the UICC with proposals for the addition of prognostically relevant criteria such as minimal extrathyroidal spread of the primary tumor and extracapsular spread of lymph node metastases

TNM	Proposal for an extended TNM classification
pT primary tumor	Includes PTC, FTC, PDTC, DHGTC, OTC, MTC
pTx	Primary tumor cannot be assessed
pT0	No evidence of a primary tumor
pT1a1	Tumor of 1 cm or less in greatest dimension, confined to the thyroid gland
pT1a2	Tumor of 1 cm or less in the largest dimension, with "minimal extrathyroidal spread"
pT1b1	Tumor of more than 1 cm to max. 2 cm in largest dimension, limited to the thyroid gland
pT1b2	Tumor of more than 1 cm to max. 2 cm in size, with "minimal extrathyroidal spread"
pT2a	Tumor of more than 2 cm to max. 4 cm in size, limited to the thyroid gland
pT2b	Tumor of more than 2 cm to max. 4 cm in size, with "minimal extrathyroidal spread"
pT3a1	Tumor of more than 4 cm in the largest dimension, limited to the thyroid gland
pT3a2	Tumor of more than 4 cm in the largest dimension, with "minimal extrathyroidal spread"
pT3b	Tumor of any size with macroscopic extrathyroidal spread and invasion of the infrahyoid muscles (sternohyoid, sternothyroid and omohyoid muscles)
pT4a	Tumor with spread beyond the thyroid capsule and invasion of one or more of the following structures: subcutaneous soft tissue, larynx, trachea, esophagus, recurrent laryngeal nerve
pT4b	Tumor infiltrates prevertebral fascia, mediastinal vessels or surrounds the carotid artery
N0/pN - regional lymph nodes	Clinical / Pathological

TNM	Proposal for an extended TNM classification
Nx/pNx	Regional lymph nodes cannot be assessed
N0/pN0	No evidence of regional lymph node metastases
N1a1/pN1a1	Metastases in level VI (pretracheal and paratracheal, prelaryngeal and Delphi lymph nodes), or in the upper mediastinum, limited to the lymph nodes without extracapsular spread
N1a2/pN1a2	Metastases in level VI (pretracheal and paratracheal, prelaryngeal and Delphi lymph nodes), or in the upper mediastinum, with extracapsular spread
N1b1/pN1b1	Metastases in other unilateral, bilateral or contralateral cervical (level I, II, III, IV or V) or retropharyngeal lymph nodes, limited to the lymph nodes without extracapsular spread
N1b2/pN1b2	Metastases in other unilateral, bilateral or contralateral cervical (level I, II, III, IV or V) or retropharyngeal lymph nodes, with extracapsular spread
pM - distant metastases	
pM1	Distant metastases confirmed microscopically
(modified according to [280])	

4.3	Consensus-based Recommendation	2025
EK	So that the pathological institution involved can correctly indicate the N-stage, the sending surgical clinic shall indicate the localization of the lymph node resectates. For this purpose, they shall be sent separately by compartment.	
	Strong Consensus	

4.4	Consensus-based Recommendation	2025
EK	The histopathological findings shall report the number of tumor-infected lymph nodes in relation to the total number of lymph nodes examined.	
	Strong Consensus	

As of the 6th TNM edition (UICC 2002), the localization of any lymph node metastases is also included in the N-stage to a more precise degree than before.

4.5	Consensus-based Recommendation	2025
EK	If new aspects regarding tumor spread become available postoperatively, the pTNM stage shall be supplemented by the cNcM stage.	
	Strong Consensus	

As of the 6th edition (UICC 2002), tumor freedom with at least 6 resected lymph nodes was no longer a mandatory requirement for the classification pN0. In the surgical guidelines for the surgical treatment of malignant thyroid diseases of the DGAV since 2012 [AWMF 088/002; 2012], prophylactic compartmental lymph node resection without clinical evidence of lymph node filiae is no longer mandatory in the primary surgical procedure when weighing up the benefits and risks. One consequence of this is that, on the one hand, pathological findings are more frequently classified as "pNX" and, on the other hand, even if only a small number of lymph nodes have been examined and are tumor-free, they are classified as "pN0", with correction of the N stage then more frequently required in the course of the procedure.

As a rule, the M stage cannot be determined during primary surgical treatment, but only during the course of the disease, primarily on the basis of the imaging diagnostics used, in particular radioiodine scintigraphy. Only in rare cases of cytologically or histopathologically confirmed distant metastasis is the stage indicated with the suffix "p" as pM1.

The pTNM stage can only be supplemented with the suffix "c" in a narrow time window of 3-6 months after surgery (e.g. from pNX MX to cN1b cM1). If changes are only detected after 3-6 months, the additional suffix "r" is used (e.g. rpT4a or rcT4a).

4.6	Consensus-based Recommendation	2025
EK	If the primary pathologic institution cannot make a conclusive histopathologic entity diagnosis, the material shall also be reviewed by a reference pathologist.	
	Strong Consensus	

Some tumors, especially histological subtypes, are sometimes difficult to classify in the pathological assessment (e.g. minimally invasive follicular carcinoma, broadly invasive follicular carcinoma, or the "non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)", differentiation of tumors with "uncertain malignant potential (UMP)"). However, the actual histological (sub)type often has a fundamental influence on the prognosis and the therapeutic approach. In case of doubt, the expertise of a reference pathologist should therefore be consulted.

4.2 Fine needle aspiration cytology of the thyroid gland

4.2.1 Definition

- Fine needle aspiration cytology (FNA cytology or FNA for short) of the thyroid gland (often called fine needle biopsy "FNA" in the international literature) is a simple and safe procedure for obtaining cells from defined lesions ("nodules"), which can be used to make a diagnostic contribution to determining the dignity of these nodules.
- The diagnosis of practically all neoplasms of the thyroid gland is based on special histological criteria and therefore cannot be made cytologically. The task of cytology is to identify lesions in which malignancy is probable or cannot be considered improbable with the necessary certainty, and which are then subjected to surgery and subsequent histological clarification.
- In contrast to the approach in other countries (particularly in the USA/Canada), conspicuous nodules are more frequently diagnosed and operated on in iodine-deficient Germany and thus subjected to histological dignity assessment; in this approach, the significance of FNA must be assessed differently than, for example, in the ATA guidelines.
- In the context of malignancy-suspected thyroid nodules, or as part of follow-up examinations for thyroid cancer patients who have undergone surgery, sonographically supported FNA of conspicuous cervical lymph nodes may also be useful with cytological (and possibly molecular pathological) analysis of the punctate, which can be supplemented by the direct determination of tumor markers (thyroglobulin, calcitonin) from the punctate washout. For more details, see Chapter 3.7 (diagnostics) and the following methodological addendum.

4.2.2 Methodology of FNAC and processing of the cytological material obtained

4.7	Consensus-based Recommendation	2025
EK	The material obtained can be further processed using both conventional smearing technology and thin-film technology.	
	Strong Consensus	

The processing by the scorer (see text under Chapter 3.7) is carried out in consultation with the pathologist making the findings as a smear or by transferring it to a container with reagents provided for subsequent thin-layer examination [191], [281]. The reagent serves the purpose of (extensive) lysis of punctate red cells and preservation of the aspirate during transportation. After subsequent fixation, a defined number of cells are standardized and applied to a slide in special devices. The mostly blood-free preparations can be microscopically assessed in a much less time-consuming manner. Disadvantages are the higher number of technically inadequate preparations and various specifics in the cytological assessment of the preparations.

4.2.3 Essential clinical information on FNAC

4.8	Consensus-based Recommendation	2025
EK	Structured communication regarding relevant clinical information shall take place between the pathology facility and the puncture specialist.	
	Strong Consensus	

The clinical information listed below increases the reliability of the cytological findings:

- Age and sex of the patient (usually evident from the patient ID).
- Size and localization of the punctured nodule.
- Metabolic location and information on whether focal autonomy in the area of the punctured nodule has been ruled out by scintigraphy (if focal autonomy is detected by scintigraphy, fine needle aspiration is generally not necessary).
- Information on cystic changes; hemorrhagic punctate.
- Clinical findings suggestive of a thyroid malignancy.
- Sonographic findings, information on TIRADS.
- Anamnestic evidence indicating an increased risk of thyroid malignancy (relevant radiation exposure, family history).
- Serum calcitonin.
- Information on other known diseases and previous thyroid therapies (e.g. previous radioiodine therapy for thyroid autonomy), medication with an effect on the thyroid [282] or other diseases that can also manifest themselves in the thyroid (extrathyroidal tumor diseases/metastases, rheumatic diseases, infectious diseases [283], [284], [285], [286], [287], [288].

4.2.4 Diagnostic finding categories

4.9	Consensus-based Recommendation	2025
EK	An established cytological reporting system shall be used. In a goiter endemic area such as Germany, the 5-stage cytologic reporting system can be used, which divides the "AUS/FLUS" reporting category of the Bethesda system and includes the following reporting categories: • Thyroid findings category I - non-diagnostic punctate • Thyroid findings category II - cytologically benign punctate • Thyroid findings category III - follicular neoplasia/suspected follicular neoplasia • Thyroid finding category IV - malignant suspicious punctate • Thyroid findings category V - cytologically certainly malignant	
	Strong Consensus	

The system recommended by the ATA for categorizing thyroid punctates is the 6-level Bethesda classification [289], [290]. In contrast, 5-level diagnostic systems are used

in Europe (Great Britain [291] and Italy [292]). Based on the strict puncture indication proposed in Germany (puncture only in the case of clinically and/or sonographically abnormal, scintigraphically non-hyperfunctional "nodules"), a 5-stage diagnostic system was recommended, in which the findings category III (abnormality of undetermined significance/follicular lesion of undetermined significance) according to the 6-stage Bethesda system is omitted and, depending on the severity of the cytological abnormalities, is de facto assigned to the findings categories II or III of the 5-stage system [293]. The following Table 15 compares the four diagnostic systems mentioned.

Table 15: Comparison of different diagnostic systems for thyroid cytology

Bethesda system [290]	**British system** [291]	**Italian system** [292]	**German system** [293]
Bethesda category I	**Thy1**	**TIR 1**	**Thyroid findings category I**
Not sufficient for cytologic diagnosis	Non-diagnostic or insufficient (cystic lesions are labeled separately [Thy1c])	Non-diagnostic (TIR 1C non-diagnostic cystic)	Non-diagnostic
Bethesda category II	**Thy2**	**TIR 2**	**Thyroid findings category II**
Benign	Non-neoplastic (cystic lesions are labeled separately [Thy2c])	Non-malignant	Cytologically benign including(thyrocyte-free) cystic punctates and milder cytologic abnormalities of various causes
Bethesda category III	**Thy3a**	**TIR 3A**	
Follicular lesion of undetermined significance (FLUS)/abnormality* of undetermined significance (AUS)	Neoplasia possible - abnormality/non-diagnostic	Unclear lesion, low risk	
Bethesda category IV	**Thy3f**	**TIR 3B**	**Thyroid findings category III**

Bethesda system [290]	British system [291]	Italian system [292]	German system [293]
Follicular neoplasia or suspected follicular neoplasia	Neoplasia possible, probably follicular neoplasia	Unclear lesion, high risk	Follicular neoplasia/suspicion of follicular neoplasia This category also includes all cytological abnormalities that probably correspond to a neoplasia
Bethesda category V	**Thy4**	**TIR 4**	**Thyroid findings category IV**
Suspected malignancy	Suspected malignancy	Suspected malignancy	Suspected malignancy With corresponding nuclear changes "suspected PTC" Suspicion of other, non-FTC/PTC malignancies
Bethesda category VI	**Thy5**	**TIR 5**	**Thyroid findings category V**
Malignant	Malignant	Malignant	Cytologically malignant

The categories of findings recommended in Germany listed below apply to punctates from the thyroid gland, but not to punctates in cases of suspected metastases of a thyroid malignancy in regional lymph nodes or other localizations. Similarly, punctates that unexpectedly show parathyroid tissue (parathyroid or intrathyroid punctate) should not be categorized according to the specified scheme. Ideally, at least five follicular cell clusters with at least 10 cells each should be available for a representative punctate (not necessary if cells are detected that can be clearly assigned to thyroid findings categories IV or V, or if cysts were punctured, see below).

Thyroid findings category I (non-diagnostic)

Even with experienced punctureres, at least 10 - 15% of punctates are expected to be technically inadequate. In addition to aspects of the puncture procedure such as missing the lesion (so-called sampling error), the nature of the punctured lesion (e.g. pronounced regression, stroma-rich lesions, or lesions with pronounced calcifications) can also be the cause of a non-diagnostic preparation. The rate of non-diagnostic punctates therefore also depends largely on the punctate collective.

Punctates from bleeding cysts (siderophages and blood) or colloid nodules (cytologically colloid-rich image) are classified as representative (category II) despite the absence of thyrocytes if the clinical picture is appropriate (for such nodules there is no indication for puncture in the sense of a dignity clarification; however, larger, locally symptomatic cystic lesions can be punctured for relief).

In the case of "Thyroid findings category I - non-diagnostic punctate", prompt re-puncture is recommended, or (especially in the case of repeated non-diagnostic punctate) histological clarification in the individual case. Malignancy rates of up to almost 30 % have been described for this category of findings [294], [295], [296]. In addition, higher malignancy rates were found in this category in children than in adults in comparative studies [297].

Thyroid findings category II - cytologically benign

Depending on the patient population and the experience of the cytopathologist, 50 - 90% of all FNAC correspond to this category. Punctures from cystic lesions should be assigned to this category of findings even if there are no adequate thyrocyte counts, provided that corresponding components are detected that are consistent with a cyst (macrophages, siderophages, fibrin, etc.).

If the indication for puncture is primarily correct, a continued residual risk (malignancy rate of up to 3 %) can also be assumed for category II findings. Therefore, even category II findings do not release the patient from the responsibility to continue to monitor the development of the lesion in order to initiate a re-puncture or further measures to clarify the dignity in the event of suspicious changes.

Slightly abnormal/unclear cytologic images that do not correspond to diagnostic categories III - V should be assigned to diagnostic category II, taking into account the clinical information; if puncture is indicated (only clinically and/or sonographically abnormal nodules), clinical control, including re-puncture if necessary, should be ensured in such cases in particular. Higher-grade cytologic abnormalities should be subjected to surgery and final histologic classification if the findings are clinically and/or sonographically abnormal. For this reason, a cytological category analogous to findings category III of the Bethesda classification (AUS/FLUS) can be dispensed with.

Thyroid findings category III - follicular neoplasia/suspected follicular neoplasia

Around 5 - 20% of all FNA correspond to finding category III, of which 10 - 40% are histologically classified as carcinomas (predominantly FTC, but also PTC) postoperatively [293]. Tumors histologically classified as NIFTP may also have corresponded cytologically to a follicular neoplasm. The cytologic diagnosis of a follicular carcinoma by classification in thyroid finding category V is generally not possible, as histologic criteria (capsular rupture/vascular rupture) are required for the diagnosis. Similarly, it does not make sense to make a suspected cytological diagnosis of "follicular carcinoma" as part of thyroid findings category IV. Even in conspicuously cell-rich punctates with pronounced atypia, the determination of a follicular carcinoma based solely on cytological criteria would not be justifiable [293]; conversely, it even represents one of the most frequent causes of "false-positive" findings.

Findings category III should be diagnosed sparingly; moderate cell proliferation and/or individual cells with variations in nuclear size do not per se justify the diagnosis of a "follicular neoplasia". These cell images should be categorized as "cytologically negative" (thyroid findings category II) with the indication of clinical control and,

if necessary, re-puncture. The method-related higher cellularity in thin layer cytology recommends a more restrictive use of this criterion [298].

Oncocytically differentiated follicular neoplasms are statistically more likely to lead to a postoperative diagnosis of Hürthle cell carcinoma (or oncocytic thyroid carcinoma according to the new WHO classification; formerly FTC, oncocytic variant) than cytologically non-oncocytically differentiated follicular neoplasms. In principle, however, no cytological differentiation between benign and malignant tumors is possible even in oncocytically differentiated neoplasms. Oncocytic cells are also found metaplastic in nodular strands and in Hashimoto's autoimmune thyroiditis. Individual oncocytes or a lymphocyte-rich punctate with oncocytic cells should therefore also be categorized as "cytologically negative" (thyroid findings category II). In contrast, punctates containing only oncocytic cells should be classified as category III.

Cases with suspected follicular variant of papillary carcinoma should be assigned to thyroid findings category IV (suspected malignancy); by using appropriate molecular markers (BRAF V600E, RET fusions, NTRK fusions), it may be possible to confirm malignancy in some of these cases, whereby these cases should then be assigned to thyroid findings category V.

In the case of "thyroid findings category III - follicular neoplasia", surgery is recommended for histological assessment of dignity. In individual cases - depending on the individual situation (comorbidity, risk factors, age, rather negative attitude towards surgery) - other criteria can be used to sufficiently reduce the risk of malignancy (see Chapter 3).

Thyroid findings category IV - suspected malignancy

A maximum of 5 % of all FNAC correspond to findings category IV. This group of findings includes cell images that do not allow classification as benign, but are not sufficient for a diagnosis of "certainly malignant"; the cells may originate from a papillary, medullary, poorly differentiated, or anaplastic carcinoma, a malignant lymphoma or a metastasis, but also from benign lesions that are accompanied by cytological abnormalities. Papillary carcinoma is suspected in at least 70 - 80% of findings in this category. With the introduction of the NIFTP, the definitive cytologic diagnosis (findings category V) of a PTC is now only possible in individual cases (clear papillae, psammoma bodies), as invasion and/or clear papillae are now required for the histologic diagnosis of a PTC [172]. According to the new WHO classification (2022), a proportion of < 1 % of clear papillae is tolerated for the diagnosis of a NIFTP; this makes the correct classification of clear papillae with regard to their dignity more difficult in the context of cytological findings. Inflammatory changes in the thyroid gland can also cause reactive nuclear changes that are extremely difficult to distinguish from those of papillary carcinoma or NIFTP. With the help of molecular pathological markers (BRAF V600E, RET fusions, NTRK fusions), some cases can be assigned to finding category V (cytologically malignant) [299]; a negative molecular pathological result cannot eliminate a well-founded cytological suspicion of malignancy.

Thyroid finding category IV is an indication for surgery with subsequent histological assessment of dignity. The histological examination of cases assigned to this category of findings should reveal a malignancy in at least 45 - 60% of cases.

Thyroid findings category V - cytologically malignant

A maximum of 2% of all FNAC correspond to findings category V. Findings corresponding to this category must either show cytological changes that indicate a carcinoma (see below) or in which a carcinoma can be confirmed by appropriate additional examinations (immunohistochemistry, molecular pathology).

The establishment of the NIFTP has significantly reduced the number of PTCs that can be clearly diagnosed on the basis of cytology; in some of the cases that can be primarily categorized as "suspected PTC" by cytology, a clear diagnosis of PTC can be achieved by detecting certain genetic alterations (BRAF V600E point mutations, RET/PTC fusions, NTRK fusions) [299]. Punctates from an MTC can regularly be identified on the basis of typical cytological criteria; in cases of doubt, immunocytological detection of calcitonin can confirm an MTC. Punctates from ATC show highly atypical tumor cells and often also abundant segment-nucleated granulocytes from necrotic tumor areas. The cytological diagnosis of a poorly differentiated carcinoma (PDTC) and also the new entity of a differentiated high-grade thyroid carcinoma (Dv HGTC, WHO 2022) is not possible in many cases; in particular, the "convoluted nuclei" detectable in part of the PDTC cannot be clearly distinguished from nuclear changes of the papillary carcinoma, which means that the vast majority of PDTC can only be correctly classified histologically. The clear cytological diagnosis of a low-malignant non-Hodgkin's lymphoma is hardly possible. Highly malignant non-Hodgkin's lymphomas are regularly confused with (poorly differentiated or undifferentiated) carcinomas; corresponding lymphocyte markers can be helpful immunocytochemically. Angiosarcomas show a typical cell picture and immunocytochemically corresponding vascular markers (CD31, factor VIII, ERG transcription factor).

The presence of malignant cells should also suggest the differential diagnosis of metastases in the thyroid gland if these cannot be clearly assigned to a primary malignant thyroid tumor (if necessary with the help of immunocytochemistry). In this context, attention is drawn to the importance of the clinical indication of known extrathyroidal malignancies when submitting FNA material (see Chapter 3.2.4).

Ideally, all punctates classified cytologically as "certainly malignant" correspond to malignancies. In practice, however, 1 - 3% false-positive findings are to be expected.

4.2.5 Molecular pathological examinations of the thyroid fine needle punctate

4.10	Consensus-based Recommendation	2025
EK	A general recommendation for molecular pathological analysis of the material from the thyroid fine needle biopsy cannot be made. The following 3 diagnostic markers are currently available for the molecular pathological analysis of the thyroid fine needle punctate - which is not yet a standard procedure in Germany - for the diagnosis of a PTC: BRAF V600E mutation, RET or NTRK fusion. The absence of genetic alterations does not prove benignity.	
	Strong Consensus	

- The sensible use of molecular pathological analyses of material obtained by FNA must be seen in the context of the position of FNA in the diagnostic cascade for the clarification of thyroid nodules. A small number of diagnostic markers can confirm the diagnosis of a PTC (see below); the majority of the genetic alterations examined can currently only be associated with a certain probability of malignancy [299].
- Molecular pathological analyses are also subject to special limitations that arise both from the processing of the material obtained using FNAC, which is only available in limited quantities, and from the genetic alterations that can currently be meaningfully examined in thyroid neoplasia.
- Diagnostic markers are genetic alterations that can be used to make a definitive diagnosis. At present, PTC can only be diagnosed by detecting a BRAF V600E mutation or RET or NTRK fusion [299]. These mutations are only diagnostic for PTC in combination with the typical cytological features, as all three biomarkers also occur in neoplasms of other organs with varying frequency and in poorly differentiated thyroid carcinomas.
- A number of other genetic alterations (e.g. point mutations, gene fusions), which can be detected in both benign and malignant thyroid tumors, are generally found more frequently in malignancies than in benign tumors; as a result, these alterations can be assigned a (high) positive predictive value (PPV) with regard to the probability of malignancy [299], but a definitive diagnosis of malignancy cannot be made in individual cases. However, the detection of these alterations proves the presence of a neoplasia (vs. hyperplastic nodules); it can therefore also support the recommendation for surgery (so-called "rule in").
- A lack of evidence of genetic alterations from FNA material, from which sufficient DNA and/or RNA can be obtained for molecular pathological analysis, is by no means conclusive evidence of a benign lesion. If the indication is correct (only puncture of "nodules" with an abnormal clinic or paraclinic), it does not appear to be indicated at the present time to withdraw the recommendation for surgery if there is no evidence of genetic alteration (so-called "rule out").
- Molecular pathological examinations of cytological material can be performed for DNA and RNA analyses (in particular for the detection of point mutations; primarily for the detection/exclusion of a BRAF V600E mutation) on cells scraped from slides, an additional puncture, from the puncture cannula or from the supernatant of thin-layer cytology.

4.11	Consensus-based Recommendation	2025
EK	If anaplastic thyroid carcinoma or lymphoma is suspected, a histological confirmation shall be carried out instead of a fine needle biopsy - e.g. by means of a punch biopsy.	
	Strong Consensus	

For the detection of anaplastic thyroid carcinoma, lymphoma or non-organ metastases, punch biopsy is clearly superior to FNA [216]. In contrast to FNA, in the case of a representative punch biopsy, histomorphological and detailed immunohistochemical findings can be obtained to confirm the diagnosis.

Even if severe regressive changes including calcifications are present in the nodes, punch biopsy is reported to be superior to FNA [213], [214].

In some punch biopsy specimens of follicular neoplasia, vascular invasions can be detected, thus confirming the diagnosis of follicular carcinoma. This is generally not possible cytologically. Park et al. report a significant superiority of punch biopsy over cytology for the diagnosis of follicular carcinoma [215].

4.3 Intraoperative frozen section

4.3.1 Definition

With intraoperative frozen sections, the removed organ, lymph nodes or biopsies are handed over to pathology unfixed by the surgeon while the operation is still in progress. The tissue is examined macroscopically in a rapid procedure and processed in a frozen state as an example - or completely in the case of small samples. The HE (hematoxylin-eosin) stained specimens obtained in this way then enable rapid intraoperative histological conclusions to be drawn in many cases.

4.3.2 General indications

4.12	Consensus-based Recommendation	2025
EK	If a malignant thyroid nodule is suspected preoperatively, an intraoperative frozen section shall be performed to clarify the dignity, except in the presence of category V findings (5-stage diagnostic system: corresponding to malignancy) from a previous FNA.	
	Strong Consensus	

- The aim of intraoperative frozen sectioning is to determine the dignity of a specimen or the histological type of a clinically conspicuous focal finding intraoperatively in order to help perform the surgical intervention appropriate to the pathological findings in good time.
- Single-stage surgery has a lower risk of complications with regard to recurrent paresis and hypoparathyroidism. Another reason for aiming for single-stage surgery may be elderly or otherwise impaired patients with an increased risk of anesthesia. This means that frozen sectioning should be used if a preoperative dignity assessment has already taken place using clinical findings, sonography, scintigraphy and/or fine needle aspiration. Depending on the findings, the probability of malignancy, the likelihood of a change in the intraoperative procedure and the histopathological significance, frozen section examination should be used. The extent of the surgical procedure can be extended or surgical overtreatment can be avoided [300], [258], [301].

- If the intended single-stage procedure is not possible, a standardized concerted approach should be used by both surgery and pathology. As a rule, this should ensure a final histological diagnosis within 48 hours of receipt of the specimen at the latest, in order to enable any necessary completion surgery within 72 hours, as otherwise the risk of complications from the two-stage surgical procedure increases significantly [258], [301]
- Intraoperative frozen sectioning of lymph nodes can also be used to help surgeons plan the extent of lymph node resection in curative surgery, particularly for papillary thyroid carcinoma (PTC) and medullary thyroid carcinoma (MTC), and if necessary to avoid lateral lymph node resection in order to avoid a higher risk of side effects for patients.
- In principle, intraoperative frozen sectioning of the thyroid gland should always be considered clinically if a defined suspicious lesion of the thyroid gland is present, a histological finding requiring clarification (follicular neoplasia, suspected non-follicular malignancy) has been obtained preoperatively, a suspicious mass has been found on imaging without cytological clarification of the findings or suspicious changes (including lymph nodes) become apparent during the surgery) that were not known preoperatively or were assessed as benign.
- Intraoperative frozen sectioning requires an appropriate level of pathological experience and should therefore only be used in centers with a high frequency (see chapter on Chapter 5.7.1) of thyroid operations. The native specimens are lamellated in the pathology department and only the macroscopically conspicuous areas are processed further. The examination of thyroid tissue without a macroscopically definable lesion is not necessary - as is the examination of inconspicuous colloid nodules of a goiter colloides nodosa. Unnecessary frozen sections do not contribute to an intraoperatively relevant gain in knowledge, but in the paraffin histology of this tissue they can certainly be responsible for a more difficult final diagnosis due to their different morphology caused by freezing (e.g. the nuclear changes in PTC). For this reason, it is also recommended that conspicuous lesions are only partially processed in the intraoperative frozen section and that other complementary parts are fixed directly in formalin for the final diagnosis. This also applies in particular to tiny lesions (0.1 to 0.2 cm in size), which should not primarily be processed in the intraoperative frozen section [302], [301].
- For the use of intraoperative frozen section in the treatment of medullary thyroid carcinoma (MTC), please also refer to the corresponding subchapter of this guideline.
- In contrast to the procedure in other countries (particularly in the USA/Canada), the use of intraoperative frozen section in iodine-deficient regions such as German-speaking countries must be assessed differently than, for example, in the ATA guidelines due to the more frequent nodular goiters and the associated more difficult preoperative diagnosis. For example, intraoperative frozen sectioning, which is part of the standard repertoire of thyroid surgery in the goiter-endemic areas of Central Europe, is sometimes vehemently rejected in Anglo-Saxon countries [303], [304], [305], [306], [307], [308], [309], [310], [311], [312], [313], [314], [302], [315], [301], [316], [317], [318], [319].

4.13	Consensus-based Recommendation	2025
EK	In the case of preoperatively tumor-suspected lymph nodes in the neck area or in the case of findings suspicious of tumor recurrence, an intraoperative frozen section should be performed to clarify the dignity if this is necessary to plan the extent of the resection.	
	Strong Consensus	

- In clinically conspicuous lymph nodes, the intraoperative frozen section can confirm a malignancy-successful finding if atypical epithelial infiltrates are detected. The type diagnosis of the tumor is often not possible with certainty due to the limited histomorphological significance of the intraoperative frozen section. If follicular thyroid tissue is detected, a further challenge may be the classification of malignant findings in terms of lymph node metastases of an FTC or the follicular variant of the PTC in contrast to ectopic thyroid tissue.
- If a recurrence of a previously characterized thyroid carcinoma is suspected, the pathologist can correlate these with the previous findings in the intraoperative frozen section if atypical infiltrates are detected and, if necessary, confirm a recurrence.
- In principle, the biopsy in the intraoperative frozen section represents a particular challenge for the evaluating pathological institution. Many criteria for the classification of entity and dignity can only be determined histomorphologically in the primary formalin-fixed resectate. Criteria such as vascular herniation, tumor or organ capsule perforation, stromal dysplasia and core criteria can occasionally be identified in the biopsy as part of the intraoperative frozen section, but the sensitivity in this respect is significantly reduced. Nevertheless, the biopsy in the intraoperative frozen section can be helpful for specific questions (e.g. suspected anaplastic thyroid carcinoma versus lymphoma or metastasis) [320], [321], [322], [301].

4.14	Consensus-based Recommendation	2025
EK	If a scintigraphically hyperfunctional (autonomous) node is present, an intraoperative frozen section shall not be performed.	
	Strong Consensus	

The presence of a scintigraphically hyperfunctional ("hot") nodule - which accounts for approx. 20 % of all thyroid nodules in Germany [323] and usually corresponds to a benign finding - is not usually an indication for intraoperative frozen section. The signs of endocrine activation of the cells of the adenoma that are frequently present in these cases can lead to misinterpretations in the intraoperative frozen section. This applies in particular if the pathology department does not have this clinical information at the time of the examination.

4.3.3 FNAC-based recommendations for intraoperative frozen section

4.15	Consensus-based Recommendation	2025
EK	The intraoperative frozen section should be performed to clarify the dignity in the presence of FNAC for findings category I (above-mentioned German 5-stage diagnostic system).	
	Strong Consensus	

If the FNAC (even if performed repeatedly) reveals diagnostically inconclusive findings group I, the intraoperative frozen section is helpful in many cases for clinically suspicious nodules in order to determine the indication for an extension of the surgical procedure.

4.16	Consensus-based Recommendation	2025
EK	An intraoperative frozen section to clarify the dignity in the presence of FNAC in findings category II (above-mentioned German 5-stage diagnostic system) can be considered if clinically indicated and the imaging is correspondingly abnormal.	
	Strong Consensus	

If there is an indication for surgical treatment despite an FNAC findings group II, an intraoperative frozen section can be considered if the imaging is conspicuous.

4.17	Consensus-based Recommendation	2025
EK	The intraoperative frozen section to clarify the dignity in the presence of FNAC should be performed with cytological findings category III (above-mentioned German 5-stage diagnostic system) - if this option is available.	
	Strong Consensus	

The indication for intraoperative frozen section in the context of follicular lesions reliably pre-diagnosed by FNA (findings category III of the German 5-stage diagnostic system) is also the subject of controversial international debate. However, if intraoperative frozen section is clearly indicated in the hands of an experienced surgical pathology team, many patients can benefit from the additional information for planning the extent of the surgical procedure [324], [316], [317], [318], [319].

4.18	Consensus-based Recommendation	2025
EK	Intraoperative frozen sectioning should not be performed to clarify the dignity in the presence of FNAC for finding categories IV and V (above-mentioned German 5-stage diagnostic system).	
	Consensus	

- In the presence of FNAC findings of finding categories IV and V (German 5-stage findings system), it is not advisable to perform an intraoperative frozen section of the primary tumor due to the already existing suspicion of malignancy. An indication for an intraoperative frozen section that is nevertheless indicated from a clinical point of view should be discussed closely with the pathology department performing the procedure.
- With the introduction of the group of non-invasive follicular tumors with papillary nuclear features (NIFTP), the role of FNAC in the reliable diagnosis of papillary thyroid carcinomas (PTC) is severely limited. Whereas previously a PTC could be clearly diagnosed both cytologically and histologically on the basis of the characteristic nuclear features, the introduction of NIFTP means that further criteria - only detectable histologically - are necessary (invasion and/or clear papillae). Here too, the method of intraoperative frozen section can in many cases provide findings that offer certainty for further intraoperative planning.

4.4 Histopathological workup including molecular pathological diagnostics

4.4.1 Histopathological workup

4.4.1.1 Introduction

Pathological-anatomical findings form the decisive basis for thyroid carcinomas to confirm the tumor diagnosis, histological typing and determination of the tumor stage on surgical specimens.

The anatomical-pathological assessment is carried out to confirm the following parameters:

- Determination of dignity and definition of the tumor entity
- Typing -> histological tumor type according to the current WHO classification
- Pathological staging according to the current TNM classification -> local tumor extension on the surgical specimen
- R classification -> Assessment of the resection margins on the surgical specimen
- Introduction and collection of diagnostic, prognostic and predictive molecular pathological biomarkers

In addition, biopsies or resectates are analyzed in histological frozen sections for specific purposes.

Further information on diagnostic, prognostic and predictive molecular pathological biomarkers can be obtained from the paraffin material following the histomorphological and immunohistochemical examinations using molecular pathological diagnostics on DNA or RNA.

4.4.1.2 Clinical information

4.19	Consensus-based Recommendation	2025
EK	The pathologist shall be provided with information relevant to the findings when surgical specimens are sent in.	
	Strong Consensus	

The adequate provision of clinical information when submitting specimens is a basic prerequisite for reliable pathological diagnosis. In case of doubt, the lack of individual details can lead the pathologist into diagnostic uncertainty. For example, the lack of information on a scintigraphically "hot" nodule can lead to a false diagnosis of malignancy, as the endocrine activation of the tissue can lead to a misinterpretation. Furthermore, the clinical information listed above helps to optimize the macroscopic work-up and the histomorphological interpretation. The correct indication of the TNM classification is not possible without clinical information on a clinically known tumor extension beyond the specimen (R2 situation) or information on the location of the removed lymph nodes (pN1a vs. pN1b).

4.4.1.3 Diagnostics

4.20	Consensus-based Recommendation	2025
EK	The following procedure shall be followed for macroscopic processing of surgical specimens: • Determine the weight of the organ/part of the organ • Dimensions in cm of the entire specimen and - if applicable - of the individual thyroid lobes and isthmus as well as the length and diameter of the pyramidal lobe • Dimensions of the focal finding(s) in cm, at least indicating the maximum diameter • Color coding of the organ capsule or resection margins according to the anatomical orientation (e.g. ventral surface, dorsal surface, resection surface of the isthmus) or traceable embedding in appropriately documented capsules • Embedding of tumor parts (complete embedding of the tumor if necessary, at least 2 paraffin blocks per centimeter of the maximum tumor diameter) with reference to the resection margins or separate embedding of the resection margins close to the tumor as well as exemplary embedding of parts of the non-neoplastic tissue. • Complete macroscopic lamination of the thyroid lobes in 0.3 to 0.5 cm thick lamellae along the cranio-caudal axis.	
	Strong Consensus	

- The size dimensions shall generally be given in cm in order to avoid a transcription error, which can easily occur due to the change in units of measurement.
- Complete embedding of macroscopically conspicuous lesions in order to avoid overlooking capsular perforations, vascular invasions or even dedifferentiated parts. This can also be done retrospectively if necessary.
- If necessary, in the case of conspicuous histological findings, a complete re-embedding of the focal finding shall be performed.

4.21	Consensus-based Recommendation	2025
EK	The surgical specimen should be sent to the pathologist without prior incisions or tissue removal in order not to impair the diagnosis of the tumor type, determination of the pT category and assessment of the resection margin or the organ capsule/tumor capsule.	
	Strong Consensus	

A complete assessment of the intact surgical specimen is a basic prerequisite for a definitive and correct opinion regarding TNM classification and R status by the pathologist. Postoperative incisions or specimen removal change the morphology of the specimen. This applies in particular to specimens that are subsequently placed in

formalin. The different fixation of the various tissues (capsule, soft tissue, tumor tissue) leads to distortion of the specimen, which can make macroscopic assessment very difficult. Furthermore, the dimensions of the tumor can be altered during postoperative sampling, especially in the case of smaller tumors, so that a TNM classification may subsequently be incorrect due to the reduced tumor diameter. In the case of encapsulated tumors, which require special care on the part of the pathologist with regard to the assessment of the capsule situation (capsule breakthrough, vascular invasion), a definitive exclusion of these diagnostically important biomarkers is no longer possible and can only be carried out on the remaining intact capsule parts as an example.

In the context of studies, biobank observations and for extensive molecular pathological analysis, it may be necessary to obtain fresh material from the tumor. In such cases, either the pathologist should take the specimen from the native material, for example in the frozen section laboratory, or, if this is not possible, the surgeon should do so in close consultation with the pathologist and document the manipulations performed on the specimen.

4.22	**Consensus-based Recommendation**	**2025**
EK	The fat tissue removed as part of the lymphadenectomy shall be completely examined macroscopically for lymph nodes. The central compartments shall be completely embedded. The lateral compartments should be completely embedded as part of the lymphadenectomy.	
	Strong Consensus	

4.23	**Consensus-based Recommendation**	**2025**
EK	The pathological report of the lymph nodes shall contain the number and localization of the dissected lymph nodes, the number of affected lymph nodes, and the maximum metastasis size in cm per region.	
	Strong Consensus	

In most chapters of the TNM classification, a minimum number of lymph nodes is now required in the pathology report. The rationale for this is the proven significance of a sufficient number of lymph nodes for a prognostically relevant pN0 classification in many organ systems. At the time the guideline was drawn up, no reliable evidence could be found for a minimum number of lymph nodes in thyroid cancer. With the recommended complete processing of the submitted material of the central and lateral lymph node compartment, there is naturally no need to specify a minimum number of lymph nodes to be dissected.

4.24	Consensus-based Recommendation	2025
EK	The following information shall be provided in the pathological findings of surgical specimens: • Staging according to the current TNM classification of the UICC. • Classification of the histological types of thyroid carcinoma according to the current WHO classification, if applicable histological subtypes - insofar as they are described in the current WHO classification. • Capsular growth of lymph node metastases.	
	Strong Consensus	

The explanatory text for this recommendation can largely already be found in Chapter 4.1 and Chapter 4.2.
Capsular metastasis to lymph nodes is described as a significant prognostic marker [277], [278], [279], and this should be indicated in the TNM classification as extracapsular extension (ece+) in the pN category.

4.25	Consensus-based Recommendation	2025
EK	The histomorphologic evaluation of surgical specimens should be completed within 48 to 72 hours.	
	Strong Consensus	

Professional histological processing of the surgical specimen must be arranged without exception. Particularly in the case of indications of malignancy, a diagnosis should be made within 48 to 72 hours in order to be able to perform any necessary completion surgery as early as possible.

It should be noted that it is not always possible for the pathologist to clarify the dignity promptly. Particularly in cases where further immunohistochemical/molecular pathological examination or staged work-up is necessary, any further surgical treatment that may be indicated must be performed at a later date after the surgical site has healed. Even in difficult cases that require assessment by a reference pathologist, the time window can usually not be adhered to. In any case, however, the precise and correct diagnosis, which is essential for further treatment and prognosis, takes precedence over the need for prompt classification of the findings.

If it is necessary to exceed the above-mentioned time frame, this should be communicated to the sending clinic, if necessary by means of a preliminary report.

4.4.2 Molecular pathological biomarkers

4.4.2.1 Introduction

The examination of molecular pathological biomarkers on formalin-fixed and paraffin-embedded material is a standard examination for many malignant tumors. In most cases, mutations such as point mutations, deletions, duplications, insertions and gene rearrangements (translocations) are examined in specialized pathologies using single gene analyses or, increasingly, parallel sequencing (next generation sequencing, NGS).

Mutations that offer tumor cells an economic growth advantage (so-called driver mutations) and are therefore generally detectable in all tumor cells are of particular clinical interest.
Molecular pathological examinations have also long been standard for thyroid carcinomas and are becoming increasingly important.

Other molecular biomarkers such as examinations of the methylome or RNA expression (transcriptome) including analyses of non-protein-coding RNA (e.g. micro-RNA), proteome analyses and complex composite molecular biomarkers for homologous recombination deficiency (HRD) or tumor mutation burden (TMB) and cytogenetics are available in principle, but are not recommended outside of corresponding studies due to the high technical challenges and insufficient evidence at the time of guideline development in the clinical context.

The molecular pathological biomarkers can basically be divided into three different categories: (1) diagnostic, (2) predictive and (3) prognostic, whereby the individual mutations in different categories can be informative.

4.26	**Consensus-based Recommendation**	**2025**
EK	If a molecular analysis with relevance for approved molecular therapy options is required, this shall be carried out promptly. This also applies to BRAF for ATC.	
	Strong Consensus	

4.27	**Consensus-based Recommendation**	**2025**
EK	The determination of prognostic molecular biological markers can be considered. This field is highly dynamic, so that no binding recommendation for a specific marker can be given.	
	Strong Consensus	

4.28	Consensus-based Recommendation	2025
EK	In advanced thyroid carcinomas with no other approved or established treatment option, an extended molecular pathological examination using parallel sequencing to detect molecular aberrations can be performed to consider an individualized treatment attempt. The results of the molecular pathological examination should be discussed in a specialized, interdisciplinary molecular tumor board.	
	Strong Consensus	

4.4.2.2 Diagnostic molecular pathological biomarkers

Among thyroid carcinomas, diagnostic mutations are only found in the group of papillary thyroid carcinomas (PTC). Here, the detection of a BRAF V600E mutation, an NTRK fusion or a RET fusion - exclusively in combination with corresponding cytomorphologic or histomorphologic criteria and excluding poorly differentiated thyroid carcinomas and metastases - is considered to be conclusive for the presence of a PTC. Molecular pathological analysis can therefore be used as a diagnostic aid in the differential diagnosis of NIFTP or follicular thyroid carcinoma in differentiation from a follicular variant of PTC. This applies in particular when only limited biopsy material or FNA material is available without the possibility of a detailed histomorphological diagnosis.

4.4.2.3 Predictive biomarkers

Molecularly targeted therapy options are now also available for the treatment of thyroid cancer in the case of advanced tumors and the detection of certain mutations. In Europe, at the time the guidelines were drawn up, targeted therapy options were available for the detection of an activating RET fusion in thyroid carcinomas arising from follicular epithelial cells and in the case of an RET point mutation in medullary thyroid carcinoma (MTC).

Another therapy option approved in Europe is the detection of an activating NTRK fusion. This approval is independent of the tumor type and also applies to carcinomas outside the thyroid gland (so-called tumor diagnostic approval).

Other approvals outside Europe, such as combined BRAF/MEK inhibitor therapy for anaplastic thyroid carcinoma (ATC) and a tumor-agnostic immuno-oncological therapy option with pembrolizumab in the case of indirect evidence of a deficiency of the mismatch repair enzymes (dMMR) or direct evidence of microsatellite instability (MSI) or a high tumor mutation load (TMB-high), can be optionally tested in individual treatment trials.

4.4.2.4 Prognostic biomarkers

At present, there are no data on prognostically relevant molecular biomarkers that would lead to a change in the therapeutic approach. Nevertheless, knowledge of prognostic biomarkers can lead to patients being kept under close clinical control.

Some of the molecular biomarkers most frequently mentioned in the context of thyroid cancer are listed below.

Inactivating mutations in the TP53 gene are among the most common mutations in the context of advanced tumor diseases. These are not classic driver mutations, but mutations that offer an additional growth advantage for tumor cells, particularly in the context of increasing genomic instability. For this reason, inactivating TP53 mutations can often be detected in combination with classic driver mutations. In various tumor entities, inactivating TP53 mutations and inactivating mutations in other tumor suppressor genes are considered to be prognostically unfavorable and, if detected in differentiated thyroid carcinomas, can be a sign of increasing dedifferentiation.

The mutations C228T and C250T in the TERT promoter lead to immortalization of the tumor cells in differentiated thyroid carcinomas due to telomere elongation of the chromosome ends. The physiological shortening of telomeres and the associated limitations of possible cell divisions until cell death are thus overridden. It has been shown that tumors with a combined BRAF V600E driver mutation in particular have a poorer prognosis. In addition, the detection of a TERT promoter mutation often appears to indicate primary resistance of the tumor cells to radioiodine therapy. Gene amplification, increased mRNA expression and hypermethylation of TERT also appear to have a similar prognostic significance.

Depending on the study, BRAF V600E mutations can be detected in approx. 40 to 70 % of PTC. In some histomorphological subtypes, such as the large cell subtype (tall cell PTC), this mutation is detected much more frequently. This mutation leads to activation of the RAS-RAF-MAPK signal transduction pathway and to increased proliferation, tumor angiogenesis and tumor invasion. A prognostically unfavorable course of the disease with the sole detection of this mutation is controversially discussed and cannot be deduced at present. However, the BRAF V600E mutation has a negative prognostic value if a mutation of the TERT promoter and tumor suppressor genes (e.g. TP53) is detected in parallel (e.g. [253]).

4.4.2.5 Molecular test algorithm

At the present time, the authors believe that initial testing for BRAF V600E is recommended for diagnostic and prognostic purposes (possibly in combination with other mutation detections, see explanations on the prognostic significance of the BRAF V600E mutation above) when a diagnosis of PTC is suspected. This can be achieved by a simple and inexpensive single-gene analysis of paraffin material or cytological material.

In the case of MTC, a genetic tumor syndrome may be present. Genetic counseling and diagnostics should be sought. Approximately 25 % of patients with medullary thyroid carcinoma have an activating pathogenic germline variant in the RET gene. If the RET mutation status is negative, the RET point mutation can be analyzed on the paraffin material of the tumor to clarify a therapy option with a RET inhibitor.

In advanced thyroid carcinomas, further mutation analysis of the predictive biomarkers is recommended. Parallel sequencing of tumor material is the best option to obtain further possible individual treatment options and to test prognostic biomarkers. Here, DNA-based parallel sequencing using hybrid capture technology and/or RNA-based parallel sequencing for sensitive fusion diagnostics should be sought.

4.5 Quality indicators of the pathology report

4.29	Consensus-based Recommendation	2025
EK	The pathology report should follow a structured scheme in which the aspects mentioned below are included.	
	Strong Consensus	

In recent decades, pathology reports have evolved from a rather informal, narrative, individualized form to documents with structured, synoptic sections due to various influences such as certifications, guidelines and advances in data processing. This makes it possible to provide important information not only for stage-oriented therapy planning, but also for personalized therapy. The implementation of evidence-based diagnostic, prognostic and predictive information in the pathology report is essential for a smooth transfer of knowledge to the medical institutions involved in thyroid tumor treatment.

Structured findings

The increasingly complex information that is required for the subsequent treatment of thyroid tumor patients has been proven to lead to the fact that purely narrative findings significantly more often do not contain important information, which subsequently leads to inquiries on the part of the treating physicians and thus to additional work and an overall poorer treatment success for various tumor entities [325], [326], [327], [328], [329], [330], [331]. This has also been shown for patients with thyroid tumors [332], [333], [334]. In addition to the classic narrative elements for macroscopy, microscopy, diagnosis and commentary, the pathology report should therefore also contain synoptic sections, e.g. in tabular form (tumor classification, biomarker analyses), in order to routinely display important information. Today, this can be implemented in many laboratory information systems (LIS) and is required by the relevant regulations for accredited institutes. In addition, a structured setup facilitates automated reporting to the cancer registry and increases the clarity of the findings, which is important, for example, when presenting in interdisciplinary tumor boards. Examples of purely synoptic approaches to the documentation of thyroid tumors are freely available as templates on the Internet from the College of American Pathologists (CAP) and the International Collaboration on Cancer Reporting (ICCR)(www.cap.org,www.iccr-cancer.org).

Minimum requirements

In the context of pathological diagnostics, the submitted material can be roughly divided into cytological specimens (e.g. FNAC), biopsies (e.g. TrueCut biopsy) and surgical specimens. What they all have in common is the basic structure of a pathology report with information about the sender, patient, clinical details, type of material, macroscopy, microscopy, diagnosis and, if applicable, comments. Depending on the type of material and diagnosis, further information such as specific classifications or results of additional examinations can be included. Mandatory and optional content is based in particular on the information from the current classification of the World Health Organization (WHO) and the TNM classification of the Union for International Cancer Control (UICC).

Surgical specimens

The histopathological processing of thyroid carcinomas naturally enables the most comprehensive information possible compared to biopsies and cytological aspirates. Postoperative risk stratification requires this important information to assess whether, for example, surgical completion, radioiodine therapy or other measures are necessary. Accordingly, the information required for a pathology report is extensive and is listed below based on the current literature [24], [335], [336], [337], [338].

- Localization information such as lateral, isthmus or e.g. retrosternal, multifocal
- Histological tumor type and, if applicable, subtype according to WHO
    - Specific diagnostic criteria depending on the tumor type
- Maximum tumor diameter
- Local tumor spread, taking into account parameters important for T classification (e.g. extent of extrathyroidal spread)
- Number of lymph node metastases, indicating the number of lymph nodes examined (desirable: indication of whether lymph node capsule has been exceeded) and the compartments of lymph node origin (for correct indication of N-stage).
- Complete TNM classification including information on peritumoral infiltration of veins (V), lymphatic vessels (L) and perineural sheaths (Pn)
- Prognostic stage according to UICC
- R classification if possible (optional metric indication of the distance to the nearest resection margin)
- Secondary findings (e.g. stromal dysplasia in MTC).

Example of synoptic text module for integration into the findings report:
Tumor classification:
Localization: ICD-O-C 73.9
Typing: ICD-O-M-8260/3
Grading: not planned
Staging (TNM 8th Edition): pT2 pN0 (0/45) M0, L0 V0 Pn0, UICC stage I
R classification: R0 (removal locally in healthy tissue)
Diagnosis: ICD-10-C 73
Biomarker status:
NTRK status (PCR): negative
BRAF status (PCR): p.V600E (mutated)

In the context of the histomorphological findings, the statement of the pathological report naturally focuses on the tumor diagnosis in the sense of indicating the histological tumor type and, if applicable, subtype according to the current WHO classification. If, based on the structures included in the report, further information is available, e.g. on parameters such as infiltration of veins, lymphatic vessels or perineural sheaths and possible extrathyroidal spread, this should also be reported and commented on.

FNAC

In addition to the aforementioned minimum requirements of a pathological report, the classification of the findings within the framework of a currently valid, standardized cytological findings system (e.g. German 5-stage system, Bethesda system) in accordance with the specific publications is required for the reporting of cytological material from fine needle aspiration material [339], [290].

5 Initial therapy of differentiated thyroid carcinoma

5.1 Resection of the thyroid gland

The terminology of thyroid resection forms applies regardless of dignity for both benign and malignant thyroid diseases [340]. They are defined here for all entities named in this guideline. For most malignant thyroid findings, complete thyroidectomy is required for curative treatment and/or as a prerequisite for radioiodine therapy.

- Enucleation: Excision of a nodule along its capsule.
- Nodal excision: removal of a nodule with a seam of normal thyroid tissue.
- Isthmus resection: Resection of the pretracheal thyroid tissue.
- Subtotal thyroid gland resection: partial removal of a thyroid lobe with a parenchymal remnant of 1 to 4 ml.
- Near-total flap resection: partial removal of a thyroid lobe with a parenchymal remnant of less than 1 ml.
- Lobectomy/flap resection: complete removal of a thyroid lobe including the thyroid isthmus and lobus pyramidalis.
- Surgery according to Riedel-Hartley-Dunhill: Lobectomy with contralateral subtotal resection and a parenchymal remnant at the upper pole or dorsally of 1 to 4 ml.
- Bilateral subtotal resection: partial removal of both thyroid lobes with bilateral parenchymal remnants of 1 to 4 ml each.
- Near-total thyroidectomy: The almost complete removal of the thyroid gland, leaving a unilateral or bilateral parenchymal remnant totaling less than 2 ml.
- Thyroidectomy: The complete removal of both thyroid lobes including the isthmus and the pyramidal lobe without leaving any parenchymal remnants.

The procedures listed under 3-10 are partial or complete extracapsular procedures, the resections listed under 1+2 are intracapsular procedures in which thyroid tissue is removed while leaving most of the thyroid capsule intact. Other procedures not listed here are defined by the indication of the thyroid remnant in the surgical report.

5.2 Resection of the lymph nodes

5.2.1 Terminology of lymph node resection procedures

Various terminologies are used in the literature to describe resection procedures [341], [342]. In many cases, the extent of resection in the lymph node area is combined with that in the area of muscular, nervous and vascular structures in different ways (e.g. radical or modified-radical neck dissection). As the aforementioned resection procedures are based on the terminology and surgical technique of the procedure for squamous cell head and neck tumors, which differ considerably from thyroid carcinomas, these guidelines are based on Dralle's compartment classification (see Figure 2) with regard to the terminology of the resection procedures: Compartment resection cervicocentral (right or left), cervicolateral (right or left) and mediastinal (right or left) [343], [344]. If muscular, nervous or vascular structures are included in the resection, this should be added to the resection definition, as should the access

designation (cervical, transsternal). If no compartment resection is performed but selective removal of individual lymph nodes or groups of lymph nodes for local control with a non-curative approach, this should also be indicated (e.g. selective lymph node dissection compartment 1, 2, 3 or 4). Prophylactic compartment resection means lymph node dissection in the absence of clinical evidence of lymph node metastases, therapeutic compartment resection means lymph node dissection in the presence of clinically, imaging or biopsy proven lymph node metastases. As with other oncological procedures, the number of examined and tumor-involved lymph nodes should be specified in the pathological work-up of the compartment resection. The central and mediastinal compartments contain an average of 10 lymph nodes each (5 on each side), the lateral compartments 20 lymph nodes each (58, 62, 66). The lymph node compartments listed are shown schematically in Figure 2a–d and apply to all entities named in this guideline.

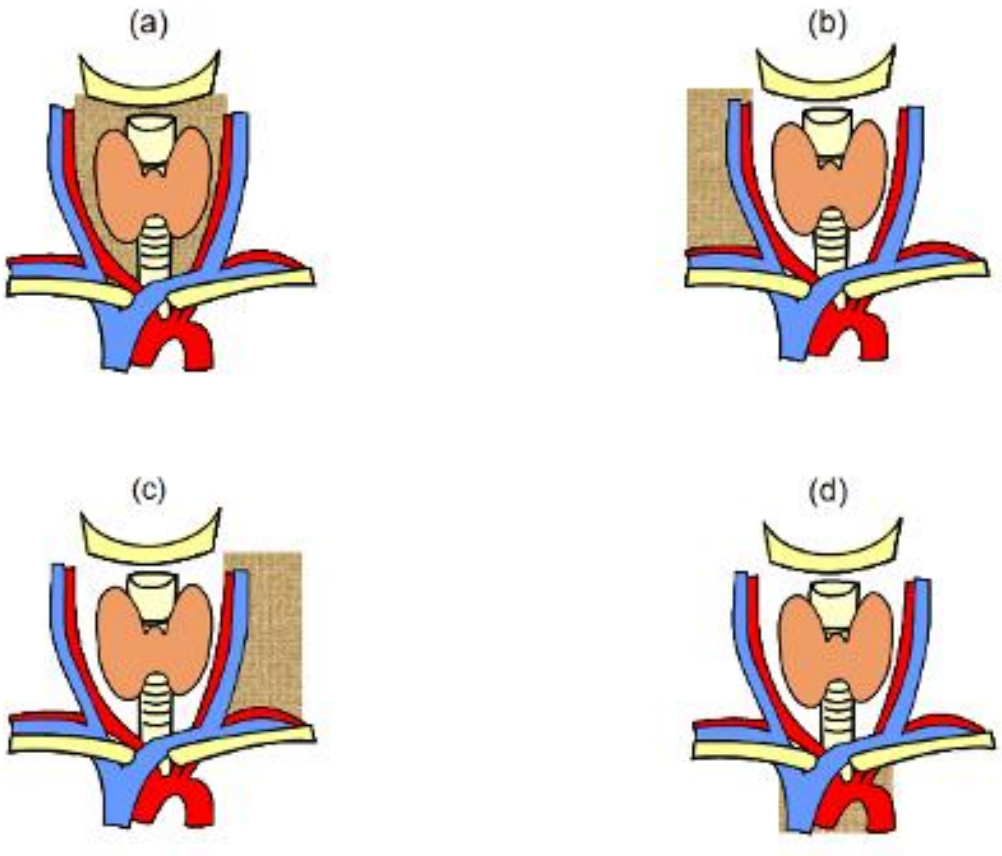


Figure 2: Compartment classification of locoregional lymph nodes in thyroid carcinoma (Dralle 2012). (a) Central (K1a, right; K1b, left), (b) right cervicolateral (K2), (c) left cervicolateral (K3), and (d) infrabrachiocephalic compartment of the upper mediastinum (K4a, right; K4b, left).
[343], [345], [341]

5.2.2 Central compartment (C1a, cervicocentral right; C1b, cervicocentral left) (Fig. 2a)

In surgical anatomical terms, the central compartment comprises the entire soft tissue space containing the lymph nodes, which is bounded laterally by the carotids and cranially by the hyoid bone. The caudal boundary is formed on the right by the brachiocephalic trunk and on the left by the V-shaped outlet of the common carotid artery from the aortic arch. The transverse V. brachiocephalica sinistra separates the cervical from the mediastinal lymph node space. The suprabrachiocephalic part of the upper mediastinum is therefore part of the cervicocentral compartment. The midline of the trachea separates the right from the left part of the central compartment without an anatomical fascial boundary comparable to the lateral boundary of the common carotid artery. Within the central compartment, the recurrent nerve divides the right and left central compartments into an antenerval (level 6) and a retronerval part (level 7). The third sub-area of the central compartment is formed by the prelaryngeal lymph nodes ("Delphi").

5.2.3 Lateral compartment (C2, cervicolateral right; C3, cervicolateral left) (Fig. 2b and c)

The lateral compartment extends on both sides of the common carotid artery laterally to the trapezius muscle, cranially to the hypoglossal nerve, and caudally to the subclavian vein. The dorsal boundary is formed by the dorsal cervical fascia. In contrast to the fascicles of the cervicobrachial nerve plexus and the accessory nerve, which pass through the lateral compartment and may therefore be at risk during lateral compartment resection, the phrenic nerve lies under the dorsal cervical fascia. The thyroid lobes and the central compartment are connected to the lateral compartment by lymphatic vessels running parallel to the thyroid veins both in front of and behind the vascular sheath [346], [347].

5.2.4 Mediastinal compartment (C4a, right; C4b, left) (Fig. 2d)

The mediastinal compartment extends seamlessly, i.e. without transverse anatomical fascial boundaries, from the V. brachiocephalica sinistra (cranial boundary) in a bidirectional direction ventrally into the anterior superior mediastinum to the thymus and the preaortic lymph nodes and dorsally to the paratracheal lymph nodes in the posterior superior mediastinum. The lateral borders on both sides are the mediastinal pleural leaves, caudally the pericardium (ventral) and the tracheal bifurcation (dorsal). Dissection of the infrabrachiocephalic mediastinum requires a transsternal approach. In the case of combined cervicocentral and mediastinal compartment resection, the entire lymph node-containing fatty tissue can be removed in an en bloc resection while preserving the vascular and nerve structures due to the lack of an anatomical barrier between the two compartments.

5.2.5 Classification of locoregional lymph nodes

Based on anatomical and clinical examinations, the locoregional lymph nodes of primary malignant thyroid tumors can be assigned to four compartments: central, ipsilateral cervicolateral, contralateral cervicolateral, and infrabrachiocephalic mediastinal [343].

Internationally, the classification of locoregional lymph nodes according to Robbins is preferred [341]. Without lateral allocation, level 1 refers to submental and

submandibular lymph nodes, level 2A, 2B to cranial jugular lymph nodes, level 3 to central jugular lymph nodes, level 4 to caudal jugular lymph nodes, level 5A, 5B to lateral jugular lymph nodes, level 6 to central lymph nodes, level 7 to central caudal lymph nodes.

5.3 PTC: Indication and extent of resection

5.1	Consensus-based Recommendation	2025
EK	If a thyroid carcinoma is clinically suspected, the case should be presented in an interdisciplinary tumor board and the procedure individually advised and recommended.	
	Consensus	

The interdisciplinary tumor board presentation serves to ensure an up-to-date, well-founded and interdisciplinary indication for the individual patient by integrating the expertise of the specialist groups involved [348], [349], [350], [351]. The aim is to develop an interdisciplinary, findings-oriented recommendation for the individual patient based on the current state of knowledge of all specialist groups involved in order to propose an optimal procedure and treatment decision.

5.3.1 Papillary thyroid microcarcinoma (PTMC) (T1a)

5.3.1.1 Observation

5.2	Consensus-based Recommendation	2025
EK	An isolated unifocal PTMC without aggressive cytological features and without risk factors can be observed if the patient > 30 years of age decides to do so as part of an informed consent process, taking into account in particular the size and age dependency of the risk of recurrence.	
	Strong Consensus	

The incidence of papillary thyroid carcinoma has risen sharply in individual countries in recent years and amounted to 4.5% of the total population in the USA in 2013 [352]. In an international comparison, however, the frequency of thyroid carcinomas in Germany is largely stable [353]. Papillary microcarcinomas (PTMC), defined as papillary carcinomas ≤1cm, account for over 80% of all incidentally detected papillary thyroid carcinomas (PTC) [354]. They are rarely diagnosed preoperatively in Germany due to the recommendation not to puncture nodules < 1cm. This recommendation is de facto equivalent to an observation strategy. This has been carried out for solitary PTMC in a normal thyroid gland by some research groups [355], [356], [357], [358].

The study by Miyauchi et al. on 1,211 patients with PTMC aimed to estimate the probability of disease progression over a lifetime, which was 60.3% for 20-29 year olds,

37.1% for 30-39 year olds, 14.5% for 40-49 year olds, 6.6% for 50-59 year olds and 3.5% for over 70 year olds over an observation period of 10 years. Tumor growth and the occurrence of lymph node metastases were seen within 10 years in 46% and 27% of 20-year-olds and in 3% and less than 1% of those over 60. None of the patients who were primarily only observed and later operated on due to progression had developed distant metastases or died from the tumor [359]. An isolated unifocal PTMC without aggressive cytological features (e.g. large cell variant, poorly differentiated variants) and without risk factors (not capsular or on the trachea, no additional nodes, no predisposition, no suspicion of metastasis, no molecular genetic risk profile) can be observed if the patient opts for this as part of an informed consent process [359].

In contrast, Oh et al. demonstrated a 100% higher risk of tumor volume doubling in patients <45 years after [360].

According to Miyauchi, low-risk patients were those who had only a solitary PTMC, no primary lymph node metastases, no infiltration of the thyroid capsule and did not directly border the trachea or the recurrent laryngeal nerve. It must be mentioned here that it is unclear how high the proportion of newly defined NIFTPs is in the patient population, as these cannot be differentiated from papillary thyroid carcinomas in fine needle aspirates.
Sugitani et al. conducted a survey in Japanese clinics, of which over 50% carried out "active observation" without surgery in low-risk patients [361]. Jeon et al. were also unable to demonstrate a negative effect on surgery delayed up to one year after diagnosis compared to patients with PTMC who were operated on immediately [362].

PTMC exhibit different biological behavior. In addition to indolent, slowly progressive forms, aggressive variants can be distinguished. This group includes multifocal PTMC and PTMC with specific genetic characteristics such as BRAF mutations or changes in genes of the stimulated cell cycle and stem cell activation [363], [364], [365], [366].

If a solitary papillary microcarcinoma is confirmed by FNAC and there are no other risk factors, an observation strategy may be an alternative to immediate surgery. However, the patient should be informed about the risk of a possibly necessary extended resection (e.g. thyroidectomy instead of lobectomy and possibly additional lymphadenectomy) if the tumor progresses and about the type, extent and duration of the necessary structured follow-up. The patient should also be informed about the established surgical therapy. The recommendation for conservative treatment should be made by an interdisciplinary tumor board, set out in writing and explained to the patient. Systematic recording of these patients and their progression in established registers is expressly encouraged.

5.3.1.2 Local ablative procedures of the PTMC

Local ablative procedures have a cosmetic advantage over surgery by avoiding a classic cervicotomy. Based on a meta-analysis of 12 studies with over 1,000 patients with PTMC, Tong et al. demonstrated that radiofrequency ablation, microwave ablation and laser ablation can effectively ablate PTMC foci locally [367]. Chen et al. came to the same conclusion, showing 13 studies with various local ablation procedures to be effective and with very few complications [368]. In long-term studies, local ablative procedures appear to have a comparable effectiveness to surgery in the treatment of PMTC, but prospective comparative studies on classic surgical procedures are lacking. A critical point to be made about the studies included in the meta-analysis is that 9 of the studies cited were from China and 3 from Korea. 9/12 studies were retrospective.

In 2 studies, including the largest with 412 patients from China, neither the age nor the sex of the patients was known. In only 76% of patients was the thyroid carcinoma no longer detectable after treatment. After MWA, bleeding occurred in 2.8% and partly persistent hoarseness in 4.4%. As no laryngoscopy was performed, the percentage of recurrent paresis may be significantly higher. In addition, the follow-up periods are not yet long enough for a conclusive evaluation of the long-term outcome.

It is essential to inform the patient about the significance of a lack of histology and possible limitations of the sonographic assessment of the course of the disease and to provide information about the established surgical treatment. The decision for local ablative therapy should be made by an interdisciplinary tumor board and ideally only in the context of a study inclusion.

5.3.1.3 Surgery of the PTMC

5.3	Consensus-based Recommendation	2025
EK	PTMC without risk factors should be treated surgically by lobectomy.	
	Strong Consensus	

5.4	Consensus-based Recommendation	2025
EK	A thyroidectomy should be performed for papillary thyroid carcinomas with a tumor diameter of 10 mm or smaller with risk factors, i.e. multifocal PTMC, histologically higher-risk subtypes of PTC, familial clustering of PTC, lymph node metastases and previous cervical radiation.	
	Strong Consensus	

With regard to long-term survival, Liu et al. were unable to identify any difference between patients whose PTMC had been treated with a thyroidectomy or with less than a thyroidectomy based on SEER data from 2004-2013 [369]. Chan et al. compared the 10-year survival rates of "low-risk PTC patients", the majority of whom are patients with PTMC, using a meta-analysis of 25 studies with 73,742 patients. According to this, patients after lobectomy showed no difference in survival compared to patients after thyroidectomy [370]. This also corresponds to the results of the study by Zhang et al. on 5,492 Korean patients with PTC, over 50% of whom had PTMC and showed no influence of the primary resection extent on survival. However, since the consensus threshold of ≤ 10 mm for the definition of PTMC reflects a biological continuum, there is a treatment corridor for borderline findings, taking individual risk factors into account. Although it is true for all PTC that the risk quo ad vitam increases with age [371] and that men have a lower probability of survival than women, with a 90% and 96% 10-year survival rate respectively [372], there is no effect of more extensive surgery on the survival of patients with PTMC.

Taking into account the fact that the PTMC threshold of 10 mm is well documented by several studies [373], but reflects a continuum in terms of tumor biology, there is a treatment corridor of alternative treatment options in individual cases of tumors of this size, especially when the diagnosis is only made postoperatively, which must be determined individually on an interdisciplinary basis, taking into account the patient's circumstances. In a study with a follow-up of 35 years, Noguchi et al. showed a recurrence-free survival rate for PTMC < 5 mm: 96.7%, 6-10 mm: 86.0%) [374].

Kim et al. used data from 8,676 patients with PTMC to compare the effect of thyroidectomy versus lobectomy on the need for a new surgery due to tumor persistence or tumor recurrence [375]. In patients with multifocal PTMC, they found a reduced recurrence rate after thyroidectomy compared to lobectomy (0/5,387 vs. 28/3,289 (0.85%)). Kwon et al. found the same in a smaller group of 688 patients [376]. However, the patients with thyroidectomy were more likely to have transient and permanent hypoparathyroidism of 13% and 2%, respectively, compared to 0%.
Wu et al. showed that 28.5% of patients with a primary diagnosis of a follicular variant of PTMC developed contralateral nodules during the course of the disease [377] and according to Sullivan et al. the vast majority of these (up to 100%) were malignant [378].

Recurrences due to contralateral PTMC foci are therefore more common in primary multifocality and a size of over 5 mm [379], [380][380] and also occur more frequently in patients with BRAF and TERT mutations [381], [382][382], [363], [366] and activation of cell cycle genes [365].

According to Joseph et al., the meta-analysis of 15 studies shows increased regional lymph node metastases and distant metastases in primary multifocality of PTMC, which can ultimately only be detected by thyroidectomy with subsequent radioiodine uptake [383]. Joseph et al. therefore advocate thyroidectomy in patients with multifocal PMTC [383].

5.3.1.4 Central lymph node dissection

5.5	Consensus-based Recommendation	2025
EK	In cN1-PTMC, bilateral central compartment resection (level VI) should be performed in conjunction with total thyroidectomy.	
	Strong Consensus	

5.6	Consensus-based Recommendation	2025
EK	Prophylactic central lymph node dissection can be performed in the presence of risk factors (e.g. multifocality, aggressive PTC variants, size (variable: from approx. 8 to 10 mm), capsular infiltration, evidence of a prognostically unfavorable mutation).	
	Strong Consensus	

Clinically inconspicuous lymph nodes show metastases in more than 20% of patients undergoing PTMC surgery with prophylactic central lymph node dissection, despite the good prognosis of the patients, so that bilateral central compartment resection (level VI) should be performed in conjunction with total thyroidectomy to ensure complete tumor removal, reduce the risk of recurrence and improve the chances of survival in cN1 PTMC. Lymph node metastases are increasingly seen in younger patients before the age of 45-55 [384], [385], [386], [387], [388], male patients [386], [387], [388], in tumors over 5 or 7 mm [389], [384], [390], [391], [384], [392], [386], [393], [387], [388], in multifocality of the PTMC [394], [390], [384], [391], [385], [380], [386], [387], [388], [395], [396], in capsular invasion [390], [393], in extrathyroidal growth (ETE) [397], [384], [391], [385], [386], [387], in lymphovascular invasion [398] and in localization of the tumor in the upper pole of the thyroid [399], [393]. In addition, PTMC with BRAF mutations and PTMC with proven Hashimoto's thyroiditis show increased central lymph node metastases [397]. Even skip metastases can occur in the upper pole of PTMC in up to 25% of cases [399]. According to Zheng et al. [395], the incidence of central lymph node metastases increases significantly with multifocality (from 26% with one focus to 29% with two foci, 48% with three foci, and 72% with 4 or more foci).

According to a comparison of over 2,000 patients by Ito et al., prophylactic central lymph node dissection of the affected side of the thyroid gland has no influence on lymph node recurrence [398]. A meta-analysis by Shan et al. [400], which was based on 11 studies and a meta-analysis by Qu et al. with 19 studies and over 8,000 patients [391] also came to the same conclusion. In contrast, Hughes et al. were able to demonstrate on the basis of 14 studies and 3 meta-analyses that thyroidectomy with prophylactic lymphadenectomy results in a reduction in the recurrence rate of PTMC from 6.8% to 4.6% compared to thyroidectomy alone, but that permanent hypoparathyroidism increases from 1.6% to 3.5% [401].

Prophylactic central lymph node dissection is therefore only recommended in the presence of risk factors (multifocality, aggressive PTC variant, size >5-7mm, capsular infiltration, BRAF positivity) and with surgical expertise.

5.3.2 Papillary thyroid carcinoma T1b to T4

5.3.2.1 Thyroidectomy

5.7	Evidence-based Recommendation	2025
GoR **B**	Thyroidectomy should be performed for PTC > 1cm, for multifocal PTC, for familial PTC, and regardless of the size of the primary tumor for encapsulating and metastatic PTC as well as for histologically more aggressive variants.	
LoE **2b**	[402], [403]	
	Strong Consensus	

5.8	Evidence-based Recommendation	2025
GoR **0**	In justified cases, lobectomy can be a treatment strategy for PTC pT1b/pT2, provided there are no risk factors such as vascular invasion, lymph node metastases, capsular infiltration, familial predisposition, or previous radiotherapy.	
LoE **2b**	[402], [403]	
	Strong Consensus	

In a retrospective cohort study, Song et al [402] evaluated 318 matched pairs from the Asan Medical Center Korea for the comparison of total thyroidectomy (TT) versus lobectomy. The risk of recurrence after TT was not statistically significantly different in the total group with tumor size 1 to 4 cm compared to lobectomy (HR of 1.35 (0.40 - 1.36)).

Vargas-Pinto et al. [403] analyzed two meta-analyses [404], [405], which included a total of 6 publications, following a systematic literature search. The work by Adam with more than 68,000 patients [404] showed better survival after total thyroidectomy. The survival advantage increases with the length of follow-up. In an analysis of the NCDB database, the survival rate after 14 years for TT is 86.6% compared to 84.4% for lobectomy. This does not take into account whether and how often completion surgeries were performed after primary lobectomy. The mean follow-up period was only 6 to 7 years. There were no statistically significant differences in recurrence-free survival. The results of all the studies cited above do not take into account whether the patients underwent radioiodine therapy after TT or whether the patients underwent completion surgery after lobectomy, so a bias in the results to the disadvantage of TT cannot be ruled out. The studies show advantages of TT over lobectomy with a low level of evidence. In addition, it must be taken into account that TT is a prerequisite for radioiodine therapy and enables highly sensitive recurrence detection with the tumor marker thyroglobulin in follow-up care. However, the stage-specific subgroup analysis shows a superiority of TT in each case, without reaching statistical significance. The above reasons lead to the recommendation to use TT as the standard procedure, but also to the recommendation to forego it in favor of lobectomy in a favorable constellation.

5.3.2.2 Central lymph node dissection

5.9	Consensus-based Recommendation	2025
EK	In cN1-PTC, a central compartment resection (level VI) should be performed in conjunction with total thyroidectomy, regardless of the size of the primary tumor and based on frozen sections.	
	Strong Consensus	

In the case of clinically recognizable lymph node metastases (cN1) in the central compartment, a central compartment resection should be performed regardless of the size of the primary tumor in order to reduce the risk of recurrence and improve survival prospects, avoid recurrence surgeries that are prone to complications, and save the radioiodine activity that may be required for radioiodine therapy of central lymph node metastases [256], [60], [24]. Confirmation should be made in the frozen section. Central compartment resection during the initial procedure does not significantly increase the surgical risk. The number of tumor-involved lymph nodes has prognostic relevance [406]. Whether compartment resection can be limited to the affected side for oncological reasons in the case of unilateral lymph node involvement [407], in order to avoid the complication risk of the contralateral cervicocentral side, has not yet been proven by studies [408], [409], [410]. A recent meta-analysis identified age < 45 years, tumor size > 1 cm, male gender, extrathyroidal growth and ipsilateral lymph node metastases as prognostic factors for contralateral lymph node involvement [411].

5.10	Evidence-based Recommendation	2025
GoR **B**	To avoid a surgical risk that may not be commensurate with the low oncological risk, a prophylactic compartment resection in cN0-PTC > 1 cm should only be performed if justified and with appropriate surgical expertise.	
LoE **1a**	[412]	
	Strong Consensus	

5.11	Evidence-based Recommendation	2025
GoR **B**	If a cN0-PTC is only diagnosed postoperatively and there is no evidence of residual tumor, a complete prophylactic central compartment resection should not be performed after total thyroidectomy.	
LoE **1a**	[412]	
	Strong Consensus	

Prophylactic lymph node dissection is defined as lymph node dissection without clinical evidence of lymph node metastasis (cN0). For cN0 low-risk PTC < 2.5 cm, an analysis of 5 RCTs with 763 patients showed no advantage of prophylactic central lymph node compartment resection (PCND) for recurrence reduction [412]. Most of the included studies had a low risk of bias. No differences were found for both structural and biochemical recurrence no difference RD -0.00; p=0.95 in the groups with or without PCND. The rate of permanent hypoparathyroidism was 3% higher with

additional PCND (CI 0%-6%). Comparing the risk difference of thyroidectomy vs. additional PCND, the complications were comparable for the recurrent recurrence rate RD=0.01; p=0.73, the permanent recurrence rate RD -0.00, for transient hypoparathyroidism RD=0.04; p=0.20 and postoperative hemorrhage RD=0.00; p=0.87. In contrast, the permanent hypoparathyroidism rate was significantly increased with PCND with RD=0.03; p=0.02.
With very good quality of evidence, PCND shows no oncological advantage with an increased risk of transient and permanent damage, which is why a negative recommendation is issued.
However, 30-60% of intraoperative central lymph node metastases found preoperatively as cN0 [401] and less than 30% of central lymph node metastases are clinically detected intraoperatively [413].

5.3.2.3 Lateral lymph node dissection

5.12	Consensus-based Recommendation	2025
EK	If the PTC primary tumor is located in the upper pole or PTC with extensive central lymph node involvement and in the case of clinical suspicion or histological evidence of lateral lymph node metastases, a primary lateral compartment resection of the tumor-bearing side should be performed, and if necessary also of the contralateral side in the case of extensive central lymph node involvement.	
	Strong Consensus	

5.13	Consensus-based Recommendation	2025
EK	If there is no evidence of lateral lymph node metastases, a routine prophylactic lateral compartment resection shall be omitted.	
	Strong Consensus	

Lateral lymph node metastases are found in around 25 % of PTC patients [414], [415]. If metastases are suspected/detected preoperatively by palpation, sonography, biopsy, or intraoperatively by macroscopic or frozen section histology, a primary lateral compartment resection of the affected compartment is recommended [416], [24], [417], [60], [414], [418], [419]. Whether lateral compartment resection can be restricted to certain regions of the lateral compartment [420], [421] has not yet been sufficiently clarified by studies, so that a complete compartment resection is generally indicated. In the case of extensive central lymph node involvement (> 5 lymph node metastases), both the ipsilateral and contralateral lateral compartments are affected in over 70% of cases [414], so that a primary unilateral or bilateral lateral compartment resection is justified in order to minimize the risk of recurrence and avoid re-surgeries. Alternatively, a sequential procedure (decision on lateral compartment resection after radioiodine therapy or other imaging) can be chosen. In principle, lateral compartment resection can be performed in two stages if indicative factors have not been clarified at the time of surgery.

If there is no evidence of lateral lymph node metastases and no or only minimal central lymph node involvement, there is insufficient evidence to recommend a prophylactic lateral compartment resection, particularly in terms of surgical morbidity (shoulder-arm syndrome, lymphatic fistula) [422], [423], [424], [425], [426], [419], [427].

In PTC, so-called "skip" metastases are present in the ipsilateral lateral compartment in 1.6 - 21.8 % of cases without simultaneous central lymph node metastases [428], [429], [430], [431], [432], [433]. This metastatic pathway is preferentially observed in primary tumors in the upper pole of the thyroid gland [431], [434], [435],[432].

5.3.2.4 Mediastinal metastases

5.14	Consensus-based Recommendation	2025
EK	In the case of mediastinal lymph node involvement without evidence of distant metastases, transsternal mediastinal lymph node dissection may be indicated.	
	Strong Consensus	

Mediastinal lymph node metastases in PTC are rare (< 5 %) [406] but can be treated surgically with curative intent in the absence of distant metastases. If infrabrachiocephalic retrosternal lymph node metastases are suspected on preoperative imaging or detected intraoperatively, the indication for transsternal (or minimally invasive video-assisted) mediastinal compartment resection should therefore be considered, taking into account the general condition of the patient and the overall tumor burden. If distant metastasis is present, the curative approach is not applicable and mediastinal lymph node dissection is used to treat locoregional symptoms or to prevent secondary complications caused by the mediastinal lymph node metastases. There is no indication for prophylactic mediastinal dissection due to the increased risk of complications [436], [437], [438].

5.3.2.5 Completion surgeries

When is completion surgery for papillary thyroid carcinoma indicated?

Completion surgery with removal of the residual thyroid gland is indicated for papillary thyroid carcinomas > 1 cm in diameter, intrathyroidal spread with R1 resection or multifocal carcinomas in order to enable radioiodine therapy. A meta-analysis consisting of 13 studies including 8 cancer registry studies [439] examined the survival time of patients with papillary thyroid carcinoma and a tumor diameter between 1.0 and 4.0 cm who had undergone thyroidectomy or lobectomy. Overall, no clear difference was found between the two surgical procedures in terms of recurrence-free survival and overall survival. What was striking in all studies with the inclusion of > 16,000 patients was that the percentage of lobectomies in the total patient population was only 6% - 36%, and that these groups were obviously very selective. Two very large studies from the National Cancer Database (NCDB) [440], [441] showed a significant survival advantage for patients with a PTC who had undergone thyroidectomy when 52,173 patients and 22,899 patients were included. Bilimoria et al. described that lobectomy alone in PTC > 1 cm led to a higher risk of local recurrence and a lower

survival rate [440]. Rajjoub et al. also found a survival benefit for PTC with a diameter of 2.0 - 3.9 cm when a thyroidectomy was performed as opposed to a lobectomy [441].

A further meta-analysis of 6 studies that analyzed the rate of local recurrence of 2.939 PTC after thyroidectomy versus lobectomy [442], after a follow-up period of 10.9 years, showed a significantly lower rate of local recurrence (4.4% after thyroidectomy, 8.3% after lobectomy) and tended to show better survival rates (mortality after thyroidectomy 0.3%, after lobectomy 1.1%, n.s.) when thyroidectomy was performed.

In multifocal PTC, thyroidectomy reduces the risk of tumor persistence or recurrence in the contralateral thyroid lobe [196]. In a recent single-center study, Harries et al. [270] found no difference in the examined survival rates (survival with contralateral PTC-free thyroid lobe (CLPFS), recurrence-free survival (RFS), disease-specific survival (DSS), and overall survival (OS)) of 849 patients with unifocal or multifocal papillary pT1/pT2 carcinomas, 85% of whom, however, were classified as "low risk" according to the ATA classification. Limiting factors of this study, which covered a period of 30 years, were the exclusion of 40 patients who underwent completion surgery just a few days postoperatively, patients with lymph node metastases, and a median follow-up period of only 58 months.

In the case of incompletely resected PTC (R1/R2 resections), completion surgery should be performed for oncologically adequate surgical therapy. Exceptions to this are very small tumor remnants that are directly adherent to the recurrent laryngeal nerve, the trachea, or the esophagus. In these cases, radioiodine therapy and follow-up can be performed first.

In the case of complete thyroidectomy, prophylactic follow-up surgery in the area of the locoregional lymph nodes is not recommended. If indicated, completion surgery should be performed at the earliest possible time, if possible within the first four postoperative days or after an interval of 3 months [443], as the period between the 4th postoperative day and 3 months has proven to be particularly risky.

5.15	**Consensus-based Recommendation**	**2025**
EK	In the case of postoperative incidental findings of a PTC, a completion surgery should be performed if the primary surgery did not correspond to the resection procedure appropriate for the primary tumor spread.	
	Strong Consensus	

The timing of the completion surgery should be determined taking into account the extent of the primary surgery, the prognosis of any existing recurrent paresis, any residual tumor and surgical expertise. Given the paucity of literature data on this question, the time 3-5 days and again from 3 months after the initial surgery has proven to be clinically appropriate if the previously operated side needs to be reopened, as adhesions are still minor to moderate or have regressed [417]. This recommendation on the timing of a completion surgery does not apply if only the unaffected opposite side needs to be operated on and is qualified if the risk profile of the tumor or the local situation makes prompt re-surgery appear more favourable.

The necessity of referral to an appropriately profiled center should be examined. The positive correlation between the better quality of results in thyroid surgery and the surgical volume of the individual surgeon, but also of a center, has been proven many times. So-called high-volume surgeons achieve significantly better results in the measurable quality parameters (recurrence savings rate, hypocalcemia rate, postoperative bleeding rate, general complications). In thyroid cancer surgery in particular, studies show a positive correlation between high-volume thyroid surgery and complete tumor resection, low complication rates and lower postoperative radioiodine storage and tumor marker burden according to [444], [445], [446], [447], [448]. Following evidence research by the European Society of Endocrine Surgeons (ESES) on the volume-outcome association in thyroid surgery, a consensus conference defined that a high-volume surgeon performs >50 thyroid procedures per year and that >100 surgeries per year are performed in a thyroid surgery center [449].

5.16	Evidence-based Recommendation	2025
GoR **B**	In the case of complete thyroidectomy with evidence of a PTC, prophylactic follow-up surgery of locoregional lymph nodes should not be performed (see Recommendation 5.6).	
LoE **1a**	[412]	
	Strong Consensus	

Sanabria et al. [412] evaluated five randomized controlled trials in their meta-analysis. The studies compared the surgical outcome of thyroidectomy alone (n=354) versus thyroidectomy plus central lymph node dissection (n=409). Most of the included studies had a low risk of bias. No differences were found between the two groups for either structural or biochemical recurrence. The rate of permanent hypoparathyroidism was 3% higher with additional central lymph node dissection (CI 0% - 6%). In summary, as there was no benefit for prophylactic lymph node dissection but an increased risk of harm with high confidence in the study results, a negative recommendation was made.

5.3.2.6 Cross-organ PTC

5.17	Consensus-based Recommendation	2025
EK	Resection of cervicovisceral tumor infiltrations can be performed if the appropriate conditions are met (general condition, absence of progressive distant metastases, resectable lesion, surgical experience with surgical and perioperative management).	
	Strong Consensus	

The widely invasive extrathyroidal extension is a significant risk factor for systemic and locoregional metastasis and local recurrence [450], [451], [452], [453]. In the rare presence of surgically resectable invasion of the tumor into adjacent cervicovisceral structures (esophagus, trachea, dorsal neck muscles) (approx. 5 - 7 %), radical resection may be indicated in the absence of progressive distant metastases and with appropriate surgical expertise [454], [455], [456], [457], [458], [459], [460]. Alternative procedures to segmental resection or fenestration of the trachea are so-called shaving (tumor resection while leaving the tumor-infiltrated wall of the larynx, trachea or esophagus) or non-surgical palliative procedures in conjunction with adjuvant measures (e.g. radioiodine therapy, external radiotherapy, antineoplastic drug therapy such as tyrosine kinase inhibitors, etc.). A shaving procedure is not recommended for transmural tumor infiltration [461].

5.3.3 PTC in childhood and adolescence

5.18	Consensus-based Recommendation	2025
EK	The diagnosis and treatment of thyroid carcinomas in children and adolescents requires special expertise in surgical management, histopathological diagnosis and postoperative follow-up care and should therefore be reserved for designated centers.	
	Strong Consensus	

Thyroid carcinomas in children and adolescents are more often bilateral (30%) and multifocal (65%) [462], [463], [464]. In a retrospective study with a follow-up of 40 years, thyroidectomy showed a significantly lower local recurrence rate of 6% compared to 35% in 215 children with papillary thyroid carcinoma [465]. It should be noted that most patients in the thyroidectomy group received RIT. Histological subgroups, which are associated with a higher risk, have a proportion of 15 to 37%: tall-cell variant 7-13%, diffuse sclerosing variant 7-16%, solid/trabecular variant 1-4% [466]. In contrast to the significantly increased risk of local recurrence of these subtypes in adults, there does not appear to be an increased risk in children compared to classic PTC [467]. Despite lower overall tumor-related morbidity and mortality compared to PTC in adults, the rate of lymph node and distant metastases in children and adolescents is significantly higher than in adults [468], [469], [470]. Lymph node metastasis rates of 60% are reported [469]. Significant differences in locoregional metastatic behavior between children and adolescents could not be demonstrated [471], [472].

Since the staging criteria of the TNM system are based on the primary tumor size of adults [473], the age-independent use of the primary tumor size for the extent of resection in children and adolescents may lead to an underestimation of the risk of metastasis and recurrence. In conjunction with the overall higher rate of locoregional lymph node metastases in both the central and lateral compartments, careful preoperative and intraoperative clarification of the lymph node status should therefore be performed in children and adolescents in order to adequately determine the extent of resection of the thyroid gland and the locoregional lymph nodes. Weighing up the benefits and risks and assuming appropriate surgical expertise, prophylactic central compartment resection in PTC > 1 cm appears to be sensible [465]. Thyroid surgery

in children and adolescents should only be performed by high-volume surgeons in appropriately profiled centers due to the particular vulnerability, the difficulty in identifying and protecting the parathyroid glands and the frequently advanced and aggressive thyroid carcinomas [445], [474], [449].

5.4 Follicular carcinomas

Follicular thyroid carcinoma (FTC) is less common than PTC, accounting for approx. 10 - 15 % of all thyroid carcinomas in Germany [475]. The incidence is higher in iodine-deficient areas than in areas with sufficient iodine supply. With an age peak at around 50 years, FTC occurs significantly later than PTC. As with PTC, women are affected about 5 times more frequently than men.

Clinically, prognostically and therapeutically, minimally invasive FTC with and without vascular invasion must be distinguished from broadly invasive FTC due to their different tumor biology and prognosis and the resulting different treatment strategy [476], [274], [172], [253]. In the 2017 WHO classification, the previous division into minimally invasive and broadly invasive follicular carcinomas is abandoned and a new division into 3 groups is carried out [172]:

Follicular carcinomas ≤1 cm are a rarity in contrast to PTMC [477], the diagnosis should therefore be checked by a reference pathologist due to the different surgical treatment for FTC and PTC.

5.4.1 Minimally invasive follicular thyroid carcinoma (MIFTC) without vascular invasion

5.19	Consensus-based Recommendation	2025
EK	For solitary MIFTC without histologically detectable vascular invasion, only lobectomy should be performed for tumor size < 4cm, but not routine primary or secondary total thyroidectomy. In the case of a histopathological diagnosis of vascular invasion, a total thyroidectomy should be performed.	
	Strong Consensus	

5.20	Consensus-based Recommendation	2025
EK	Due to the low risk of lymphogenic metastasis, prophylactic lymph node dissection should not be performed in MIFTC.	
	Strong Consensus	

5.4.2 Minimally invasive follicular thyroid carcinoma (MIFTC) with vascular invasion

5.21	Consensus-based Recommendation	2025
EK	In solitary MIFTC with histologically detectable vascular invasion and MIFTC without vascular invasion, a total thyroidectomy should be performed if the tumor size is ≥4 cm.	
	Strong Consensus	

5.22	Consensus-based Recommendation	2025
EK	In MIFTC with vascular invasion, a prophylactic lymph node dissection can be performed.	
	Strong Consensus	

Around two thirds of follicular carcinomas are MIFTC [478]. Differentiation from follicular adenomas and the follicular variant of PTC or NIFPT is generally possible neither cytologically nor by frozen section, but predominantly histologically on the paraffin section based on nuclear morphology and evidence of minimal capsular and/or vascular invasion [479], [480]. As frozen section examinations only provide histological evidence of a MIFTC in exceptional cases [481], [482], [483], the use of frozen section histology for cytologically follicular neoplasia is more likely to serve the purpose of detecting other tumor entities [481], [484], [485].

In contrast to broadly invasive FTC, lymph node metastases are found in less than 10 % of cases (in patients with vascular invasion) in MIFTC [478], [486]. Prophylactic lymph node dissection is not indicated [24], [487], [60], [258]. In a prospective study by Asari et al., 14% of patients had distant metastases, of which 9.1% at diagnosis and 4.7% during the first postoperative year [478]. Long-term studies have demonstrated a very good overall prognosis for MIFTC [488].

5.4.3 Widely invasive follicular thyroid carcinoma (WIFTC)

5.23	Consensus-based Recommendation	2025
EK	A total thyroidectomy should be performed for WIFTC.	
	Strong Consensus	

5.24	Consensus-based Recommendation	2025
EK	If lymph node metastasis is detected preoperatively or intraoperatively, a central compartment resection should be performed. In the case of WIFTC with synchronous distant metastasis, a prophylactic central compartment resection can be performed.	
	Strong Consensus	

The widely invasive follicular carcinoma can be recognized macroscopically by its blurred borders and usually pronounced invasion into the surrounding thyroid tissue and can usually be confirmed by a frozen section examination. Due to the risk of metastasis in around one third of cases [478], the prognosis of WIFTC is less favorable than that of MIFTC, and the average age and tumor size are significantly higher than for MIFTC [488], [489]. WIFTC often metastasize primarily hematogenously and are then diagnosed through the detection of distant metastases [478]. Due to the regularly detected vascular invasion, a total thyroidectomy with postoperative RIT including diagnostics should always be performed, i.e. especially in the case of primary distant metastasis [24], [318], [60], [416], [490], [491], [492], [493], [494], [495], [496], [497]. This requires a completion thyroidectomy if the diagnosis is only made postoperatively after a primary non-total thyroidectomy. Lymph node metastases are detected in around 20 % of cases of WIFTC, usually in conjunction with distant metastases [478], [498]. The indication for compartment resection is therefore generally only given in cases where lymph node metastasis has been detected preoperatively or intraoperatively. The extent of the compartment resection should be based on the local findings. The same treatment principles apply to organ-transcending FTC as to PTC. If distant metastasis is present at the time of surgery, a prophylactic central compartment resection can be performed [24], [318], [258].

5.5 Oncocytic thyroid carcinoma

5.25	Consensus-based Recommendation	2025
EK	Due to the less favorable tumor biology compared to classic FTC and PTC, a total thyroidectomy should be performed for oncocytic carcinoma regardless of the primary tumor size.	
	Strong Consensus	

5.26	Consensus-based Recommendation	2025
EK	If an oncocytic carcinoma (non-encapsulated, possibly with vascular invasion) is detected preoperatively or intraoperatively, a thyroidectomy should be performed in conjunction with a central compartment resection.	
	Strong Consensus	

Oncocytic thyroid carcinoma (synonyms: oxyphilic carcinoma, Hürthle cell carcinoma) is a rare (< 5 %) histological variant of differentiated, mostly follicular, rarely papillary carcinomas. Oncocytic carcinomas are characterized by the presence of at least 30% oncocytic cells in the tumor and show a more aggressive tumor biology with an increased rate of lymph node and distant metastases and a lower radioiodine uptake than PTC and FTC [499], [500], [501], [502], [503], [504], [505]. Due to the less favorable tumor biology compared to classic FTC and PTC, a total thyroidectomy with postoperative radioiodine ablation should be performed primarily or secondarily in oncocytic carcinoma, regardless of the primary tumor size [258].

Due to the rarity of oncocytic carcinomas, no major studies are available on the question of the prognostic advantage of prophylactic compartment resection or completion surgery following lobectomy. However, due to the frequency of lymph node metastases and the limited radioiodine uptake capacity, a routine central compartment resection is recommended at least in the case of a preoperative or intraoperative diagnosis [258]. In the case of postoperative diagnosis after lobectomy, completion surgery can be dispensed with in individual cases if there are no risk factors (e.g. R0, encapsulated, lack of vascular invasion, cN0) and clinical follow-up is confirmed. If non-encapsulated oncocytic carcinoma is detected postoperatively, completion and compartment resection should only be performed if thyroglobulin is elevated or there is clinical evidence of lymph node metastases [258]. After primary total R0 thyroidectomy without central lymph node dissection, a completing compartment resection should only be performed if thyroglobulin is elevated or there is evidence of lymph node metastases. Follow-up care, recurrence therapy and distant metastasis surgery correspond to the therapy principles of PTC.

5.6 Poorly differentiated papillary carcinomas (PDTC)

5.27	Consensus-based Recommendation	2025
EK	In the case of resectable PDTC, a complete tumor resection with systematic compartment resection shall be performed even if the M1 situation is present.	
	Strong Consensus	

5.28	Consensus-based Recommendation	2025
EK	In organ-transcending PDTC with infiltration of surrounding cervical structures (esophagus, trachea, larynx, dorsal neck muscles), resection of the cervical aero-digestive tract should only be performed with local curative intent.	
	Strong Consensus	

Poorly differentiated thyroid carcinomas (PDTC) are tumors with a significantly poorer prognosis than differentiated PTC and FTC [506]. They were first defined in 2004 by the WHO [476] as an independent entity with a prognosis between that of differentiated and undifferentiated carcinomas. The frequency of these tumors is stated to be around 0.7-5 % of all clinically manifest thyroid carcinomas [476], [507].

Based on the Turin criteria, the WHO defines PDTC as a thyrocytic neoplasm with limited follicular cell differentiation and a morphological as well as clinical intermediate position between PTC and FTC on the one hand and undifferentiated (anaplastic) carcinomas on the other [252]. Solid/trabecular/insular growth, necrosis and an increased mitotic rate are typical of PDTC [261], [508], [509], [510]. For the diagnosis of PDTC, it is sufficient if 10 % of the tumor exhibits the typical morphological characteristics of PDTC [511], [512]. PDTCs are rarely smaller than 3 cm at the time of diagnosis, often show locally invasive growth, lymph node metastases (64 %) and not infrequently distant metastases (50 %) in the lungs, liver and bones [513], [512], [511], [514], [515], [484], [516].

Due to the more aggressive growth behavior compared to PTC and FTC and the lack of radioiodine uptake in 20 % of resectable tumors, a total thyroidectomy with radical tumor resection should be performed primarily or secondarily even in an M1 situation [516], [517], [145], [458], [518]. In a study by Walczyk et al., the tumor size of > 4cm, pT3-4, extensive extrathyroidal growth, R1 resections, TNM stages III-IV showed a significantly poorer survival rate for patients [519], [520]. Due to the frequent primary lymph node metastasis, the indication for systematic lymphadenectomy or compartment resection of the affected compartments is usually given. There are currently no studies on the question of prophylactic lymph node dissection in PDTC. However, if the diagnosis of PDTC has already been made preoperatively or intraoperatively, it is recommended to perform at least a central lymph node dissection/compartment resection due to the high risk of lymph node metastases. Radioiodine uptake is often limited. The detection of a TERT promoter mutation appears to be significantly associated with radioiodine refractoriness [521]. Ho et al. described a 10-year survival rate of 45.1% [522].

5.7 Quality assurance

5.7.1 Volume and outcome

5.29	Evidence-based Recommendation	2025
GoR **B**	Thyroid carcinomas should be operated on by surgeons experienced in thyroid surgery.	
LoE **2a**	[449]	
	Strong Consensus	

Numerous studies have shown that "hospital and surgeon volume" have a significant influence on the complication rates of thyroid surgery. The evidence report includes a review of meta-analyses [449], which evaluates the publications [445], [523], [524], [525], [526], [527], [528]. The overall data situation is heterogeneous, particularly with regard to the requirements for the individual surgeon, which is not least due to the fact that the studies do not always explicitly differentiate between thyroidectomies and thyroid surgery. With overall low confidence in the quality of the evidence, the recommendation is made. On the basis of the data, the requirement of a minimum number of 100 thyroidectomies per year in the institution and more than 50 thyroidectomies per surgeon per year appears appropriate [449].

5.7.2 Neuromonitoring

5.30	Evidence-based Recommendation	2025
GoR **A**	Intraoperative neuromonitoring (IONM) shall be used for bilateral thyroid surgery, preferably in the form of continuous neuromonitoring (CIONM) in the case of special risk constellations.	
LoE **1a**	[529]	
	Strong Consensus	

Intraoperative neuromonitoring (IONM) does not replace the gold standard of visual nerve imaging, but is used in addition to it. The identity of the recurrent laryngeal nerve can be reliably confirmed and nerve function can be demonstrated by stimulating the superior vagus nerve after resection. A meta-analysis [529][529] of 5 RCTs - 4 of them with very low certainty of evidence - with 1,558 patients (781 randomized IONM, 777 visual nerve identification) showed no significant advantage of IONM to

avoid permanent recurrent nerve palsy (RR 0.77, 95% CI 0.33 - 1.77; 4 studies 2,895 nerves at risk. In contrast, there is a tendency towards an advantage for the avoidance of transient recurrent nerve palsies when using IONM (RR 0.62, 95% CI 0.0 - 1.08;). It must be taken into account that studies are generally carried out by particularly experienced surgeons and that the success of IONM is presumably less clear as a result. Only IONM makes it possible to review the strategy (e.g. two-stage surgical approach, which can reduce the risk of bilateral recurrent nerve palsy) if bilateral surgery is planned and the signal is lost on the first side. For this reason, and since there are no disadvantages associated with IONM, a strong positive recommendation is made.

5.8 Radioiodine therapy

5.8.1 Radioiodine therapy - definition

Definition: Radioiodine therapy (RIT) is the systemic application of ^{131}I (as sodium iodide) for the selective internal irradiation of benign or malignant iodine-storing thyroid tissue. RIT has a wide therapeutic range and is used as an adjuvant, curative or palliative treatment.

Malignant tumors that can be treated with RIT due to their ability to accumulate and store iodine include PTC with its histological subtypes and FTC, oncocytic thyroid carcinoma (historic name: Hürthle cell tumors) and PDTC (= poorly differentiated thyroid carcinoma). The probability and ability to accumulate radioiodine and thus respond to RIT differs between these histological types. Oncocytic thyroid carcinomas and PDTC respond less well on average to RIT.

The aim of initial adjuvant radioiodine therapy (RIT) is to eliminate occult iodine-storing tumor tissue (metastases, residual tumor or secondary tumors) after thyroidectomy. Non-iodine-storing tumor tissue located in residual thyroid tissue can also be killed. Dosimetry is not possible as the tumor volume is usually not known. A risk-dependent standard activity is used. Adjuvant RIT also ablates the remaining postoperative thyroid tissue. This increases the diagnostic value of both subsequent radioiodine diagnostics (RID) and thyroglobulin determination. The term "ablative" RIT is often used in the international literature. This means that the elimination of residual tissue is the sole therapeutic goal. The literature results (see section Chapter 5.8.6.8) for "ablative" therapy should therefore only be applied with caution to adjuvant therapy. An increase in thyroglobulin indicates a recurrence of thyroid cancer. The detection of newly occurring pathological iodine stores is evidence of a recurrence.

Radioiodine therapy (RIT) can be used for both curative and palliative treatment of iodine-enriched metastases. The distinction between curative and palliative is not disjunctive in thyroid cancer and RIT. Several non-curative radioiodine therapies can delay the course of the disease so that the thyroid cancer is not life-limiting.

5.8.2 Indications for radioiodine therapy (RIT)

5.31	Consensus-based Recommendation	2025
EK	The recommendation for radioiodine therapy shall be made on the basis of the clinical and histopathological findings in an interdisciplinary tumor board.	
	Strong Consensus	

To prevent the development of hypothyroidism, patients who can, should or are due to undergo radioiodine therapy should be placed on L-thyroxine replacement therapy following the operation, or should be presented to a nuclear medicine therapy ward promptly after surgery (before hypothyroidism develops) for consultation, information about radioiodine therapy and determination of the therapy concept. The indication for RIT is determined by a doctor with specialist knowledge in radiation protection & nuclear medicine [530], [531], [532]. The patient shall be appropriately involved in the treatment decisions [533].

Krajewska et al. point out the influence of the time latency between surgery and RIT. Patients at low risk of recurrence who received RIT up to 9 months after surgery had a significantly lower risk of recurrence than patients who received RIT between 9 and 24 months or after more than 24 months since DTC diagnosis, namely 0%, 5.5% and 7.1% respectively [534]. Yu et al. also reported poorer treatment outcomes with delayed RIT, although a 3-month latency between surgery and RIT was reported here [535].

The TNM stage plays a key role in determining the indication for RIT. This classification is supplemented by an extended histopathological classification, so that the extent of extrathyroidal spread can be depicted, supplemented by a description of lymph node metastases, which are associated with a poorer prognosis [536], [537]. The classification into risk classes is initially concerned with the risk of recurrence (see table Table 16) [60], [24], [538], [539], [540], [541]. Other factors are relevant for the treatment decision, such as overall survival with versus without RIT [542], [543] and the simplicity of follow-up if an excellent response is subsequently achieved through the combination of surgery and RIT. This risk assessment is also important for the surgical procedure, in particular for the question of completion surgery and the indication for radioiodine therapy.

In addition to the staging system based on the TNM system and the prognosis groups I-IV of the UICC/AJCC derived from it, taking into account patient age, a whole series of other systems for estimating the prognosis of thyroid cancer are described in the international literature, mainly developed in the USA [544], [545]. In addition to the TNM prognosis groups, these systems take into account gender, tumor invasiveness parameters, and follow-up data from surgery and/or RIT as well as imaging and/or thyroglobulin levels after primary therapy in different ways for risk classification; they are therefore not comparable or only comparable to a limited extent and have not been evaluated in Germany.

Table 16: Classification of the risk classes for papillary and follicular thyroid carcinomas with regard to the risk of recurrence. The percentages are averaged values from the literature; the individual risk of recurrence may differ.

Risk of recurrence	Extended pTMN classification
Very low risk (≤2%)	Papillary thyroid carcinoma • Unifocal thyroid carcinoma ≤ 1 cm pT1a (PTMC) • Complete surgical removal • No extension beyond the thyroid capsule • No lymph node metastases • No vascular invasion
	Follicular thyroid carcinoma, minimally invasive, without vascular invasion
Low risk (≤5%)	Papillary thyroid carcinoma pT1b, pT2, N0/pN1*, M0 • Clinically N0 or *pN1 ≤ 5 micrometastases (tumor infiltration < 0.2 cm) • No distant metastases • No tumor invasion into locoregional tissue • No aggressive histology • No vascular invasion
	PTMC (multifocal +/- BRAF V600E mutation)
	Follicular thyroid carcinoma intrathyroidal FTC with capsular invasion or with minimal (≤ 2 foci) vascular invasion
Intermediate risk (5-25%)	Papillary thyroid carcinoma • pT3 N0 M0 or pT1-3 N1 M0 • Microscopic tumor invasion into perithyroid tissue • Aggressive histology • Vascular invasion • Clinical LN or pN1 (≥ 0.2 - 3 cm)
High risk (> 15 - > 25%)	Papillary thyroid carcinoma pT3, pT4, N1, M1 • Macroscopic tumor invasion into extrathyroidal tissue • No R0 resection • Distant metastases • pN1 with LN > 3 cm

Risk of recurrence	Extended pTMN classification
	Follicular thyroid carcinoma, grossly invasive with extensive vascular infiltration (> 2 foci)

The WHO classification of DTC (differentiated thyroid carcinoma) is changed approximately every 10 years. This makes it considerably more difficult to compare study results and transfer them to clinical application. A new histopathological classification was published in 2022. The latest, 8th edition of the UICC/AJCC TNM classification from 2017 brought significant changes to the risk groups compared to the previous version on the basis of published studies on the influence of clinical data on prognosis, resulting in a "downstaging" of approx. 30% of patients with DTC: the age limit was increased from 45 to 55 years; the criterion of minimal extrathyroidal tumor invasion was dropped; N1 cases are no longer classified in a higher stage, stage III; DTC > 4 cm are classified as pT3a; DTC of any size with macroscopic extrathyroidal growth are classified as pT3b; pN1b cases are no longer assigned to stage IV; distant metastases are grouped as stage IVB (previously IVC) [172]. These changes are based on retrospective studies of large patient cohorts, primarily from the USA [546]. This classification led to the vast majority of patients with DTC being assigned to the low-risk group in stage I (assumed tumor mortality 0-2%). However, the American literature emphatically points out that patients < 50 years of age in prognosis group I have "the full spectrum of recurrence risk", as it includes patients with lymph node metastases (prognosis group I) and distant metastases (prognosis group II) [547]. In a study on tumor-related mortality based on 85,740 DTC cases from the SEER database from 1973-2009, it is pointed out that there is no clear age limit in the range of 35 - 55 years [548]. A study from the Netherlands and Germany [549] on 3,074 patients with a higher proportion of follicular thyroid carcinomas than is typical for the USA (23% FTC and 77% PTC) focuses on age-dependent tumor-related mortality. The study confirms an age-dependent "threshold value" of approx. 50 years for papillary thyroid carcinoma. However, for FTC, which is considered separately here, this threshold is 10 years lower at around 40 years [549]. These two studies should give rise to a differentiated view of the age limit of 55 years recently raised in the 8th edition of the UICC/AJCC.

The classification of tumors > 4 cm or with infiltration in the neck muscles (regardless of age) in "intermediate" prognosis group II with an assumed tumor mortality of 5-15% also appears questionable with regard to the risk of recurrence. Prognosis groups with a high (mortality) risk of >20% are group III, which only includes patients older than 55 years with tumors infiltrating locally into the neck structures, and group IV, which also refers to older patients with tumors with even more aggressive local tumor growth (mortality risk > 50%). It must also be emphasized that this classification completely ignores the high risk of recurrence compared to mortality and the impairment of quality of life associated with recurrence therapy.

The risk stratification according to the 8th edition of the TNM system of the UICC/AJCC and the dependent restrictive indication for RIT by the ATA has been criticized by European experts [550], [551]. At a consensus conference in Martinique at the end of 2015, an attempt was made to identify international commonalities in the indication of RIT. These included the statement that "there is no one right way to treat patients" and that "local factors such as the quality of preoperative and postoperative

diagnostics, the quality of thyroglobulin determination and radioiodine diagnostics, the experience of the operating surgeon and clinical aspects of local care by the treatment team must be taken into account when determining the indication for RIT [547]. The American approach of reducing or abolishing the indication for RIT should be questioned, if only because, in contrast to Germany, mortality from DTC has risen in the USA in recent years [552].

In addition to the histopathological findings, patient-specific aspects must be taken into account when determining the indication for RIT. These include the completeness of the resection (R0 versus R1 versus R2), lymph vessel or vascular invasion, multifocality of the tumor, aggressive tumor behavior, molecular genetic characteristics, lymph node and distant metastases and their localization. In their analysis of the National Cancer Database with 45,415 patients, Pontius et al. pointed out that 11.6% of patients had lymphatic infiltration. These patients had more frequent lymph node metastases (74.1% versus 32.5%, $p< 0.01$) and also distant metastases (3.0 versus 0.5%, $p < 0.01$). The treatment of patients with lymph vessel infiltration with radioiodine significantly reduced their mortality (HR=0.43, $p<0.01$) [553].

Additional molecular genetic characteristics of the tumors listed in this classification (such as BRAF V600E mutations, TERT mutations, etc. [554] can play an additional role in the individual risk assessment for the indication. However, Li et al. were able to show that RIT after surgery is no less effective in patients with BRAF V600E mutations than in wild-type patients [542], which is why such a mutation is by no means a reason to exclude RIT [555].

The classification of differentiated thyroid carcinoma into risk classes for the probability of recurrence has changed over time. The American Thyroid Association (ATA) distinguishes between patients with low, intermediate, and high risk of recurrence. Papillary microcarcinomas (PTMC or PTC pT1a) are not listed as a separate risk category, but are integrated into the low-risk category. There is no consensus on the percentage value for a recurrence at which a transition to the next higher risk category should take place. The choice of a percentage value such as very low risk (probability of recurrence after oncology-oriented surgery < 2%), low risk (2 - <5%), intermediate risk (5 - 15/20%), high risk (> 15/20%) is a possible but ultimately arbitrary classification. When assessing the risk, it should be borne in mind that both classifications are based on different WHO classifications that are no longer up to date. Not least the introduction of NIFTP ("noninvasive follicular thyroid neoplasms with papillary-like nuclear features"), which are not considered malignant, has led to a risk migration and the tumors now classified as DTC are associated with a higher risk. The assignment of a patient to a risk class with regard to the risk of recurrence of the DTC must not be done statically and only once postoperatively. It is a dynamic process in which therapeutic measures and the response to them must be regularly taken into account [547].

Adjuvant RIT reduces the recurrence rate and mortality (HR of thyroid cancer-related mortality) with an HR of 0.53 - 0.79, depending on the study; for T3 tumors with an HR of 0.43; for T4 tumors with an HR of 0.29 [556], [557], [558]. Due to the high benefit of RIT at high risk of recurrence and the extrapolation into the low risk range, RIT has established itself as the standard procedure for low, medium and high risk of recurrence of differentiated thyroid carcinoma - not only in Germany.

Sawka et al. published systematic reviews and meta-analyses on the effectiveness of RIT in patients with papillary and follicular thyroid carcinoma in the periods 1966-

2002 in the first publication [556] and 2002-2007 in the second publication [557]. Bilateral resection was the guideline for patient selection with regard to thyroid surgery. The minimum follow-up period allowed for inclusion of publications in the review was 5 years. Outcomes examined were tumor-specific survival, tumor recurrence or late lymph node/distant metastases. In studies with overlapping patient cohorts, only the publication with the largest number of patients was evaluated. It should be critically noted that Sawka et al. [556] stated that the selection of "low-risk" patients was based on the 4th edition of the UICC/AJCC TNM system [544]. Patients with UICC/AJCC stages I and II were then assigned to the "low-risk" group. At that time, the age limit for classification was 45 years and not 55 years as in the current 8th edition. The changed age limit means that patients aged 45-55 years with an age-related higher risk are now included in group II.

The pooled analysis of 13 selected cohorts mainly from the USA of the first review [556] showed statistically significant, favorable effects of RIT in the 10-year course with regard to locoregional recurrences (clear effect, relative risk 0.31, 95%CI 0.2-0.49) and metachronous distant metastases (weak effect, reduction of the absolute risk by approx. 3%, 95% CI 1-4%). However, the results were inconsistent between centers, and the additional benefit of RIT in low-risk group I patients was considered inconclusive [556].

The second review by the same first author used exactly the same selection criteria as the previous publication [557]. This review included 21 publications from the first review and 7 new publications. The heterogeneity of the data from international centers in North America, Europe, and Asia made pooled data analyses difficult. However, with regard to tumor-related mortality, data pooling of 11 studies was possible. There was a significant reduction in the recurrence rate: in the collectives with PTC and PTC/FTC (Figure 2 of the publication), 248/2,121 patients with RIT (11.7%) and 583/3,005 patients without RIT (19.4%) had a recurrence. Significantly fewer distant metastases occurred in the group treated with RIT, namely 28/1,107 in the RIT group and 45/1,156 without RIT (p = 0.02). For recurrence-free survival, 5 studies with the largest number of patients (n=3,474) showed a considerable reduction in the risk of recurrence from 24.2% recurrence rate without RIT to 12.5% recurrence rate with RIT [557].

An analysis of 2,936 DTC patients in the National Thyroid Cancer Therapy Cooperative Study Group (NTCTCS) showed an improvement in disease-specific and overall survival in patients with advanced tumor disease and regional lymph node and/or distant metastases who received postoperative RIT [559]. A later analysis of 4,941 patients in the NTCTCS trial with a median follow-up of 6 years (range 0 - 25 years) confirmed an improvement in overall survival in stage III and IV patients and also showed an improvement in disease-free survival in stage II patients after surgery and RIT [560].

The benefit of postoperative RIT was demonstrated in patients with locally advanced tumor disease and/or distant metastases: In 11,832 patients from the National Cancer Database, USA, Yang et al published that RIT was associated with significantly better 5- and 10-year survival in both PTC and FTC patients with stage IV A, B, or C disease, in contrast to a non-radioiodine-treated control group and also to external beam radiotherapy [561]. Mortality in the PTC cohort (n=10,796) at 5 and 10 years was 11% and 14% for patients who received RIT compared to 23% and 26% for patients who did not receive RIT. Mortality in the FTC cohort (n=1,036) at 5 and 10 years was 29% and 37% in patients receiving radioiodine therapy compared to 46%

and 51% in patients not receiving RIT. These survival rates were also significantly better than those of patients who received external beam radiotherapy as an alternative, where the mortality rate was between 47% and 60% [561].

In 2018, the European Association of Nuclear Medicine (EANM) commissioned a literature study on adjuvant RIT for thyroid cancer from the German Agency for Quality in Medicine, Berlin (ÄZQ). This study was reported on in the EANM journal [551]. As part of the preparation of this guideline, Cochrane Cancer was commissioned to review the literature published between 2015 and the end of 2018 using the same search criteria as the ÄZQ. This identified 12 publications, including 5 that were already included in the ÄZQ report. The 7 "new" publications included 6 register studies and one systematic review with a meta-analysis. One study had to be subsequently excluded as it focused on the safety rather than the effectiveness of RIT. The review and two other studies dealt exclusively or predominantly with papillary microcarcinoma. At a 10-year follow-up, there were no survival benefits from RIT in this group. Disease-free survival, which is actually more relevant as an outcome parameter, was not investigated. Two registry studies in the SEER database investigated the effectiveness of RIT in low-risk cases of UICC/AJCC Group I (<55 years) and II (≥ 55 years) with regard to central lymph node metastases. While one study demonstrated a clear survival benefit of RIT in stage pN1a in terms of reduced overall mortality (HR=0.54, P < 0.001) [558], the second study on the same data set found a similar effect only if the later pathologically-anatomically proven lymph node metastases pTN1 had not been clinically detected (cNx/0) [562]. The last study identified by Cochrane deals with the clinically important question of which prognostic factors play a role in patients with stage pT2-4. First, it was shown that RIT significantly improves disease-specific survival in patients with tumors > 2cm (HR = 0.60, P< 0.01) if one of the additional risk factors age > 45 years, locally invasive tumor growth, lymph node or distant metastases is present [563].

As data from RCTs on the benefits of RIT in low and intermediate stages are lacking worldwide, data from clinical follow-up registries must be used as a substitute. The Würzburg Thyroid Cancer Registry has been collecting clinical follow-up data on around 3,000 DTC patients since 1980. A prospective observational study from this registry on 2,011 DTC patients of all tumor stages from 1980-2011 (median follow-up 7.1 years) allows indirect conclusions to be drawn about the effectiveness of RIT in terms of survival in the intermediate stages pT1b-4a pN0-1 M0 [564]. Despite the higher risk, the 10-year survival probability of this group treated with radioiodine does not differ from that of the "very-low" risk patients pT1aN0M0 who did not receive RIT and a matched comparison group from the general German population without DTC: The 10-year survival rates of the DTC patients with low and intermediate risk, who made up 86% of the total collective, and that of the comparison group from the general German population was 95%. Patients older than 45 years with advanced tumor disease in stage pT4a, b or c (according to the 7th edition of the UICC classification), patients with lymph node metastases in the lateral neck compartment or with distant metastases had poorer long-term survival. Of the patients with tumor stage IVc, only around 30% were still alive after 20 years [564].

There are analyses from Europe [551] and the USA, particularly from their national cancer registries, which show a clear benefit of RIT in higher, but also in intermediate and low stages [565], [548], [543], [566]. Orosco et al. determined a benefit for RIT in 199,371 patients from the NCDB database and 77,187 patients from the SEER database across all stages with the exception of papillary microcarcinoma. In the group treated with RIT, there was a lower overall mortality (NCDB: RAI hazard ratio (HR)

0.55, P<0.001; SEER: HR 0.64, P<0.001) as well as a reduction in cancer-specific mortality (SEER: HR 0.82, P=0.029) [543].

Recent publications also demonstrate the benefit of RIT in low and intermediate stages [567], [568]. Zhao et al. reported in a multivariate Cox regression model that low to intermediate risk PTC patients had better OS when RIT was performed. Subgroup analysis showed that RIT predicted better OS in patients ≥55 years, AJCC stage II and extracapsular extension with HR (95% CI) of 0.57 (0.45-0.72), 0.57 (0.45-0.72) and 0.68 (0.51-0.91), respectively. Patients with at least 2 cervical lymph node metastases or multifocal tumors or extracapsular extension treated with surgery and RIT had better survival than those treated without RIT [569].

Sutton et al. analyzed treatment decisions of surgery and RIT according to patient age. age dependence. 72,368 were young adults aged 18-54 years; 23,726 were middle-aged adults aged 55-64 years; 18,119 were older adults aged 65-79 years and 2,885 were very old adults aged over 80 years. With increasing age, the rate of patients operated on (99.0%, 98.4%, 97.4%, and 89.1%; p < 0.001) or treated with RIT (48.7%, 42.5%, 39.7%, and 30.7%; p< 0.001) decreased. Middle-aged, older and very old adults had a higher risk of death from differentiated thyroid cancer (HR: 4.0, 95%CI: 3.2-4.8, p < 0.001; HR: 7.6, 95%CI: 6.3-9.1, p < 0.001; and HR: 17.2, 95%CI: 13.8-21.3, p < 0.001). In multivariable Cox regression adjusting for clinicopathologic factors, treatment was a significant prognostic factor (surgery HR: 0.26, 95%CI: 0.22-0.32, P < 0.001; and no RAI HR: 1.42, 95% CI: 1.25-1.67, P < 0.001) [570].

5.8.2.1 Papillary micro-carcinoma PTC pT1a (= PTMC) N0 M0: Papillary thyroid micro-carcinoma (PTMC)

PTC pT1a is described in section statistics with up to 36% and thus represents a very frequent incidental finding ("incidental PTC") [571]. Papillary microcarcinoma (PTC pT1a, i.e. a PTC ≤ 10 mm) is usually detected as an incidental finding after (lobectomy or) thyroidectomy of a goiter. In its guideline published in 2014, the British Thyroid Association (BTA) devoted considerable space to risk assessment and personalized decision-making in the treatment of PTMC (PTC pT1a) [60], in particular with data on metastasis. The prevalence of nodal micrometastasis is given as 12 - 50%. On the basis of 15 studies with 4,096 patients and a follow-up of 3.7-11.2 years, the BTA calculated a probability of 0.4% for distant metastasis in PTMC and, after analyzing 16 studies with 5,256 patients, put the risk of locoregional recurrence at 2.5%. The previous therapies were very heterogeneous and in some cases also included radioiodine therapy [60].

5.32	Evidence-based Recommendation	2025
GoR **A**	In the case of a postoperative incidental finding of a papillary microcarcinoma (unifocal PTMC, PTC pT1a) with no evidence of locoregional or distant metastases and no other risk factors, no further ablative therapy (surgical therapy or radioiodine therapy) shall be performed.	
LoE **1b**	[572]	
	Consensus	

In their meta-analysis of papillary microcarcinoma, Hu et al. found no advantage for RIT in reducing the risk of recurrence at a follow-up period of 10 years [572]. Nineteen retrospective cohort studies comparing patients with RIT with those without RIT met the inclusion criteria of this publication. A multivariate analysis of the efficacy of RIT in relation to recurrence or thyroid cancer-related mortality in patients with papillary microcarcinoma was performed in several studies, of which only one study yielded a positive result. In PTMC patients treated by total or near-total thyroidectomy (TT/NT) with or without RIT, the meta-analysis found that RIT did not significantly reduce the 10-year risk of tumor recurrence (relative risk [RR] 0.96; 95 % confidence interval [CI] 0.63-1.48; P = 0.87), nor locoregional recurrence (RR 1.15; 95 % CI 0.75-1.76; P = 0.51), distant metastases (RR 0.32; 95 % CI 0.08-1.32; P = 0.11) or thyroid cancer-related mortality (RR 0.76; 95 % CI 0.22-2.63; P = 0.66). With low confidence in the quality of the evidence, this justifies the negative recommendation.

5.33	Evidence-based Recommendation	2025
GoR **0**	In PTC in stage pT1a with risk factors (e.g. multifocality, aggressive subtype, organ capsule infiltration, genetic risk profile, percutaneous pre-irradiation of the head/neck region), radioiodine therapy can be offered after an individual risk/benefit assessment if a thyroidectomy has been performed.	
LoE **2a**	[569]	
	Consensus	

If risk factors are present, the prognosis is also worse in the pT1a situation. Risk factors for the increased probability of lymph node metastases are multifocality, aggressive subtype, low degree of differentiation, infiltrative tumor growth with infiltration of the thyroid capsule, but also surrounding desmoplastic fibrosis [573], [574], a tumor diameter of 6 mm or more, familial clustering or a history of percutaneous pre-irradiation of the head and neck region [575], [576], [577], [578], [60].

Shattuck et al. published an important aspect of multifocality, namely that in multifocal PTC the individual tumors arise from independent tumor clones, so that in multifocal PTC RIT (if necessary after completion surgery) was advised to prevent the development of a new tumor in the residual thyroid tissue [579].

Genpeng et al. reported on 285 patients with multifocal PTC. Multifocal PTC had a higher rate of capsular invasion, extrathyroidal extension, N+ stage and local recurrence and therefore received RIT more frequently. Capsular invasion (hazard ratio [HR], 1.589; 95% confidence interval [CI], 1.352-1.984), advanced pathologic T classification (HR, 3.582; 95% CI, 2.184-5.870), and pathologic N+ stage (HR, 1.872; 95% CI, 1.278-2. 742) were associated with an increased risk of multifocality and there was a significantly increased HR for central cervical lymph node compartment involvement in male sex (HR, 2.694; 95% CI, 1.740-4.169), advanced pathologic T classification (HR, 2.403; 95% CI, 1.479-3.907), and multifocality (HR, 1.988; 95% CI, 1.361-2.906). Genpeng therefore recommend a total thyroidectomy with prophylactic bilateral central lymph node dissection for multifocal PTC in view of the increased probability of lymph node metastases in level VI [580].

Zhao et al. [569] investigated whether patients benefit from radioiodine therapy if they have a papillary microcarcinoma with an intermediate risk of recurrence. Zhao et al. identified 8 studies that matched the search strategy and a total of 2,847 patients were analyzed. The analysis of PTMC patients with intermediate risk of recurrence showed that patients without RIT had a higher rate of cancer recurrence than those who had undergone RIT (RR 0.23, 95% CI 0.11-0.49, P = 0.0001). Patients with risk factors for lymph node metastases (RR 0.16, 95% CI 0.06-0.42, P = 0:0002), microscopic extrathyroidal extension (RR 0.19, 95% CI 0.06-0.60, P = 0:005) and multifocality (RR 0.13, 95% CI 0.04- 0.45, P = 0.001) had a significantly higher risk of recurrence without RIT. RIT reduces the cancer recurrence rate over 5 years in PTMC patients with risk factors such as lymph node metastases, microscopic extrathyroidal extension and multifocality.

If these risk factors are present, RIT can be performed in the case of a total thyroidectomy after individual risk-benefit assessment and patient information. In the prospective ESTIMABL2 study, in which RIT was not performed for low PTC tumor stages, patients with aggressive histological subtypes of PTC were excluded [581].

With low confidence in the quality of the evidence, recommendations were made with appropriate strength for the different risks,

5.8.2.2 Papillary thyroid carcinoma with preoperatively diagnosed LN or distant metastases, PTC pT1a N1 and/or M1 (papillary thyroid microcarcinoma = PTMC ≤ 10 mm)

5.34	Evidence-based Recommendation	2025
GoR **A**	In the case of initially lymphogenous or hematogenous metastasized PTC pT1a (PTMC), radioiodine therapy shall be carried out after thyroidectomy.	
LoE **2b**	[569], [582], [583]	
	Consensus	

The publication by Zhao et al. identified the presence of lymph node metastases in patients with papillary microcarcinoma as a risk factor for recurrence, meaning that these patients benefit from radioiodine therapy [569].

For papillary microcarcinoma diagnosed preoperatively, a meta-analysis by Mehanna et al. showed a 14.7-fold higher probability of recurrence compared to histopathologically incidentally detected microcarcinoma [578].

In a retrospective cohort study from Seoul, Korea, Kwon et al. investigated the effect of radioiodine therapy on papillary microcarcinoma. Of a total of 1,932 patients, 1,648 had received radioiodine therapy and 284 had not received RIT after total thyroidectomy. The risk of recurrence was identical at a mean follow-up time of 8.3 years, but only on condition that the patients had no lymph node metastases in the lateral neck compartment and no distant metastases [582].
Al-Qahtani et al. investigated the benefits of radioiodine therapy in patients with papillary microcarcinoma in a retrospective cohort study conducted between 2000 and 2012[583]. 326 patients had papillary microcarcinoma, of whom 144 patients received radioiodine therapy and 182 did not receive radioiodine therapy. During the median follow-up period of 8.05 years, 23 recurrences occurred, 8 (4.4%) in the radioiodine-treated group and 15 (10.4%) in the patients who had not received radioiodine therapy. The presence of lymph node metastases was a statistically highly significant risk factor for disease-free survival in the univariate and multivariate analysis (univariate analysis LN positive 4.45 versus LN negative 1.17, $p < 0.0001$ and multivariate analysis LN positive 3.74 versus LN negative 1.01, $p < 0.0001$).

These publications justify the recommendation of radioiodine therapy for papillary microcarcinoma in the presence of lymph nodes and distant metastases.

Further publications deal with the question of how frequent lymph node metastases are in papillary microcarcinoma and how often disease persistence occurs at this tumor stage.

In a meta-analysis by Qu et al., a probability for the presence of lymph node metastases in the central compartment of 30.2% (847/2,801 patients) for unifocal PTMC and 47.7% (460 / 964 patients) for multifocal PTMC was extracted from 11 studies. Risk

factors were male gender, younger age of onset < 45 years, tumors > 5 mm, multifocality and extrathyroidal extension [391]. In unifocal papillary carcinoma, the probability of lymphogenic micrometastases increased with increasing tumor diameter, depending on the tumor diameter, even below 10 mm (tumor diameter 6 to 10 mm).

Goran et al. found similar figures for lymph node metastases in a total of 237 PTMC patients. Lymph node metastases were found in 33% of patients. The distribution was 27% in the central lymph node compartment and 20% in the lateral lymph node compartment; skip metastases were found in 6%. A PTMC diameter of 5 mm or more was a risk factor: PTMC ≤ 5 mm had LN metastases in 20.3% (521/2,570 patients) and PTMC > 5 mm in 36.3% (1,457/4,012 patients) [584].

Gao et al. confirm that PTMC does not always follow a favorable course. 40/358 patients (14.3%) developed disease persistence. The variables male gender, initial tumor size >5 mm, lymph node metastases and a stimulated thyroglobulin level ≥ 10 µg/L were associated with disease persistence in univariate regression analysis. A post-stimulation thyroglobulin level ≥ 10 µg/L was the only independent prognostic variable that predicted disease persistence in multivariate regression analysis (odds ratio: 36.057, p = 0.000) [585]. Accordingly, a PTMC is not always considered a clinically or prognostically favorable tumor, with Gao et al. reporting distant metastases in only 1/280 patients (0.4%) [585]. Based on their analysis, Gong et al. therefore suggested a diameter of 8.5 mm as the best cut-off between "indolent" and lymphogenously metastasized tumors [586].

Al-Qurayshi et al. also investigated whether papillary microcarcinoma always presents as "indolent". Of a total of 30,180 adult patients with PTMC from 2010 to 2014 in the National Cancer Database, 5,628 patients (18.7%) were identified as having advanced tumor characteristics, including central lymph node metastases (8.0%), lateral LN metastases (4.4%), microscopic extrathyroidal extension (6.7%), grossly invasive extrathyroidal extension (0.3%), lymphatic vessel invasion (4.4%), and distant metastases (0.4%) [587]. Huang et al. published on the frequency of lymph node metastases: Of 484 patients with PTMC, 49.6 % had central and 9.1 % lateral lymph node metastases [588].

5.8.2.3 Papillary thyroid carcinoma in stages with low and medium risk of recurrence, PTC pT1b, pT2 and pT3

5.35	Evidence-based Recommendation	2025
GoR **B**	Patients with PTC pT1b pN0 without risk factors should not undergo radioiodine therapy if an excellent result has already been achieved by surgery, otherwise the advantages and disadvantages of radioiodine therapy should be discussed individually.	
LoE **1b**	[581]	
	Consensus	

Leboulleux et al. published a prospective randomized study (ESTIMABL2) on the benefit of RIT in patients with tumor stages pT1aN0, pT1aNx, pT1bN0 and pT1bNx [581]. In this French prospective ESTIMABL2 study, PTC patients in these stages underwent thyroidectomy and were then randomized into 2 groups: 389 patients received RIT and 387 patients did not receive RIT. The surgeries had already been planned primarily as oncological surgeries and were performed in 35 selected expert centers. In both groups, 44% of patients had undergone lymphadenectomies as part of the thyroidectomy. Patients with aggressive tumor histologies were excluded. Information on the side effect profile (recurrent paresis, hypoparathyroidism) is missing in the publication. After 3 years, the results were comparable in both groups, whereby a composite endpoint was examined, namely the occurrence of functional, structural or biochemical abnormalities. More than 95% of patients had an unremarkable course and the advantage for RIT was only 0.3% (with a small number of cases, p = n.s.). During the follow-up period, abnormal findings occurred in 16/367 patients (4.4%) in the observation group and in 15/363 patients (4.1%) in the radioiodine-treated group. The endpoints were defined differently in the groups. In the radioiodine-treated group, iodine accumulations outside the thyroid bed were counted as events, which, as expected, was not possible in the non-radioiodine-treated group. This means that the more sensitive method was used in the radioiodine-treated group. In the radioiodine-treated group, findings requiring treatment were found in 10 patients; this was the case in only 4 patients in the observation group. The results suggest that the benefit of RIT in oncologically oriented surgery is limited to a small number of patients and that the decision to use RIT at this tumor stage depends on multiple factors. It should be critically noted that the follow-up period of 3 years was very short and that many more recurrences were diagnosed in the radioiodine-treated group. This suggests that radioiodine therapy has enabled more sensitive follow-up. RIT was carried out with the low activity of 1.1 GBq, which was determined à priori. Results with higher activities are therefore not available. It is also noteworthy that the risk profile was less favorable in the group of patients receiving radioiodine therapy. Taking into account the points of criticism and the sometimes very critical international view [589], it should be noted that the occurrence of functional, biological and structural events in the patient group of pT1a and pT1b tumors (with a high rate of lymph node dissection) with and without RIT appears to be comparable over three years. However, it is also conceivable that the sensitivity of the diagnosis is worse without RIT, which is why the recurrences were not detected within 3 years. If there is little confidence in the quality of the evidence, a negative recommendation is made.

The following criteria can be used to define an excellent result after a thyroidectomy:

- The removal of a representative number of lymph nodes from the central compartment without evidence of tumor (the guideline value is 6 removed and histopathologically processed lymph nodes in tumor stage pT1b).
- A low postoperative serum Tg value, measured 3-4 weeks after surgery (guideline value < 0.5- 1ng/ml). There are no reliably defined limit values for thyroglobulin. In the ESTIMABL2 study, the recurrence rate with a Tg value of >1ng/ml was 14.6%.
- No Tg antibody detection. If this is the case, the Tg value may be falsely negative.

5.36	Evidence-based Recommendation	2025
GoR **A**	In patients with PTC pT1b pN0/Nx and patients with PTC pT2 pN0 with prophylactic compartment resection, the advantages and disadvantages of radioiodine therapy shall be discussed individually.	
LoE ⊕⊕⊖⊖	⊕⊕⊖⊖: OS [567]	
	Consensus	

5.37	Evidence-based Recommendation	2025
GoR **B**	Adjuvant radioiodine therapy should be performed in patients with PTC pT2 pNx/1 or pT3.	
LoE ⊕⊕⊖⊖	⊕⊕⊖⊖: OS [567], [590], [566], [543]	
	Consensus	

At higher tumor stages and in the presence of lymph node metastases, patients benefit from radioiodine therapy. Liu et al. investigated the effect of radioiodine therapy on survival depending on the 7th and 8th edition of the AJCC/TNM stages [567]. They analyzed 89,204 patients from the SEER database in the period from 2006 to 2015. In particular, patients in T-stages pT2, pT3 and pT4 benefited from radioiodine therapy in terms of overall survival according to both the 7th and 8th editions of the classification. Hazard ratios were between 0.293 and 0.575 in the 7th edition and 0.132 and 0.443 in the 8th edition (95%CI all less than 1). The benefit of radioiodine therapy also applied to patients with lymph node metastases and even more clearly to distant metastases (HR of 0.332, 95% CI 0.269-0.410 after the 7th edition and HR of 0.272, 95% CI 0.207-0.358 after the 8th edition for patients with distant metastases).

Zhao et al. [590] analyzed patients in the SEER database from 2004-2018 according to a propensity score matching analysis. A total of 15,179 patients were included, including 3,387 (22.3%) who underwent total thyroidectomy only and 11,792 (77.7%) who received total thyroidectomy and radioiodine therapy. Subgroup analysis showed that RIT in patients ≥55 years, American Joint Committee on Cancer (AJCC) stage II and extracapsular extension resulted in a significantly better prognosis for survival with hazard ratios (HR) (95% CI) of 0.57 (0.45-0.72), 0.57 (0.45-0.72) and 0.68 (0.51-0.91), respectively. The data from Liu et al. and Zhao et al. justify recommendations 5.36 and 5.37.

Based on the SEER database (USA) from the survey years 1973-2009, Orosco et al. were able to show in a collective of 6,049 patients that not undergoing RIT increases carcinoma-specific mortality. For patients with tumor stage pT2 N0 M0, < 45 years,

male, of Caucasian descent without adjuvant RIT, a significantly higher hazard ratio of 1.3 ($p < 0.0002$, confidence interval 95% of 1.1-1.5) was calculated in comparison to a corresponding reference collective in which adjuvant RIT had been performed [543].

Ruel et al. analyzed the data from the National Cancer Database (USA) from 1998-2006 with a focus on the risk of recurrence at pT3 N0 M0 or pT1-3 N1 M0 (intermediate risk group) on the basis of 21,870 patients [566]. The multivariate analysis showed a 29% reduction in mortality for patients with adjuvant RIT compared to patients without adjuvant RIT. This clear effect was found despite the fact that the group of patients who underwent RIT had a statistically more advanced tumor spread at diagnosis than the patients without adjuvant RIT (non-randomized design): Thus, compared with the non-adjuvant treatment group, multifocality at initial diagnosis existed in 51% versus 47% of patients receiving adjuvant therapy, lymph node metastasis in 74% versus 68%, and R1 resection in 19% versus 15% of patients. However, the decision in favor of adjuvant RIT more than compensated for the more advanced tumor stage and improved mortality. Adjuvant RIT also reduced mortality in the subgroup < 45 years ($n = 12,612$, $p = 0.002$, mortality reduced by 36%) and in the subgroup > 65 years ($n = 2,122$, median OS 140 versus 128 months, $p = 0.008$). In the NCDB analyzed by Ruel et al. the recurrence rate is not recorded, which is why there is no statement on this. It must be taken into account that in the U.S. no distinction is made between adjuvant and ablative RIT (potentially underdosed with RIT at 1.1 GBq).

In a non-systematically reviewed study, Sun et al. compared two groups of patients, each with 12,128 patients, who were treated once with thyroidectomy alone and the other time additionally with RIT [558]. The patients without RIT had a statistically significantly worse overall survival, especially in the group > 55 years. The improvement in overall survival with thyroidectomy and RIT was highly significant for patients in T-stage T3 with an HR of 0.34 (95% CI = 0.27 - 0.43; $p < 0.001$) and for patients with lymph node metastases who had received RIT: pN1a HR = 0.30 (95%CI = 0.25 - 0.36; $p < 0.001$) and pN1b HR 0.56 (95% CI = 0.44 - 0.71; $p < 0.001$). This highly significant benefit of RIT was found both in patients with 1 - 4 lymph node metastases (HR = 0.40, 95% CI = 0.33 - 0.48; $p < 0.001$) and in patients with ≥ 5 lymph node metastases (HR = 0.46, 95% CI = 0.37 - 0.57; $p < 0.001$). In absolute numbers, there were 383 deaths in the thyroidectomy group with 1-4 lymph node metastases and 221 deaths with ≥ 5 lymph node metastases. The number of deaths was lower in the group additionally treated with RIT: 175 for 1-4 lymph node metastases and 139 for ≥ 5 lymph node metastases.

When deciding for or against radioiodine therapy, it is important to consider the risks associated with lymph node metastases and the certainty of an "N0" diagnosis.

In most lymphogenously metastasized PTC tumors, a clinical N0 situation is found preoperatively on ultrasound. On histopathology, however, lymph node metastases are found in approx. 20 - 80% of PTC patients (if a sufficient number of lymph nodes have been removed) [591].

Wang et al. found more than 5 lymph node metastases in the central compartment in 67/611 cN0 patients (11%), each with a tumor size of ≥ 2 mm [592]. Lei et al. found "skip metastases" in the lateral neck compartment in 39/450 patients (8.7%) who had undergone both central and lateral neck lymph node dissection for PTC, [593]. Nie et al. reported a probability of skip metastases of 15% (30/203 patients) [594].

The probability of detecting existing lymph node metastases histopathologically depends on the number of lymph nodes removed at thyroidectomy and examined histopathologically [595], [60], [596], [597].

Robinson et al. stated that in order to exclude lymph node metastases with a 90% probability, 6 lymph nodes would have to be examined histopathologically for pT1b tumors, 9 for pT2 tumors and 18 for pT3 tumors [598]. See also background text to recommendation Recommendation 4.5.

Randolph et al. published a comprehensive analysis of the risk of recurrence depending on detailed descriptors of lymph node metastasis [599], [600]. With less than 5 LN metastases ≤ 0.2 cm, the risk of recurrence is given as less than 5%, whereas the risk of recurrence increases to up to 19% if more than 5 LN metastases are detected. In the clinical N1 situation, the risk of recurrence is up to 22% and up to 33% for macroscopic LN metastases of > 3 cm.

Table 17: Advantages and disadvantages of radioiodine therapy

	Radioiodine therapy	No radioiodine therapy
Elimination of residual thyroid tissue	yes	no
Significance of the Tg value in tumor aftercare	yes	no (at least limited)
Detection of iodine-avid lymph node metastases	yes	no
Detection of iodine-avid distant metastases	yes	no
Elimination of tumor tissue	yes	no
Certainty of tumor stage	high	low
Radiation exposure	existent	not existent
Benefit on recurrence-free survival (PFS)	no direct comparative studies of patients with versus without RIT on recurrence risk	
Benefit on overall survival (OS)	retrospective studies show benefit, particularly with a follow-up period of 10 years or more	

5.8.2.4 Papillary thyroid carcinoma in stages with a high risk of recurrence or in the metastatic situation, PTC pT4, M1

5.38	Evidence-based Recommendation	2025
GoR **A**	For PTC in the risk group pT4 every N every M, radioiodine therapy shall be carried out after thyroidectomy.	
LoE ⊕⊕⊖⊖	⊕⊕⊖⊖: OS [567], [543]	
	Strong Consensus	

T4 and M1 patients have reduced tumor-specific survival [601].

Liu et al. [567] examined PTC patients from the SEER database from 2006 to 2015. Of the total 89,204 patients, 944 patients in the T4a and T4b stages had not received radioiodine therapy and 1,764 patients had received radioiodine therapy. The hazard ratio (improvement in survival) due to radioiodine therapy was 0.489 (95% CI 0.392-0.609) for T4a patients and 0.372 (95%CI 0.284-0.487) for T4b patients (7th edition of the TNM classification); for metastatic patients, the hazard ratio was 0.332 (95% CI 0.269-0.409).

Orosco et al. [543] also analyzed the SEER database and the NCDB database with a total of 276,558 patients. Patients who had radioiodine therapy had an improvement in all-cause mortality in almost all cohorts. High-risk metastatic patients had the greatest benefit. For metastatic patients, the hazard ratio for overall survival was 0.51 (95% CI 0.42-0.61, n=1532) according to the NCDB database and 0.39 (95% CI 0.29-0.52, n=564) in the SEER database. The significant results justify the strong positive recommendation.

5.8.2.5 Special histologies of the PTC

5.39	Evidence-based Recommendation	2025
GoR **B**	Aggressive subtypes of PTC (including the large cell, columnar cell, and hobnail variants) should be treated with radioiodine therapy.	
LoE **2b**	2b: OS [602]	
	Strong Consensus	

Histological features such as vascular and/or lymphatic invasion, angiogenesis, multifocality, high cell proliferation rate, dissemination of neoplastic cells and histological variants, together with clinical factors such as age, gender, and tumor size, indicate a

poor prognosis [603]. Subentities of PTC with a poorer prognosis include the columnar cell variant and the encapsulated variant [604].

Holoubek et al. [602] recorded a total of 155,940 patients with papillary thyroid carcinoma, 4,011 patients with tall cell carcinoma and 507 with diffuse sclerosing carcinoma in the National Cancer Database. Overall survival was compared for matched cohorts of patients who received radioiodine therapy or no radioiodine therapy after total thyroidectomy. The median duration of follow-up was only 4.3 years. For tumor sizes 20 mm and larger, a significant (p=0.004) survival advantage was found for the radioiodine-treated group, 83.4% versus 70.0% in 338 patients. For tumors between 10 and 20 mm, the corresponding values were 88.1% versus 72.7% (n.s.) in 520 patients. Although there is only a low level of confidence in the quality of the evidence, a statistically proven survival benefit from radioiodine therapy was already evident in the comparatively short follow-up period

Cribriform variant of the PTC

Compared to classic papillary thyroid carcinoma, lymph node metastases (12 %) and distant metastases (3 %) are observed less frequently in the rare cribriform variant at primary presentation. In addition, the recurrence rate (8.5 %) and mortality rate (2 %) are lower [605]. The recommendations of the classic PTC can be applied to this variant. In around 40% of cases, it is associated with a germline mutation, which is also the cause of familial adenomatous polyposis [606]. A corresponding clarification should be arranged.

Follicular variant of the PTC

Based on 10,740 patients from the SEER database, the follicular variant of papillary thyroid carcinoma resulted in a metastatic pattern between classic papillary thyroid carcinoma and follicular thyroid carcinoma and the long-term outcome was similar to that of classic papillary carcinoma [607]. Therefore, the recommendations for classic papillary thyroid carcinoma can in principle be transferred to the follicular variant. In the publication by Yu et al., 58% of patients with classic PTC and 56% of patients with the follicular variant of PTC received radioiodine therapy. The overall survival of both variants was practically identical (10-year and 15-year survival for both PTC entities 93% and 89% respectively) and significantly better than the survival rate of patients with an FTC (10-year survival 87% and 15-year survival 79%). The multivariate analysis showed a significant effect for patients with classic PTC (hazard ratio 0.7 [0.5 - 0.8]). For patients with follicular variant of PTC, a trend-like advantage could be proven with only half the number of cases (HR = 0.9 [0.6 - 1.4]) [607].

Diffuse sclerosing variant of PTC (PTC-DSV)

PTC-DSV is a rare histologic subgroup of PTC with a frequency of 0.7 - 6.6% of PTC cases. This variant predominantly affects adolescents and young adults and accounted for over 40% of thyroid carcinomas in the age group < 20 years in a retrospective analysis from South Korea [608]. Whether this distribution is transferable to Germany has not yet been investigated. This subtype is associated with therapeutic external cervical irradiation, has a higher rate of lymph node metastases at diagnosis and distant metastases in around 5% of cases, and showed a recurrence rate of 14% and a mortality rate of around 3% in a study by Pillai et al. [574]. In the study by Fukushima et al., disease-free survival in this group was worse than in the matched control group of classic PTC, which the authors attributed to the non-routine implementation

of adjuvant radioiodine therapy in this group [609]. Assuming more aggressive treatment with additional surgery and/or radioiodine therapy, the outcome of these patients is comparable to the high-risk group of the classic PTC [610]. The recommendations for classic PTC can therefore be transferred to PTC-DSV.

Solid variant of PTC (PTC-SV)

The solid variant of PTC is one of the rarest subtypes, accounting for only 3% of all PTCs [611], [612]. PTC-SV frequently occurred in children after the Chernobyl accident and accounted for over 30% of PTC variants in this group [613]. Despite advanced disease in some cases, this group showed a very good prognosis with a very low mortality rate of less than 1% in some cases [614]. However, a meta-analysis by Vuong et al. found that sporadic PTC-SV tends to occur in older patients compared to classic PTC and that the disease-free survival rate is lower than that of classic PTC [615]. As a limitation, however, it should be noted that the authors point out that the overall result was dominated by a single Japanese study [615]. Individual studies in this group also reported higher rates of lymph node metastases and distant metastases [612], [616]. However, Chang et al. did not find an increased risk of lymph node or distant metastases or an increased recurrence rate in their small group [617]. Data regarding the prognosis of PTC-SV therefore remain partly contradictory due to insufficient data. Overall, the recommendations for classic PTC should be applied to PTC-SV.

Tall cell variant of PTC (PTC-TCV)

The tall cell variant of PTC is regarded as an aggressive subtype of PTC, which has been attributed a poorer prognosis in various studies [618], [619], [620], [621], [622]. Compared to classic PTC, this group of patients more frequently exhibits extrathyroidal spread, macroscopic or microscopic residual tumor tissue, lymph node or distant metastases, as well as significantly shorter disease-free survival [619], [620], [621]. The published 10-year survival rates are between 50% and 80% [620], [623]. Surgery and radioiodine therapy significantly improved survival in this group [619]. In the comparative study by Holoubek et al., patients with a PTC-TCV who were treated more aggressively overall (total thyroidectomy and radioiodine therapy) showed a similar overall survival to the group of matched classic PTC [624]. In a further analysis, the same author found no improvement in patients with tumors up to 2 cm, whereas RIT improved survival in the group with tumors between 21 and 40 mm (83.4% vs 70%, p = .004) [602]. Overall, the prognosis in this group worsens as soon as invasive features are present [625]. In contrast, Regalbuto et al. were able to show that the treatment results of PTC-TCV patients were not worse than in the overall group of classic PTC patients. The treatment results of PTC-TCV patients were also better than those of patients with a classic "high risk" PTC [626]. In general, PTC-TCV have lower sodium iodide symporter expression [627]. These patients often require higher cumulative therapeutic activities to improve prognosis and are also more likely to be radioiodine refractory [627], [628]. However, it is important to note that the WHO modified the morphological criteria for the large cell variant of PTC in 2017 [629]. Among other things, ≥ 50% large-cell cells were previously required; in the updated version, ≥ 30% is sufficient. It is therefore assumed that this change will lead to an approximate tripling of the incidence of this variant [629]. Further studies using these new criteria are therefore needed to investigate and better assess the outcome of these patients. Currently, patients with PTC-TCV should be treated similarly to "high risk" PTC patients.

Columnar cell variant of PTC (PTC-CCV)

The columnar cell variant of PTC can be divided into two groups. On the one hand, there is the clinically indolent tumor type, which mainly affects younger patients (median 38 years) and predominantly women with smaller (mean 2.1 cm), encapsulated or well-circumscribed tumors and, on the other hand, the aggressive carcinomas, which occur in older, predominantly male patients (median 60 years) and have larger tumors (mean 6.7 cm) with diffuse infiltrative growth and extrathyroidal spread as well as lymph node and distant metastases [630], [631]. In their study, Song et al. showed that patients with PTC-CCV had a significantly shorter disease-free survival compared to classic PTC [632]. In addition, this PTC-CCV represents an independent risk factor for structurally persistent or recurrent disease [632]. Based on an analysis of the SEER database, it was shown that PTC-CCV is an independent predictor of tumor-specific mortality and that survival is significantly shorter than with classic PTC [633]. In their study, Wenig et al. concluded that although PTC-CCV is a distinct morphologic type, it is not a distinct clinical type of PTC and that treatment should therefore be based on the clinical stage and not the morphologic picture [634]. In view of this unfavorable histology, RIT is recommended [633].

Hobnail variant of PTC (PTC-HV)

The hobnail variant of PTC was first systematically described by Asioli et al. in 2010 and only recently included in the 2017 WHO classification of endocrine tumors [631], [635], [636]. Compared to patients with a classic PTC, this group often shows extrathyroidal spread (58% [637]), lymph node (75% [638]) and distant metastases (23%-44% [631], [639]) and responds only moderately to radioiodine therapy, which also leads to increased mortality overall [639]. However, in a study by Morandi et al. 6/18 patients showed a good response to RIT. 5/6 patients showed a recurrence 50 months after initial response to RIT. 7/18 patients showed a partial response to RIT [640], [639]. In the study by Asioli et al. the 10-year survival rate of these patients was only 64% [637]. Patients with PTC-HV should therefore be treated similarly to classic "high risk" PTC patients. In their review article, Donaldson et al. confirm the aggressive histology with the development of lymph node metastases in 66% of patients and distant metastases in 23% of patients in a follow-up period of 50 months [639].

Oncocytic variant of PTC (PTC-OV)

In the past, the oncocytic variant of PTC was often presented as a more aggressive and invasive variant of PTC [641], [642], [643]. However, other studies have concluded that PTC-OV has a similar prognosis to classic PTC after adjustment for risk factors [644], [645], [646]. In general, patients with PTC-OV are older [642], [645], [646] and have a larger tumor size [647], [646]. Wenter et al. [646] found a recurrence rate of 9% in the PTC-OV group, which was significantly lower than in other studies (19%-31%) [643], [648]. The authors [646] attributed the lower recurrence rate to the multimodal therapy. In contrast to the study by Hong et al. [643], in which only 50% of patients received radioiodine therapy, this was routinely carried out in the group of Wenter et al. Overall, the recurrence rate in patients with PTC-OV after adequate surgical treatment and adjuvant radioiodine therapy is low, which underlines the indication for RIT in patients with this entity.

5.8.2.6 Follicular thyroid carcinoma (FTC)

5.40	Consensus-based Recommendation	2025
EK	Minimally invasive, follicular thyroid carcinoma without vascular invasion that has been confirmed by quality-assured histopathology should not undergo radiotherapy.	
	Strong Consensus	

5.41	Consensus-based Recommendation	2025
EK	In minimally invasive, follicular thyroid carcinoma with vascular invasion, radioiodine therapy should be performed.	
	Strong Consensus	

5.42	Consensus-based Recommendation	2025
EK	Radioiodine therapy shall be carried out for grossly invasive follicular thyroid carcinoma.	
	Strong Consensus	

FTC (MIFTC without and with vascular invasion and grossly invasive FTC)

In follicular thyroid carcinomas, a distinction is made between minimally invasive follicular thyroid carcinoma (MIFTC) with the subgroups without and with vascular invasion and grossly invasive follicular thyroid carcinoma.

Cipriani et al. reported that the histopathologic classification of follicular thyroid carcinoma (FTC) can be difficult. In a retrospective analysis, the initial histopathologic diagnosis was revised in 47/66 FTC patients (71%). Survival in the FTC group was 77% after 10 years and 34% after 20 years [649]. The number of proven vascular invasions required to separate the entities has long been the subject of debate. Earlier work from the Sloan Catering Hospital described a maximum of 4 vascular invasions. Yamasaki et al. analyzed the data of 303 patients with encapsulated angioinvasive FTC from 2005 to 2014. 13/303 patients (4.3%) already had metastases at the time of diagnosis. In the remaining 290 M0 patients, the 10-year disease-free survival was 85.6%. Patients with a single (n = 131) vascular invasion had a 10-year disease-free survival of 94.9%. With 2 or more vascular invasions (n = 159), this fell to 77.9% ($p < 0.001$). An age of 55 years or older was an additional unfavorable prognostic factor. Patients aged 55 years or older with at least 2 vascular invasions had a disease-free 10-year survival of 66.4%. ($p < 0.0001$) [650].

Based on the SEER database, among 1,200 patients with MIFTC in 2000-2009, lymph node metastasis was observed in 0.9% and distant metastasis in 0.5% of patients, with 53.3% of patients having received RIT [259]. MIFTCs without vascular invasion, in which the classification as malignant is based solely on infiltration of the tumor capsule, have a favorable prognosis. In this case, thyroidectomy is not considered mandatory. Due to the low risk, RIT does not appear to offer a convincing advantage in this entity, although there is little data available. However, the observational study by O'Neill et al., in which the majority of patients with MIFTC without vascular invasion (43/61 patients, 70.5%) received RIT, showed that a lower rate of lymph node (n = 1) and distant metastases (n = 2) as well as tumor-associated deaths can also be expected in this tumor entity [651]. Disease-free survival with a median follow-up time of only 40 months was better in the group of MIFTC without vascular invasion (97%) than in patients with MIFTC with vascular invasion (81%) or in patients with grossly invasive FTC (45%) [651].

Ito et al. pointed out the significant impact of distant metastases in MIFTC and reported disease-specific 10-year survival rates of 99% for MIFTC patients without, as opposed to only 22% with, metastatic disease [652]. D'Avanzo et al. described distant metastases in only 1 of 45 patients (2.2%) with MIFTC without vascular invasion [653]. Recurrence occurred in 11% of these patients, most of whom were treated by lobectomy, and 8.8% died of tumor-related causes [653], [654].

Wu et al. reported on the poor prognosis of patients with FTC and distant metastases. 7-23% of FTC patients have distant metastases. 190 patients were followed up for a mean of 7.7 years, of which 29 patients already had metastases at the time of diagnosis and 14 patients developed metastases during the course of the disease. Patients with FTC that was already metastatic at diagnosis had the lowest cancer-specific 10-year survival rate (26.0%), followed by those who developed metastatic disease only after initial treatment (76.6%), while patients without metastases all survived (100%) ($p \leq 0.002$ for all comparisons) [655].

In one of the few studies that examined the survival of a larger number of patients with follicular thyroid carcinoma (FTC), Yang et al. conducted a retrospective analysis of 1,036 FTC patients from the National Cancer Database [561]. The survival rates for patients treated with RIT were significantly better than for patients who had only undergone surgery or external radiotherapy. In the univariate analysis, the hazard ratio for 5-year mortality with or without RIT in stage pT4aN0-1M0 was 0.54 (95% CI = 0.41 - 0.70; $p < 0.001$), in stage pT4bN0-1M0 0.31 (95% CI = 0.12 - 0.80; $p < 0.05$) and in stage pT1-4N0-1 M1 0.54 (95% CI = 0.38 - 0.76; $p < 0.001$). The hazard ratio for 10-year mortality in stage pT4aN0-1M0 was 0.62 (95% CI = 0.53 - 0.72; $p < 0.001$), in stage pT4bN0-1M0 0.35 (95% CI = 0.19 - 0.64; $p < 0.001$) and in stage pT1-4N0-1 M1 0.61 (95% CI = 0.46 - 0.81; $p < 0.001$). In FTC patients with stage pT1-4N0-1 M1, there was a clear difference in survival depending on the treatment modality: In the group treated with external beam radiation therapy (EBRT), mortality was 51% after 5 years and 60% after 10 years. Mortality in the group without adjuvant therapy was 46% after 5 years and 51% after 10 years. The group treated with radioiodine had the lowest mortality at 29% after 5 years and 37% after 10 years. Yang et al. were thus able to show that RIT in stage IV leads to both improved 5-year and 10-year overall survival.

5.8.2.7 Oncocytic thyroid carcinoma

5.43	Consensus-based Recommendation	2025
EK	In patients with oncocytic thyroid carcinoma, it should be checked once whether there is a therapeutically useful radioiodine storage or whether it can be treated with radioiodine. The exceptions are encapsulated oncocytic thyroid carcinomas with few capsular perforations and no vascular invasion, which are adequately treated by lobectomy.	
	Consensus	

According to the latest version of the WHO classification of endocrine tumors, oncocytic thyroid carcinoma (also known as oxyphilic or Hürthle cell carcinoma) is listed as an independent variant of differentiated carcinomas [656]. Oncocytic thyroid carcinoma is characterized by the fact that the sodium iodide symporter may be non-expressed or only very weakly expressed, whereas thyroglobulin production may be preserved. Patients with this histology should not be excluded from RIT from the outset. It should be checked at least once whether a therapeutically useful radioiodine storage is present or whether it is possible to treat with radioiodine. In addition, any tumor remnants/nests in the residual thyroid tissue can be eliminated by intensive co-irradiation in the crossfire.

Exceptions are encapsulated oncocytic carcinomas with few capsular perforations and no vascular invasion, which are adequately treated by lobectomy.

The recurrence rate of oncocytic thyroid carcinoma varies between 6% (12/207 patients, mean follow-up 55 months) [657] and 12.1% (239 patients, mean follow-up 91 months) [658].

The extent to which follicular oncocytic thyroid carcinoma behaves more aggressively than classic follicular thyroid carcinoma is still the subject of controversy. Hundahl et al. were able to show that after 10 years there is a significantly lower overall survival in the group with Hürthle cell carcinoma (76% vs. 85%) [659]. However, other studies conclude that the prognosis of Hürthle cell carcinoma and classic FTC is similar, provided the risk factors are matched [660], [661], [646].

López-Penabad et al. showed in a subgroup analysis that overall mortality was lower in patients who received adjuvant RIT compared to patients who did not receive adjuvant RIT or received RIT only in the case of persistent disease (p=0.0022 and Fig. 3 in the publication) [662]. Of the 37 metastatic patients with Hürthle cell carcinoma, 14 patients with metastases (38%) showed radioiodine accumulation [662]. In their study, Jillard et al. were able to show that the 5- and 10-year survival rates were significantly higher in patients after RIT compared to patients without RIT (88.9 vs. 83.1% and 74.4 vs. 65.0%) [663].

5.8.2.8 PDTC (poorly differentiated thyroid carcinoma)

5.44	Evidence-based Recommendation	2025
GoR **B**	In patients with poorly differentiated thyroid carcinoma (PDTC) and differentiated high-grade thyroid carcinoma (DHGTC), it should be checked once whether there is a therapeutically useful radioiodine storage or whether it can be treated with radioiodine.	
LoE **2b**	2b: OS [664]	
	Consensus	

Poorly differentiated thyroid carcinoma is a rare but aggressive variant of thyroid carcinoma. PDTC most frequently metastasizes to the lungs and bones [513], [665], [666]. Apart from anaplastic thyroid carcinoma, poorly differentiated thyroid carcinoma accounts for the largest proportion of thyroid carcinoma-associated deaths [665], [666]. The survival rate is 72% after 5 years and 46% after 10 years [635].

Poorly differentiated thyroid carcinoma is characterized by the fact that the sodium iodide symporter may be absent or only weakly expressed, whereas thyroglobulin secretion is well preserved.

Xu et al. [664] conducted a retrospective cohort study and included a total of 882 patients from the SEER database with poorly differentiated thyroid cancer and compared the overall survival of patients with and without radioiodine therapy. The hazard ratio in favor of radioiodine therapy was 0.57 (0.44 - 0.75; P <0.001). It should be noted that the risk profile was less favorable in the radioiodine therapy group, which means that the actual positive effect of radioiodine therapy is not fully captured. In the case of low confidence in the quality of evidence of the study, which also proves a survival advantage for radioiodine therapy for the PDTC, the recommendation arises to at least check the iodine storage capacity of a PDTC.

Differentiated high-grade thyroid carcinoma was an undefined subgroup of PDTC before the new WHO classification in 2022. A differentiated consideration of the subgroups has not yet taken place. DHGT should therefore continue to be considered in the same way as PDTC.

5.8.3 Postoperative thyroglobulin value

5.45	Consensus-based Recommendation	2025
EK	A postoperatively low basal thyroglobulin value (< 2ng/ml) does not rule out lymph node and distant metastases and shall therefore not be used as the sole parameter for further treatment decisions.	
	Strong Consensus	

After complete thyroidectomy and RIT, thyroglobulin (Tg) is usually no longer measurable or is below 0.5 ng/ml (calibrated to the European standard), making it an excellent tumor marker. After incomplete thyroidectomy, however, the significance of the Tg determination is limited. The thyroglobulin determination has a high clinical value in follow-up care.

A low basal thyroglobulin level after thyroidectomy alone cannot be used to rule out metastases. For example, in the study by Park et al. [667], iodine-avid metastases were found in 6.3% of patients (52/824) after thyroidectomy for thyroid carcinoma despite a postoperatively low thyroglobulin level < 2 ng/ml without antibodies against thyroglobulin. A similar observation for patients with an intermediate risk of recurrence and a postoperative Tg level < 0.6 ng/ml comes from the Memorial Sloan-Kettering Cancer Center in New York. Post-therapeutic ^{131}I-SPECT/CT identified iodine-storing metastases in 17/146 patients (12%); lymph node metastases were predominant [668].

Prabhu et al. reported that a stimulated thyroglobulin value without interfering antibodies < 1 ng/ml largely excludes metastases, whereas a value of > 5 ng/ml has a 26% probability of metastases [669]. In this study, however, planar whole-body scintigraphy, which is no longer adequate today, served as a reference. Other authors come to the opposite conclusion - also on the basis of planar whole-body scintigraphy [670]. Matrone et al. showed in 505 patients after thyroidectomy that metastases could be detected despite a low thyroglobulin value: 15/287 (5%) patients with a thyroglobulin value ≤ 1 ng/ml and 11/68 patients (16.2%) with a thyroglobulin value > 1 ng/ml had metastases [671].

Campenni et al. reported in 570 DTC patients at low and intermediate risk of recurrence that posttherapeutic radioiodine imaging including SPECT/CT identified 82 patients (14.4%) with metastases, of whom 73 patients (90.2%) had a non-stimulated Tg ≤ 1 ng/ml after surgery. In addition, 44 patients (54 %) of 82 metastatic patients had a stimulated Tg ≤ 1 ng/ml [672].

5.8.4 Diagnostics before radioiodine therapy

5.46	Consensus-based Recommendation	2025
EK	CT, MRI, [^{18}F]FDG-PET/CT, or [^{18}F]FDG-PET/MRI examinations should be reserved for special questions and can be carried out after radioiodine therapy if necessary.	
	Consensus	

5.47	Consensus-based Recommendation	2025
EK	If imaging using iodine-containing contrast agents is indicated, this examination shall be performed after ^{131}I whole-body scintigraphy, if clinically justifiable.	
	Strong Consensus	

5.48	Consensus-based Recommendation	2025
EK	After thyroidectomy and before radioiodine therapy, TSH and thyroglobulin including TgAb shall be determined. Other laboratory parameters (blood count, kidney function) should be known.	
	Strong Consensus	

5.49	Consensus-based Recommendation	2025
EK	A lung function test can be performed in the case of multiple or disseminated lung metastases.	
	Strong Consensus	

As a rule, the postoperative presentation for RIT takes place shortly after the surgery. Examinations prior to RIT are used to detect residual thyroid tissue and to plan RIT.

Scintigraphy

Postoperative functional residual thyroid tissue can be detected by scintigraphy if this is of clinical relevance for planning the further therapeutic procedure. Scintigraphy with a suitable radiopharmaceutical (e.g. ^{123}I, ^{131}I in low activity) is used to visualize functional residual thyroid tissue and possibly lymph node metastases. This is the case in special situations when relevant thyroid remnants or lymph node metastases are suspected after surgery that would prevent radioiodine therapy. In the study by Mallick et al., ^{99m}Tc scintigraphy (pertechnetate scintigraphy) was performed prior to RIT in order to visualize thyroid remnants. 2.3% of patients had a large remnant [673]. If diagnostics are performed with ^{131}I, the lowest possible activities ≤ 15 MBq ^{131}I may be used to avoid interference in subsequent therapy.

Examinations prior to RIT for suspected or known lung metastases

If a CT scan is planned for suspected lung metastases, this must be performed without iodine-containing CA, i.e. natively. If X-ray contrast medium has been used, RIT will be postponed by at least 2-3 months. In the case of pronounced lung metastasis, a pulmonary function test serves to document the functional lung status prior to RIT and is a starting point for any follow-up examinations. Forensic considerations also speak in favor of this.

CT, MRI, [^{18}F]FDG-PET/CT, or [^{18}F]FDG-PET/MRI examinations

Further imaging with CT, MRI or PET is generally not required at the time of the immediate postoperative presentation.

Laboratory

The determination of TSH and thyroglobulin using a modern assay with a low lower detection limit (≤ 0.2 ng/ml) is mandatory and is part of the standard examination in

combination with Tg antibodies. The biological half-life of Tg is approx. 1 to 2 days, which must be taken into account when interpreting the measured values. The bone marrow dose is not only influenced by the applied ^{131}I activity, but also by the kidney function. A differential blood count and the creatinine value are therefore usually determined before RIT.

The measurement of iodine excretion in urine is suitable for identifying patients with high iodine incorporation.

5.8.5 Special aspects of pre-therapeutic iodine imaging/dosimetry

5.50	Consensus-based Recommendation	2025
EK	Pre-therapeutic iodine imaging and dosimetry may be performed in individual cases.	
	Strong Consensus	

For valid dosimetry, the use of[^{124}I]-PET/CT is to be regarded as a superior method. This method is only available to a few centers. Stunning is not to be expected due to the low required activities (25-50 MBq) of the positron emitter. Dosimetry enables an individual treatment decision to be made in the case of detectable metastases. If iodine uptake is low, RIT can be dispensed with or - if possible - the planned focal dose can still be achieved by increasing the activity [674], [675], [676].

In a retrospective, monoinstitutional study from the USA, an improvement in survival was shown for patients with lymph node metastases and distant metastases through individual dosimetry [677]. There is a lack of prospective, randomized data showing that pre-therapeutic dosimetry has a clear beneficial effect on the response rate for metastases as measured by response criteria (RECIST 1.1) or on the survival rate compared to the use of standard activities.

The pre-therapeutic use of ^{123}I or ^{131}I is not a standard procedure, but can be used in individual case indications [678]. As there are no outcome-based data on dosimetry prior to adjuvant RIT, no general recommendation can be made for such a procedure. Regular pre-therapeutic dosimetry is not necessary, but in individual cases it can be helpful in determining treatment activity. The caution with regard to iodine imaging prior to RIT is shared by experts [679].

5.8.6 Preparatory measures for radioiodine therapy

5.8.6.1 Pregnancy exclusion before RIT

5.51	Consensus-based Recommendation	2025
EK	Pregnancy shall be ruled out before radioiodine therapy.	
	Strong Consensus	

Pregnancy is an absolute contraindication for RIT and must therefore be ruled out before RIT in order to prevent therapeutic irradiation of the embryo or fetus.

5.8.6.2 Weaning and radioiodine application

5.52	Consensus-based Recommendation	2025
EK	There should be a latency of at least 8 weeks, but preferably 6 months, between weaning and radioiodine application.	
	Strong Consensus	

The lactating breast accumulates radioiodine to a considerable extent. Robinson et al. calculated that after administration of 4.0 GBq ^{131}I the lactating mamma receives 1.6 Gy dose [680]. Breastfeeding should be stopped at least 8 weeks before a ^{131}I application in order to limit the radiation exposure of the mammae [680]. An increased mammary uptake may still be detectable 3 - 4 months after discontinuation of breastfeeding, so that an appropriate latency phase until RIT should be considered on an individual basis. If necessary, mammary iodine retention can be checked pre-therapeutically with a low activity of ^{123}I. The actual risk of additional radiation exposure can only be estimated theoretically. For a woman without a disease-related reduction in life expectancy whose breast is exposed at the age of 30 years, the expected additional lifetime risk of radiation-induced breast cancer is 0.3% per 100 mGy [681].

5.8.6.3 Relative contraindications

5.53	Consensus-based Recommendation	2025
EK	Relative contraindications shall also be taken into account when determining the indication for radioiodine therapy.	
	Strong Consensus	

Relative contraindications to RIT include

- Severe bone marrow depression if high-dose therapy is planned.
- Significant impairment of lung function if relevant pulmonary storage is to be expected.
- Symptomatic spinal or cerebral metastases that pose a risk of progressive compression symptoms under RIT.
- Pre-existing significant xerostomia with proven symptomatic functional impairment of the salivary glands must be considered as an additional risk when determining the indication for RIT

5.8.6.4 Contraception after RIT

5.54	Consensus-based Recommendation	2025
EK	After radioiodine therapy, patients of childbearing age should avoid pregnancy for 6 to 12 months.	
	Strong Consensus	

Schlumberger et al. [682] reported on 2,113 pregnancies in women with thyroid carcinoma. Before any therapy, the rate of miscarriage was 11%, after thyroidectomy 20% regardless of RIT. However, 4/10 women who had RIT one year before conception suffered a miscarriage. There was no increase in the incidence of premature birth, low birth weight, malformations, or infant death [682].

Metallo et al. reported no fertility impairment in women who had been treated with radioiodine for DTC in childhood or adolescence. 30 pregnancies after RIT were found in patients from the > 3.85 GBq group and 10 in patients from the ≤ 3.85 GBq group. The frequency of miscarriages was 17 % (group > 3.85 GBq) and 10 % (group ≤ 3.85 GBq) with 9 and 24 live births respectively. A causal relationship with the RIT has not been proven. Other possible causes could be an unstable thyroid hormone setting or pregnancy at an older age. Metallo et al. found no congenital malformations and no increased mortality in the first year [683].

In 111,459 Korean women aged 20-49 years after thyroidectomy for differentiated thyroid carcinoma, Kim et al. found no increased rate of miscarriage, preterm birth or congenital malformations when conception occurred 6 months after RIT [684].

After RIT, the avoidance of pregnancy by adequate contraceptive methods is therefore recommended for at least 6 months in patients of childbearing potential. A more recent meta-analysis by Zhang et al. analyzed 125,591 women with 13,811 pregnancies. It was found that postoperative RIT had no significant effect on the spontaneous abortion rate (OR = 1.05, P = 0.701), induced abortion (OR = 1.06, P = 0. 859), the rate of miscarriages (OR = 1.07, P = 0.098), the rate of premature births (OR = 1.02, P = 0.756), the rate of stillbirths (OR = 1.58, P = 0.364), or congenital malformations (OR = 1.00, P = 0.986). The cumulative treatment activity >3.7 GBq or <3.7 GBq had no significant effect on miscarriages (OR = 0.94, P = 0.252) or congenital malformations (OR = 1.05, P = 0.752). If the interval between the last RIT and the pregnancy > was 1 year, this group had a significantly lower risk of miscarriage than the group with an interval of < 1 year (OR = 0.60, p = 0.001) [200].

If a pregnancy or conception occurs within the above-mentioned waiting periods, this does not automatically constitute an indication for an abortion. Risk assessment counseling is recommended. Good hydration with frequent emptying of the bladder and avoidance of constipation reduce the radiation exposure of the gonads.

5.8.6.5 Cryopreservation/procreative leave

5.55	Consensus-based Recommendation	2025
EK	Cryopreservation of sperm can be offered if the expected cumulative gonadal dose exceeds 1 Gy, which is only exceeded in exceptional cases for total activities up to 12 GBq ^{131}I. In men, contraception should be observed for 4 months after radioiodine therapy.	
	Strong Consensus	

Aspects of cryopreservation are clinically relevant if family planning has not yet been completed. Reference should be made here to the corresponding S2k guideline "Fertility preservation in oncological diseases" (https://register.awmf.org/de/leitlinien/detail/015-082).

The estimated dose for the testicles is 85 mGy/3.7 GBq - an increase in gamete mutations is only expected above 1 Gy [685]. The occurrence of transient or permanent oligospermia or azoospermia is described as dependent on the cumulative treatment activity. The gonadal organ dose can be reduced by adequate hydration and regular, sufficient bladder and bowel emptying [686].

The risk of permanent fertility reduction after a single adjuvant RIT is very low for men [687], [60], [688]. Regular cryopreservation is therefore not considered necessary. A mostly transient oligospermia as well as a reduced percentage of morphologically normal spermatozoa can occur after a single administration of 3.7-5.5 GBq radioiodine, whereby normalization can be expected after 12-18 months [689], [690], [688]. Increased levels of follicle-stimulating hormone (FSH) in the blood have been reported. However, an increase in FSH can also be expected as a result of low-dose irradiation of the pituitary gland.

Permanent oligospermia to azoospermia have been reported from an activity of 13 GBq radioiodine, which is why some authors recommend cryopreservation of sperm from therapy activities of 12 GBq ^{131}I [691]. Performing multiple cycles of RIT can lead to permanent impairment of gonadal function in men [692]. If high accumulated therapy activities (e.g. ≥ 11-15 GBq ^{131}I or ≥ 2 high-dose radioiodine therapy) are to be expected, sperm cryopreservation can be considered for patients without completed family planning.

For men, a fertility waiting period of 4 months after RIT is recommended. This recommendation is based on the life cycle of the spermatozoa of 4 months.

5.56	Evidence-based Recommendation	2025
GoR **B**	A negative influence of radioiodine therapy on female fertility is not to be expected with adjuvant radioiodine therapy and earlier radioiodine therapy should not be seen as an obstacle to pregnancy.	
LoE ⊕⊖⊖⊖	⊕⊖⊖⊖: Infertility [693], [694]	
	Strong Consensus	

Piek et al. [693] considered 26 publications in their meta-analysis and investigated the influence of radioiodine therapy on ovarian function and fertility in women with thyroid cancer. Irregularities in the menstrual cycle were found in 12 to 31% of patients in the first year of radioiodine therapy and thyroid hormone replacement therapy. 8 to 16% of patients had amenorrhea in the first year. The patients who had radioiodine therapy entered the menopause slightly earlier at 49.5 years than a comparison group without radioiodine therapy at 51 years. In four studies, the anti-Müllerian hormone was lower in patients who had radioiodine therapy than in comparison groups without radioiodine therapy. However, the meta-analysis did not show any restriction in becoming pregnant, i.e. no restriction in fertility. The result is associated with a very low quality of evidence.

It is unclear what influence the diagnosis of malignancy, thyroidectomy and thyroid hormone replacement therapy had on the cycle disorders. Cycle disorders with oligomenorrhea or amenorrhea may be the result of inadequate adjustment of thyroid hormone replacement. Patients who wish to have children should have their thyroid hormone parameters adjusted to euthyroid levels.

Zhang et al. [694] published a meta-analysis of seven observational studies with 125,591 women and 13,811 pregnancies. Postoperative radioiodine therapy for DTC had no significant effect on the spontaneous abortion rate (OR = 1.05, p = 0.701), induced abortion (OR = 1.06, p = 0.859), the miscarriage rate (OR = 1.07, p = 0.098), the premature birth rate (OR = 1.02, p = 0.756), the stillbirth rate (OR = 1.58, p = 0.364), or congenital malformations (OR = 1.00, p = 0.986). No dependence on the radiation dose was found. The cumulative radioiodine activity >3.7 GBq or <3.7 GBq had no significant effect on abortions (OR = 0.94, P = 0.252) or congenital malformations (OR = 1.05, P = 0.752).

These observations are supplemented by observations on radiation exposure: The dose for the ovaries is approx. 140 mGy (= 0.14 Gy) /3.7 MBq. An increase in gamete/oocyte mutations is only expected above 1 Gy [694]. There is insufficient data on the cryopreservation of oocytes. An individual decision would have to be made here, especially if an ovarian dose of over 1 Gy is to be expected, which corresponds to a cumulative activity of > 26 GBq ^{131}I.
Radioiodine therapy, especially adjuvant radioiodine therapy, is therefore not an obstacle to pregnancy.

Women in whom the interval between the last radioiodine therapy and pregnancy was

>1 year had a significantly lower risk of miscarriage than women in whom the interval was <1 year (OR = 0.60, P = 0.000). [694]

5.8.6.6 Iodine restriction

5.57	Consensus-based Recommendation	2025
EK	A diet rich in iodine shall be avoided for approx. 14 days prior to radioiodine therapy. Any increased iodine intake (e.g. iodine-containing medication and food supplements, disinfectants, algae products) shall be avoided for at least 6 to 8 weeks.	
	Strong Consensus	

High iodine intake shall be avoided before RIT, as this competitively reduces iodine uptake in metastases and residual tissue [695]. High iodine incorporation ("iodine contamination"), e.g. through iodine-containing X-ray contrast media, iodine-containing medication, and cutaneous contact with iodine, e.g. with iodine-containing disinfectants, prevent successful RIT, sometimes for a longer period of time. This also applies to external agents such as disinfectants or iodine-containing ointments (e.g. povidone-iodine [Betaisodona®]) for external application (also when used on other people or on animals), as iodine is easily absorbed through the skin. Just one drop of an iodine-containing solution on the skin can impair RIT.

Foods particularly rich in iodine are iodine-containing multivitamin or trace element combinations or seaweed. The duration of a low iodine diet prior to RIT is largely based on expert consensus based on clinical experience. Dietary iodine restriction (1-) 2 weeks prior to RIT appears to be advisable. High iodine exposure requires postponement of RIT for up to 4 months until normalization of urinary iodine excretion.

A study conducted by Pluijmen et al. on 120 patients showed that a low-iodine diet reduced 24-hour urinary excretion of iodine by 83%; at the same time, radioiodine uptake in thyroid remnants increased compared to controls. The effectiveness of RIT in terms of successful ablation was better in the low-iodine group in 65% compared to 48% of patients in the control group ($p < 0.001$) [696]. Sohn et al. also showed that high urinary iodine excretion (> 250 µg iodine / g creatinine) reduces the effectiveness of RIT [697]. Dobrenic et al. confirmed that a two-week low-iodine diet can significantly reduce urinary iodine excretion prior to RIT [698].

The short-term discontinuation of levothyroxine medication prior to thyrotrophin alpha administration, e.g. starting 5 days before the first thyrotrophin alpha injection, is another way of reducing iodine intake pre-therapeutically [699]; however, the effect is small. If iodine-containing X-ray contrast medium has been given, a period of 8 - 12 weeks before RIT is recommended. Lan et al. were able to show that X-ray contrast medium prior to RIT worsens the response rate, which is why these authors recommended a waiting period of 3-4 months [700]. Significantly longer time intervals of ≥ 12 months until RIT is performed may be necessary after discontinuation of amiodarone, if necessary measuring urinary iodine excretion [60], [701]. In these cases, it is recommended to determine the iodine excretion in the urine before the RIT.

However, an iodine allergy is not a contraindication for carrying out an RIT [702]. One GBq ^{131}I corresponds to about 200 ng iodide and thus roughly the natural amount of iodine in 5g of bread.

5.8.6.7 Salivary gland protection

5.58	Consensus-based Recommendation	2025
EK	Lemon or (acidic) candies can be used to stimulate salivation with the aim of increasing radioiodine secretion; the evidence for measures to protect the salivary glands is limited.	
	Strong Consensus	

Whether and when the stimulation of salivary flow (e.g. lemon juice, sour candies) is of benefit in reducing the radiation exposure of the salivary gland remains unclear. There is little evidence on the clinical benefit and optimal timing of the use of salivary gland protection. The available data do not allow a clear recommendation as to when the administration of lemon should be started [703]. If these measures are used, this should not be done immediately after administration of the therapeutic activity, as otherwise there may be an undesirable increase in blood flow and thus an increased accumulation of activity in the salivary glands at the time of the highest radioiodine concentration [704]. Other measures to minimize damage to the salivary glands, such as the infusion of amifostine, the administration of cholinergic substances or good hydration are also insufficiently proven in their benefit to make a recommendation for or against them. Such drug therapy is not generally used. The saliva empties significantly during meals (through chewing), so it may be advantageous to schedule the time of application on the day of admission sufficiently early before the midday meal [705].

5.8.6.8 Endogenous versus exogenous stimulation (hypothyroidism versus thyrotrophin alpha)

5.59	Evidence-based Recommendation	2025
GoR A	If the risk of recurrence is low, the variants of TSH stimulation (endogenous versus exogenous with thyrotropin alpha) for adjuvant radioiodine therapy shall be discussed with the patient and the procedure determined together with the patient.	
LoE ⊕⊕⊕⊖ - ⊕⊕⊖⊖	⊕⊕⊕⊖: Successful ablation, follow-up 12 months ⊕⊕⊖⊖: Quality of life, follow-up 12 months ⊕⊕⊕⊕: Side effects [706]	
	Strong Consensus	

5.60	Evidence-based Recommendation	2025
GoR **B**	In high-risk patients, TSH secretion should be stimulated endogenously, provided there are no contraindications to hypothyroidism.	
LoE ⊕⊕⊕⊖	⊕⊕⊕⊖: Endogenous TSH stimulation [706]	
	Strong Consensus	

For radioiodine therapy after surgery, TSH stimulation is required to optimize iodine uptake into the residual thyroid tissue. This can be achieved either by hormone deprivation (endogenous) or by injection of thyrotropin alpha (recombinant TSH = rhTSH). Thyrotropin alpha is not approved for metastasis therapy, but aims to ablate residual thyroid tissue.

In the case of endogenous stimulation, the effectiveness of ablative radioiodine therapy and radioiodine therapy of metastases depends on the TSH level; a TSH > 30 mU/l is favorable. This TSH level is usually reached 2 - 3 weeks after thyroidectomy or 4 - 5 weeks after discontinuation of levothyroxine (T4) medication. In order to shorten the period of hormone abstinence, a bridging 1 to 2-week triiodothyronine (T3) medication can be given up to 2 weeks before radioiodine therapy after discontinuation of levothyroxine medication, although an improvement in quality of life through bridging triiodothyronine administration has not been proven [707].

Fu et al. published a meta-analysis of 7 randomized controlled trials and 1,325 patients [706]. The results compared thyroid hormone withdrawal versus thyrotropin alpha. The thyroid restablation rate was not significantly different between the two methods (OR 0.87, 95%CI 0.56-1.37, p=0.56). Significantly different were aspects of quality of life with a mean difference of 3.59, 95%CI 2.81-4.37, p < 0.00001) on a scale of 0 to 100 as well as adverse events during and after ablation (OR 0.57, 95% CI 0,44 to 0.73, P<0.00001) and radiation exposure of blood and bone marrow (mean difference -0.01, 95% CI -0.02 to -0.01, P<0.00001), the associated higher irradiation of tumor tissue could not be recorded for methodological reasons. In addition, no significant difference in the successful ablation rate was found between the low activity (1.11 GBq and 1.85 GBq) and the higher activity (3.7 GBq) of radioiodine using rhTSH (OR 0.85, 95% CI 0.49 to 1.47, P=0.56). There were no deaths and no serious adverse effects in DTC patients treated with either rhTSH or THW. Thyrotropin alpha is thus as effective as hormone deprivation in radioiodine ablation of thyroid remnants, with significant benefits in health-related quality of life, adverse effects during and after ablation, and reduced whole-body radiation exposure [706]. This justifies the preferred use of thyrotropin alpha in patients with a low risk of recurrence (recommendation Recommendation 5.60).

In the case of certain comorbidities such as cardiopulmonary diseases, diabetes mellitus, renal insufficiency, neurological and psychiatric diseases (e.g. manic-depressive illness or schizophrenia) and bilateral recurrent paresis (risk of glottic edema in the case of severe hypothyroidism), several weeks of hormone abstinence with the consequence of manifest hypothyroidism is not indicated. In these situations, thyrotrophin

alpha is the stimulation method of choice. In patients with a hypothalamic/pituitary disorder in the thyroid hormone control circuit, treatment with thyrotrophin alpha is the only way to achieve sufficient TSH stimulation. The medication history is also important, as prolonged hypothyroidism increases (e.g. lithium) or decreases (e.g. anticoagulants) the effect of individual medications [708]. In a retrospective study, Gomes-Lima et al. showed that preparation with endogenous and exogenous TSH stimulation made no difference in PFS or OS even in high-risk patients with limited follow-up time.

In the publication by Fu et al. [706], special reference should be made to two prospective studies: HiLo with 438 patients [673] and ESTIMABL with 752 patients [709]. These prospective studies compared the efficiency of residual tissue elimination in terms of "ablative" therapy. The inclusion criteria varied between the studies and mainly included patients with pT1-T3 tumors, N0 or Nx. The definitions of successful ablation were not homogeneous. Distant metastases (M1) were regularly an exclusion criterion. Therefore, hormone deprivation is preferred for patients with a high risk of recurrence or for metastasis therapy, as a higher focal or tumor dose can be expected with hormone deprivation [710], [676]. The statement that lower and higher therapy activities bring the same success is also not homogeneous. In fact, the HiLo study in the thyrotrophin alpha group showed a 6 percentage points worse ablation success in the low-dose group (1.1 GBq ^{131}I) compared to the group treated with 3.7 GBq ^{131}I. Therefore, the selected therapy activity should be based on the risk of recurrence.

5.8.6.9 Laxatives

5.61	Consensus-based Recommendation	2025
EK	To reduce radiation exposure, a (mild) laxative should be used and the bladder emptied frequently in the first few days after application of the therapy activity.	
	Strong Consensus	

Adequate fluid intake and regular emptying of the bladder reduce radiation exposure. Laxatives can be used to regulate the stool and also aim to reduce radiation exposure; in addition, the informative value of ^{131}I whole-body scintigraphy is improved due to less non-specific intestinal accumulation. Drug intervention must be considered in relation to possible side effects. It is obvious that a shorter dwell time of the activity in the body and close to the gonads reduces the dose. Therefore, the indication for laxatives can be generous in terms of radiation protection. Lactulose syrup is suitable as a (mild) laxative (10-20 ml), possibly in combination with dimethicone (sab simplex). Alternatively, lecicarbon suppositories or sodium picosulphate (drops/suppositories/tablets) can be used. As far as the bladder is concerned, a good filling is already very helpful due to the self-shielding effect. Even more important than frequent emptying is therefore a good fluid intake, taking into account individual patient factors (e.g. cardiac or renal insufficiency).

5.8.7 Therapy activity in radioiodine therapy

5.62	Evidence-based Recommendation	2025
GoR **B/0**	For radioiodine therapy, the activity of ^{131}I should be selected in a risk-adapted manner, so that the therapeutic success is achieved as far as possible through single-stage radioiodine therapy. If metastasis is known, higher therapy activities can be given.	
LoE ⊕⊕⊕⊖ - ⊕⊖⊖⊖	⊕⊕⊕⊖: successful ablation rate under high dose higher than under low dose, adjuvant RIT / metastasis therapy ⊕⊖⊖⊖: tendency towards more side effects in the high dose group [711], [712], [713], [714]	
	Strong Consensus	

Table 18: The table shows the range usually depending on the risk of the therapy activities used.

Risk classification	Activity of ^{131}I
Papillary microcarcinoma (PTC pT1a, PTMC) without risk factors	No RIT
Papillary microcarcinoma (PTMC) with risk factors	1.0 - 4.0 GBq
PTC pT1b	1.0 - 4.0 GBq (individual decision)
PTC pT2	1.0 - 4.0 GBq
PTC pT3	2.0 - 5.5 GBq
PTC pT4	3.5 - 7.5 GBq
PTC, aggressive histologic subtypes	2.0 - 7.5 GBq
PTC Nx / N1	2.0 - 7.5 GBq (with N1 persistence up to 12 GBq)
PTC M1	5.5 - 12 GBq (or individually or dosimetry-controlled with a target dose of ≥ 100 Gy in the tumor, taking into account bone marrow and lung tolerances)

Risk classification	Activity of ^{131}I
FTC, minimally invasive, without vascular invasion	No RIT
FTC, minimally invasive, with vascular invasion	3.5 - 7.5 GBq
FTC, grossly invasive	3.5 - 12 GBq (or individual or dosimetry-guided with a target dose of ≥ 100 Gy in the tumor, taking into account bone marrow and lung tolerances)

Studies on radioiodine therapy usually focus on the ablation of residual thyroid tissue that remains after thyroidectomy, but which still produces thyroglobulin and thus makes thyroglobulin-based follow-up at least more difficult if it is left in place. In these studies, different therapeutic activities were compared in order to achieve a defined ablation success. A "low-dose" activity is usually defined as 1 GBq (27 mCi) or 2 GBq (54 mCi), while a "high-dose" activity is defined as 3.7 GBq (100 mCi) or an even higher radioiodine activity. The definition of ablation success varies between studies. It is usually defined as an unremarkable ^{131}I whole-body scintigraphy 6 to 12 months after radioiodine therapy and a stimulated (rhTSH) thyroglobulin level below a certain threshold, which is sometimes below the functional assay sensitivity and sometimes below 1 or 2 ng/ml.

Ma et al. studied 278 evaluable Chinese PTC or FTC patients with stage T1 to T3, N0 or Nx or N1, M0 tumors, of which 155 patients had received 1.85 GBq (50 mCi) and 123 patients had received 3.7 GBq (100 mCi) [711]. Ablation success was defined by a thyroglobulin value of ≤ 2 ng/ml 6 or 9 months after radioiodine therapy. This was achieved by 87.1% in the "low dose" group and 89% in the "high dose" group; this was not statistically significantly different (p = 0.569). A second ablation was required by 27 patients (17.4%) in the low dose group and 17 patients (13.8%) in the high dose group. No recurrences occurred during the 2 to 3-year follow-up. Changes in blood count, liver or kidney function were seen in less than 4.1% of patients and were not significantly different between the groups. Side effects such as nausea, taste changes, or salivary gland dysfunction were not investigated in this study.

Qu et al. examined the effects between a "low-dose" group treated with 1.1 GBq (30 mCi) and a "high-dose" group that received 3.7 GBq (100 mCi) of radioiodine [712]. The patients had a differentiated thyroid carcinoma with a low or intermediate risk of recurrence T1 N0-1M0. In the low-dose group 53/66 patients (80%) and in the high-dose group 56/66 patients (85%) had an excellent response. The remaining patients had an intermediate (13/66 in the low-dose group and 7/66 in the high-dose group) or biochemically incomplete (0/66 in the low-dose group and 3/66 in the high-dose group) response. The differences were not significant (p = 0.087). Patients with lymph node metastases (N1b) had significantly worse ablation results. Side effects were higher in the high-dose group (39%) than in the low-dose group (18%).

In their study, Jin et al. chose staggered treatment activities of 1.1, 1.85, 3.7 and 5.5 GBq radioiodine depending on the radioiodine uptake (≤2%, 2-5%, 5-15%, > 15%) and the thyroglobulin level (≤ 2, 2-5, 5-10, > 10 ng/ml) [714]. 215 patients with differentiated thyroid carcinoma were treated; patients with distant metastases were excluded. In addition, there was a group of 62 patients with fixed therapy activity of 3.7 GBq radioiodine. The radioiodine uptake was measured after application of 0.185 MBq radioiodine. If the radioiodine uptake and the thyroglobulin value were not in the same category, the next higher therapy activity was applied. Successful radioiodine therapy was defined as a negative whole-body scintigraphy and a stimulated (rhTSH) thyroglobulin value below 1 ng/ml (TgAb negative) or only a negative whole-body scintigraphy with positive thyroglobulin antibodies at the earliest 6 months after radioiodine therapy. The success rate between the groups was not statistically significantly different between the groups (p = 0.543). In contrast, the rate of side effects was lower in patients treated according to radioiodine uptake and thyroglobulin levels. This was particularly true for xerostomia, with 9.2% in the group treated according to radioiodine uptake and thyroglobulin level versus 19% (p = 0.038) in the group treated with 3.7 GBq radioiodine.

Shengguang et al. published a meta-analysis of 14 randomized controlled trials. Three groups were compared according to treatment activity (1.1 GBq versus 1.85 GBq versus 3.7 GBq, corresponding to 30, 50, and 100 mCi) [713]. When comparing 1.1 with 1.85 GBq and 1.85 and 3.7 GBq radioiodine, there were no significant differences. The comparison of 1.1 with 3.7 GBq showed a 5% lower rate of successful residual tissue ablation. The analysis showed that 3.7 GBq (100 mCi) radioiodine is favored in Europe, especially when the extent of surgery was not a total thyroidectomy and residual thyroid tissue was still present after incomplete resection. The rate of side effects was not investigated.

These studies justify the recommendation Recommendation 5.32 on the choice of treatment activity so that, depending on the extent of resection, an excellent response is achieved with a single radioiodine therapy if possible and a second ablation therapy is avoided. The studies ([711], [712], [714] and [713]) excluded metastatic patients and refer to the situation of "radioiodine ablation". For the success rate of residual tissue ablation therapy, there is an advantage for a higher activity with moderate quality of evidence, but also a margin for the choice of activity - side effects appear to be more frequent with higher activity with very low quality of evidence. Therefore, the recommendation leaves room for an individualized decision.

All studies investigate the ablation of healthy residual thyroid tissue. The success of treatment in terms of recurrence-free survival or overall survival is only marginally assessed at best.

Table 18 reflects the necessary broad corridor to treat patients individually, especially if lymph node metastases or distant metastases are present. The main objectives of RIT are to achieve an excellent response, avoid recurrence and achieve very good long-term survival without reducing life expectancy compared to the normal population and, if possible, without impairing quality of life [715].

The available literature is heterogeneous in terms of patient population and treatment concepts. In some cases, only low-risk patients were included [716] but sometimes also T3 or stage III patients [717] and also patients with lymph node metastases [673]. The exclusion criterion was usually an M1 situation. The ablation criteria for success varied; sometimes an unremarkable sonographic examination of the neck,

sometimes an unremarkable ^{131}I whole-body scintigraphy, sometimes an unremarkable thyroglobulin value (< 1-2 ng/ml) or a combination of unremarkable imaging and thyroglobulin value were required. The timing of the ablation check also plays a role. A time interval of 6-12 months after the first RIT is usual.

In the ESTIMABL study (France), the residual tissue ablation success was 90% in the study arm with 1.1 GBq I-131 after thyrotrophin alpha and 92 to 94% in the three other study arms [718]. In the HiLo study (UK), residual tissue ablation was primarily successful in 84% of patients after 1.1 GBq ^{131}I with thyrotrophin alpha; in the three other study arms, the success rates were 88 to 92%, which means a failure rate of 16% compared to 12% and 8% respectively [673].
No statements on the success of treatment with regard to progression-free long-term survival or overall survival can be found in these studies.

In a review, Andresen et al. compiled indications for RIT and a broad corridor of treatment activities. In high-risk patients, including those with positive surgical margins, gross extrathyroidal extension, lymph node involvement, subtotal thyroidectomy or > 5% uptake, higher-dose RIT offers better ablation rates and tumor control [719].

Jentzen et al. published that the lowest effective therapeutic activity for ablation of the thyroid remnant is around 2.2 GBq [720]. Verburg et al. reported poorer disease-specific survival (disease-free survival = DFS) after 15 years in the low-risk group 16.1% and in the high-risk group 44.4%) when using treatment activities ≤ 2.0 GBq I-131 [721]. Long-term data on recurrences are rather sparse: Kukulska et al. report an equivalence of results 5 years after RIT, but 22% of the patients treated with 1.1 GBq required a second RIT compared to 11% of the patients treated with 3.7 GBq [722].
The table summarizes typical risk-adapted therapy activities.

5.8.8 ^{131}I-Whole-body scintigraphy / ^{131}I-SPECT/CT

5.63	Consensus-based Recommendation	2025
EK	A whole-body scintigraphy, possibly supplemented by a SPECT/CT, shall be carried out for every radioiodine therapy.	
	Consensus	

In addition to therapy monitoring, radiation protection legislation requires that a maximum of diagnostic information is obtained from a radiation application. Scintigraphic visualization of the therapy activity distribution is therefore mandatory. Scintigraphy using therapy activity enables highly sensitive localization and activity assessment of residual thyroid tissue and distant metastases. The detection of local lymph node metastases is also possible - with decreasing sensitivity with increasing proximity to the residual tissue.

Due to the high probability of lymphogenic metastasis, iodine-avid lymph node metastases are found more frequently after adjuvant RIT using modern nuclear medicine imaging, in particular SPECT/CT. Miller et al. investigated how frequently lymph node metastases could be found after thyroidectomy with ^{131}I-SPECT/CT in the context of RIT. 146/352 patients at intermediate or high risk (41.5%) had lymph node metastases on diagnostic ^{131}I scintigraphy [723]. Spanu et al. confirmed the higher number of

iodine-avid lymph node metastases by SPECT/CT compared to planar ^{131}I whole-body scintigraphy [724]. SPECT/CT therefore has a high diagnostic value for the detection and precise localization of iodine-avid metastases.

In a group of 320 thyroid cancer patients referred for postoperative RIT, Avram et al. showed that diagnostic imaging with ^{131}I including SPECT/CT after thyroid hormone withdrawal (THW) visualized regional metastases in 35% and distant metastases in 8% of cases. TNM staging was altered by this imaging in 4% of younger and 25% of older patients [725]. Avram et al. reported that such information changes the risk classification in about 15% of patients and changes the clinical management in about 30% of patients [726]. This statement is confirmed by studies by Szujo et al. that SPECT/CT can provide a gain in diagnostic information compared to planar whole-body scintigraphy [727].

In another study by Avram et al., postoperative ^{131}I imaging data and stimulated thyroglobulin levels provided information that changed the treatment of patients in 29% of cases compared to the original strategy based on surgical pathology information and clinical information alone [728]. Banerjee et al. reported that the use of ^{131}I whole-body scintigraphy was associated with better disease-specific survival due to improved diagnostics [729].

SPECT/CT therefore aims to detect iodine-avid lymph node metastases that escape planar imaging due to superimposition effects. If this examination modality is not available, it should be examined whether iodine accumulations can be morphologically correlated post-therapeutically by using MRI, for example.

5.8.9 Response evaluation using ^{131}I whole-body scintigraphy / ^{131}I-SPECT/CT + stimulated thyroglobulin value

5.64	Consensus-based Recommendation	2025
EK	After radioiodine therapy, monitoring shall be carried out at 3 - 6 monthly intervals using sonography, determination of hsTg (highly sensitive Tg assay), TgAb and thyroid-specific hormones, initially for a period of 12 to 24 months.	
	Strong Consensus	

5.65	Evidence-based Recommendation	2025
GoR **A**	In the case of TgAb positivity and an initially medium or high risk of recurrence, a ^{131}I whole-body scintigraphy shall be performed after 6 - 12 months.	
LoE **2a**	[730]	
	Strong Consensus	

5.66	Evidence-based Recommendation	2025
GoR **B**	A ^{131}I whole-body scintigraphy should be dispensed with if the initial RIT has already produced an excellent result and if hsTg values are undetectable over the course of time or if hsTg values are falling at a low level.	
LoE **2a**	[730]	
	Strong Consensus	

The response evaluation of radioiodine therapy is carried out using ^{131}I whole-body scintigraphy and stimulated tumor marker thyroglobulin. This allows classification into response classes with excellent, acceptable, biochemically incomplete and structurally incomplete response, which has consequences for further aftercare and therapy (see Chapter 6.2 and Chapter 6.3). In Germany, the need to check the success of treatment is a result of the general nuclear medicine treatment standard and is stipulated in the Radiation Protection Act and the Radiation Protection Directive. The quality assurance of nuclear medicine treatments requires that the data of all patients are reviewed by the treating physician with regard to their treatment outcome [530], [531], [731], [532]. Iodine-avid metastases can escape detection during initial radioiodine therapy if there is a strongly accumulating thyroid remnant that outshines weaker accumulating metastases ("stellate artifact"). These are then only detectable after elimination of the residual thyroid tissue in the subsequent ^{131}I whole-body scintigraphy after rhTSH stimulation. An inconspicuous ^{131}I whole-body scintigraphy and a stimulated thyroglobulin value below the functional assay sensitivity are a desirable therapeutic goal and document an excellent response [732].

Over the years, increasingly sensitive thyroglobulin assays have been developed. Therefore, Giovanella et al. [730] analyzed whether an inconspicuous basal (i.e. non-stimulated) thyroglobulin value makes a ^{131}I whole-body scintigraphy unnecessary, because such a result of the thyroglobulin measurement suggests an inconspicuous ^{131}I whole-body scintigraphy or makes the later occurrence of a relapse very unlikely. Giovanella et al. analyzed 10 retrospective studies with 1,796 DTC patients (1,542 PTC and 151 FTC patients), of which 8 retrospective studies with 1,568 DTC patients investigated the diagnostic significance of a non-stimulated thyroglobulin value under ongoing levothyroxine medication. The functional assay sensitivity of the assays used was between 0.03 and 0.1 µg/l. The methods used to rule out metastases and serve as the "gold standard" varied between studies and included sonography, chest X-ray, CT, MRI, PET, fine needle aspiration, sestamibi scintigraphy and iodine-131 whole-body scintigraphy. Accordingly, there was only a low positive predictive value of 21.3% (95% CI 11.9-30.7%). In contrast, there was a very good negative predictive value of 99.4% (95% CI 98.9-99.9%). Five studies made it possible to investigate the prognostic significance with regard to the occurrence of recurrences with median follow-up periods of 23 to 64 months. Here too, the negative predictive value was 99.4% (95%CI 98.8 - 100%). It should be emphasized that in 8 studies, only patients with negative thyroglobulin antibodies were included. If patients test positive for thyroglobulin antibodies, there is a risk of false negative thyroglobulin measurements. This justifies recommendation Recommendation 5.65, that in TgAb-positive patients,

^{131}I whole-body scintigraphy should continue to be used for response evaluation, and recommendation Recommendation 5.66, that in patients with an initially medium or high risk of recurrence, ^{131}I whole-body scintigraphy should not be dispensed with, because the studies predominantly examined patients with low tumor stages and the evidence for higher tumor stages is low. If, on the other hand, there is already an excellent therapeutic result after the initial radioiodine therapy or if a thyroglobulin value below the functional assay sensitivity (< 0.1 - 0.2 ng/ml) is found in patients at low risk of recurrence, ^{131}I whole-body scintigraphy can be dispensed with [730]. It should be noted that the collectives examined in the individual studies were heterogeneous. In the two German publications [733] and [734], patients were included who had received one or two high-dose radioiodine therapies and subsequently had an unremarkable ^{131}I whole-body scintigraphy, so it is not surprising if a negative ^{131}I whole-body scintigraphy results in an unmeasurable thyroglobulin value after such initial therapy and follow-up care.

5.8.10 Side effects of radioiodine therapy

In general, RIT is a well-tolerated therapy with few side effects. A distinction is made between early side effects occurring soon after administration of the radioiodine and late long-term side effects, which occur with varying frequency in children and adults. The risk of side effects and their possible intensity depend, among other things, on the level of activity applied. The side effects described below primarily concern recurrence and metastasis therapies in which high cumulative therapy activities are used.

5.8.10.1 Early/acute side effects

Radiogenic gastritis

Radiogenic gastritis can occur transiently (for a few hours); the main symptom is nausea with a frequency of <5% to 60% [735], [736], [737]. In patients with a corresponding predisposition, gastroprotection should be considered before treatment; alternatively, symptom-oriented treatment is carried out if radiogenic gastritis occurs.

Radiogenic thyroiditis

Radiogenic thyroiditis is a transient, painful local swelling of the postoperative thyroid remnant/tumor remnant/metastases that usually lasts only a few hours. The reported frequency varies greatly between approx. 5-50% and is primarily dependent on the residual tissue mass after the surgery [738], [739]. This side effect is rare in thyroidectomies performed according to oncological aspects. Therapy is carried out with ice packs and, if necessary, with anti-inflammatory medication. Radiogenic thyroiditis is easily treatable.

Sialadenitis/later xerostomia

RIT causes irradiation of the salivary glands, which can lead to sialadenitis. This depends on the therapy activity and is reported in <5% of patients, sometimes with a frequency of 12.8% - 33% [740], [741], [742], [739], [743]. This side effect occurs more frequently primarily during activities above adjuvant therapy [744]. Clinically, there is pain and swelling in the area of the parotid gland, sometimes with transient changes in taste [744], [745], [715]. The symptoms are predominantly transient. However, persistent damage is also observed. In a complex dosimetric study, Jentzen et al. showed an average salivary gland radiation dose so low that deterministic damage is not to be expected with normal treatment activities. The study showed that

chewing leads to a considerable excretion of activity and thus a reduction in dose [704]. Numerous medications have an effect on the salivary glands, so that such a cause should also be sought [746].

Xerophthalmia/later sicca syndrome

Lacrimal gland dysfunctions are reported with frequencies of <5%, sometimes with 4.1% - 22.1% [740], [738], [745]. Fard-Esfahani et al. showed a significant difference in the symptoms of a "burning sensation" and eye redness after RIT, the Schirmer test was significantly lower after RIT (p = 0.016). However, there was no correlation between the Schirmer test and the ^{131}I activity administered [747], a result that casts doubt on causality with RIT. Irradiation of the lacrimal glands was reported to cause tearing ("epiphora") [745]. Since a sicca syndrome can also occur independently of RIT and a clear dependence on activity cannot be proven, a causal relationship cannot be clearly established.

Blood count changes

Grünwald et al. described blood count changes (Hb ≤ 9.0 g/dl in women / 10.5 g/dl in men, or erythrocytes ≤ 3.1 x 1012/l in women / 3.5 x 1012/l in men, leukocytes ≤ 2.5 x 109/l, thrombocytes ≤ 0.5 x 1011/l) in only 5/469 (1.1%) patients who were treated cumulatively with up to 18.5 GBq ^{131}I. At higher therapy activities (18.5-37 GBq ^{131}I), only 1/77 patients (1.3%) showed blood count changes. These changes were without clinical relevance [748].

Tumor/metastasis swelling

Rare individual cases of tumor/metastasis swelling have been described. Neurological symptoms as compression syndrome or possibly (also independent of RIT) as hemorrhage in spinal or cerebral metastases [749], [750], [751]. In the presence of metastases in critical locations, prophylactic glucocorticoid administration or additional local therapy should be considered.

5.8.10.2 Late/chronic side effects

5.67	Consensus-based Statement	2025
EK	Side effects that occur acutely can persist or occur late.	
	Strong Consensus	

Chronic xerostomia/chronic sialadenitis

Chronic inflammation of the salivary glands can lead to a reduction in function, possibly with a change in taste and an increased risk of caries. The frequency of chronic xerostomia reported in the literature varies considerably between <5% with ranges of 5.4% - 72% [752], [742], [745]. Examination times and methods vary in the literature and are not very standardized [738], [741], [745]. Clement et al. reported symptomatic salivary gland dysfunction with a prevalence of 16-54%. Abnormal salivary gland scintigraphy findings were reported with a prevalence in the range of 37 - 72% [738]. However, the extent of dysfunction is difficult to determine due to differences

in definition and the lack of a gold standard. There are clear differences between the results of a salivary gland scintigraphy and the patient's perceived symptoms. Jeong et al. showed a significant correlation between the salivary gland dysfunctions observed by scintigraphy and their symptoms. Nevertheless, in their study, patients classified as asymptomatic were also in the groups with moderate to severe decrease in uptake score (29% asymptomatic) and ejection fraction (60% asymptomatic) [753]. Klein-Hesselink et al. were able to demonstrate a decrease in saliva production after RIT in a group of 67 patients, 21% of patients reported frequent or constant xerostomia, although 7.5% of patients already had these complaints before RIT [754]. Solans et al. described xerostomia in 32.9% of patients in the first year after RIT, after 3 years in 15.2% of patients, 5.1% of patients developed severe xerostomia [755]. Hyer et al. reported chronic swelling and pain in the area of the salivary glands in 21.1% of patients; in 12% of patients, these symptoms did not develop until 3 months after treatment [742].

In a study by An et al., 29.7% of patients showed signs of sialadenitis in the late phase (median 336 days after treatment), 66% of these patients already showed these in the early phase (7 days post RIT) [752].

In a study by Rosario et al., 5.4% of patients reported symptoms of salivary gland hypofunction or inflammation after 12 months [745]. According to Clement et al., a correlation between the administered ^{131}I activity and the salivary gland scintigraphy findings was found in all 6 studies examined; 3 out of 5 studies also showed a correlation in symptomatic salivary gland dysfunction [738].

Wu et al. found no unfavorable effects with regard to xerostomia in activities up to 5.5 GBq (150 mCi) ^{131}I [756]. In the case of taste changes and xerostomia, it should be noted that there are a number of drug influences; statements on concomitant medication are often missing in the above-mentioned studies [746].

Chronic xerophthalmia/sicca syndrome

Chronic lacrimal gland dysfunction is rare, but is reported by some authors with frequencies of 4.1% - 22.1%. [740], [738], [745]. Solans et al. described xerophthalmia in 25.3% of patients in the first year after RIT with improvement over time. Keratoconjunctivitis sicca was still present in 7.6% of patients 3 years after RIT. Reductions in lacrimal gland function can be reversible [755]. Jonklaas et al. report a frequency of approx. 10% of nasolacrimal complaints [757]. This raises the question of a selection phenomenon, because side effects of this type or frequency have not been published for RIT in German-speaking countries and a convincing connection between applied activity and functional impairment cannot be proven.

Bone marrow depression with thrombocytopenia and neutropenia

Bone marrow depression with thrombocytopenia and neutropenia is relatively rare. The frequency depends on the cumulative activity. Grünwald et al. described that at very high therapy activities above 37 GBq ^{131}I, platelet formation is impaired, pancytopenia was observed in 4 patients [748]. The bone marrow dose with potentially resulting complications is also influenced by renal function, which is why the creatinine value and renal function should be known in addition to the differential blood count before RIT. A significant decrease in leukocytes and thrombocytes was described within the first year after RIT by Molinaro et al. [758]. Prinsen et al. described transient decreases in leukocytes and platelets up to one year after RIT with normalization

of values up to 5 years after RIT. 4.2% of patients developed thrombocytopenia, risk factors were older age, male gender and the cumulative dose, relevant (long-term) side effects were not found [759].

It should be noted that the studies were generally retrospective studies and the side effects were not objectified or quantified. There is also often a lack of information on treatment activity and further treatment such as percutaneous radiotherapy. The rate and intensity of side effects depends on the treatment activity. The side effects mentioned are primarily observed in high-dose therapy for targeted treatment of recurrence/metastases. If a study does not explicitly describe a dose dependency of the side effect, a causal relationship between RIT and the side effect described is not plausible.

5.8.10.3 Secondary malignancies after radioiodine therapy

5.68	Evidence-based Statement	2025
ST	A certain risk of secondary malignancies due to RIT can be assumed in principle. The risk of secondary malignancies depends on the cumulative dose and the age at exposure and could only be proven in large case series with cumulative activities above 5.5 GBq ^{131}I. In patients with a low risk of recurrence, the radiation risk should be taken into account when weighing up the individual benefit/risk of RIT.	
LoE ⊕⊖⊖⊖	⊕⊖⊖⊖: Secondary malignancy rate [760], [761]	
	Consensus	

Radiation experts assume a linear risk model. This means that the risk of cancer induction is proportional to the radiation dose and there is no threshold. This linear model has been proven above about 100 mSv and there are no studies for lower doses. On this basis, a lifelong additional risk of secondary carcinoma is expected after radioiodine therapy, depending on age and actual exposure. In athyroid adults, the doses typically expected in risk-relevant organs are usually between 40 and 90 mGy per GBq ^{131}I [762], but vary depending on body size and kidney function and can be higher, especially in older people. At these low radiation doses, a latency period of up to decades can be assumed.

Nappi et al. published a systematic review and meta-analysis on the risk of breast cancer due to radioiodine therapy [760]. 14 studies with a total of 200,247 patients with differentiated thyroid carcinoma were identified, of which 98,368 were treated with radioiodine and 101,879 without radioiodine. The relative risk with compared to without radioiodine therapy was 0.83 (95%CI 0.70 - 0.99) with a range of 0.45 - 2.55. Thus, no increased carcinoma risk was found for the particularly radiosensitive organ after radioiodine therapy.

Reinecke et al. analyzed the risk of secondary malignancies due to radioiodine therapy [761]. In 10 studies, the risk increase for secondary malignancies was 1.14 to 1.84 when comparing patients treated with radioiodine therapy with comparison collectives without radioiodine therapy, whereby in 5/7 studies, in which the 95%

confidence interval was given, a value of 1.0 was included and only in 2/7 studies a value of 1 was exceeded (Silva-Vieira RR for SPM 1.84, 95% CI 1.02 - 3.31 and Molenaar SIR for SPM 1.30, 95% CI 1.12 - 1.51). However, most of the results were not statistically significant. It should be noted that these studies and the studies cited below are not limited to adjuvant radioiodine therapies, but also included high-dose therapies. In seven out of eight studies, the risk increased - as expected - with increasing cumulative treatment activity. The studies did not take into account whether the patients received percutaneous radiotherapy. Furthermore, a bias due to more intensive examinations after diagnosis of thyroid carcinoma is to be expected. This is always the case if the secondary carcinoma is diagnosed within the latency period for the development of a radiation-induced malignancy. Taking into account the low quality of the studies, the risk of secondary malignancies is therefore considered to be low at best and justifies the above recommendation.

Further, non-systematic studies show a low but statistically significant higher probability of secondary carcinoma with higher treatment activity. For example, Silva-Vieira et al. found a small but significant increase in the risk of secondary malignancies from a cumulative activity of 7.4 GBq ^{131}I [763], Teng et al. from a cumulative activity of 5.6 GBq [764]. The rate of percutaneous irradiation is unknown.

Hematological diseases and the risk of leukemia are discussed in detail below, as a higher radiation risk is expected for these than for solid tumors. Molenaar et al. found a higher risk after RIT (RR: 1.30 [95% CI: 1.12-1.51]) based on 148,215 patient data from the SEER registry [765], [766]. These results are in line with the results of Rubino's working group, even if they are not statistically significant (RR: 2.5 [95% CI: 1.0-7.4]) [767]. The absolute number of hematologic diseases caused by RIT is given by Rubino et al. as 0.8 cases per GBq radioiodine and 100,000 person-years and is thus in the very low range. However, it is not known whether these patients also received percutaneous radiotherapy. With regard to a dose-response relationship, Seo et al. were able to demonstrate a significantly increased, but in absolute terms low risk only above 3.7 GBq ^{131}I activity in 211,360 participants [768]. However, with a median follow-up of 2.4 years, these results should be viewed with caution, as a longer latency period is to be expected for secondary malignancies and the data are therefore likely to represent a screening bias.
Korean data on 211,360 patients examined the risk of leukemia after radioiodine therapy. No increased leukemia rate was observed in the group with activities up to 3.7 GBq ^{131}I. However, an increased leukemia rate was seen in the group of patients who were treated with a higher activity and who were therefore in an advanced tumor stage. In this group, 1 in 2,000 patients developed leukemia. At 8 months, the latency phase until leukemia developed was so short [768] that a causal relationship with RIT can be virtually ruled out. Depending on the activity used and the follow-up period, there are studies that found no increased leukemia rate [769], [770], [771] and others that describe a slightly increased leukemia rate [767], [772]. Rubino et al. analyzed three large cohorts from Sweden, France and Italy and found 3 additional leukemias per 10,000 patients (0.03%, RR = 2.5) [767]. Sawka et al. reported a slightly increased leukemia rate with a relative risk of 2.5 as well [772].

The risk of secondary malignancies is considered slightly higher in children. Seo et al. reported on 18,617 children and young adults treated for differentiated thyroid carcinoma in South Korea [773]. During the 120,474 person-years of follow-up, a total of 124 cases of secondary malignancies occurred; 43 (0.5%) in the operated patients and 81 (0.8%) in the cohort additionally treated with RIT. The RIT cohort thus showed a

slightly increased risk of secondary malignancies (adjusted HR 1.52 [95% confidence interval 1.03-2.24], p = 0.035).

5.8.10.4 Pulmonary fibrosis

5.69	Consensus-based Recommendation	2025
EK	In the case of disseminated lung metastasis, lung function tests should be performed when using high cumulative therapy activities due to the possible development of pulmonary fibrosis.	
	Strong Consensus	

Radiation-induced pneumonitis and subsequent pulmonary fibrosis in radioiodine-positive pulmonary metastases occur rarely in patients with pulmonary metastasis and depend on the cumulative treatment activity and the extent of pulmonary metastasis (approx. 1%) [774], [775]. Diffuse pulmonary metastasis can be dose-limiting for radioiodine activity [776], [777], [778], [779]. Patients who develop pneumonitis should be monitored more intensively in order to be able to initiate therapeutic steps in good time in the event of progressive, potentially life-threatening symptoms, such as glucocorticoid therapy, e.g. high doses of 1 mg/kg body weight prednisolone daily for 2-4 weeks [780], [781]. The presence of pulmonary fibrosis can limit the implementation of further RIT cycles [782], [783].

5.8.10.5 Cardiovascular system

In a retrospective cohort study of 4,845 patients in Korea, Kim et al. found no negative effects of RIT (mean treatment activity 3.8 GBq ^{131}I) with regard to the occurrence of ischemic or hemorrhagic apoplexy, coronary heart disease, or heart failure. 2,533 patients with thyroid carcinoma and RIT were compared with the remaining patients who did not receive RIT [784].

5.8.10.6 Side effects in children

The possible side effects of RIT do not differ in their main features between children and adults. Albano et al. reported on 302 treatment cycles in 105 children. The treatments were given in a metastatic situation with correspondingly high activity. Early side effects were reported in 35% of patients, mainly nausea in 29% and sialadenitis in 22% of patients. Transient blood count changes occurred in 6%. Late side effects were significantly less frequent in only 11% of patients, 2 patients showed sialadenitis, 4 patients permanent blood count changes, 5 patients each showed pulmonary fibrosis and fertility disorders (between 2 and 7%) [785].

Brown et al. reported in their work that there is a slightly increased risk of second malignancies after RIT for younger patients [786]. It remained unclear whether repeated therapies with higher cumulative activities occurred here. In a study by Hay's team, which only examined pediatric patients, a number of second malignancies and increased mortality between the ages of 30 and 50 were described, with 68% of deaths resulting from a second malignancy [465].

In an analysis of the SEER database, Marti et al. also showed an increased risk of second malignancies for pediatric patients and patients <25 years of age. Of the 1,571

children treated with radioiodine, 26 children (1.7%) were diagnosed with a secondary malignancy; this would have been statistically expected in 18 children compared to the healthy population as a whole. The increased risk of secondary malignancies was mainly due to the fact that 3 children developed salivary gland carcinoma, statistically only 0.9 children should have been affected [771]. Overall, it should be noted that few patients are reported to be affected by secondary malignancies.

Further studies express the suspicion that prepubertal testes react more sensitively to the effect of radiotherapy, which is why cryopreservation of sperm should be discussed individually in pubertal patients [787]. The risk of pulmonary fibrosis in pediatric patients with extensive lung metastases is more age-dependent than in adults, which is why pre-therapeutic dosimetry can be discussed in these cases [788].
Pasqual et al. reported a slightly increased risk of secondary malignancies in children treated with RIT, especially in a period of 20 years after RIT. This concerned uterine carcinomas

6 Follow-up care for differentiated and poorly differentiated thyroid carcinoma

For patients with differentiated thyroid carcinomas, a long tumor follow-up for at least 10 years is recommended, as local recurrences or distant metastases can still occur even after many years or decades. The frequency and extent of follow-up care are based on the risk assessment of the carcinoma. Prompt detection of tumor recurrence or lymph node metastases enables rapid intervention and therefore offers the best chances of treatment, even in the event of recurrence.

One large unicenter study [564] on the prognosis of 2,011 patients with differentiated thyroid carcinoma with a follow-up period of up to 20 years (median 7.1 years) showed a normal life expectancy for the majority of patients. The initial treatment was thyroidectomy followed by radioiodine therapy. Compared to the normal population in Germany, however, life expectancy was reduced, with the exception of patients < 45 years and a maximum of one lymph node involvement of the cervicocentral compartment. Significant risk factors for reduced life expectancy were: follicular thyroid carcinoma, extrathyroidal tumor growth, cervicolateral lymph node metastases, distant metastases, age > 45 years.

A second unicenter study [789] with 2,476 differentiated thyroid carcinomas showed, with a median follow-up of 6.6 years, a comparable life expectancy compared to the normal German population with the exception of patients > 45 years with distant metastases. In patients with carcinomas < 2 cm without lymph node or distant metastases, life expectancy was even better than that of the general population. Thyroidectomy was performed in 90.4% of these patients, lymph node dissection in 39.9% and radioiodine therapy in 91.1%.

6.1 When does aftercare begin?

According to the definition of this guideline, the follow-up period begins after completion of all primary therapies, in the case of radioiodine therapy including the success control (see Chapter 5.8.9) or after completion of all recurrence therapies with corresponding success control. The diagnostics in follow-up care are used for the early detection of recurrence or progression and end accordingly when recurrence or progression is confirmed.

Follow-up care includes checking and adjusting the thyroid hormone substitution or suppression with medication as well as the diagnosis and treatment of typical complications of the primary therapy. This includes sonography of the thyroid gland and soft tissues of the neck including lymph nodes, determination of the tumor marker thyroglobulin (Tg) and thyroglobulin antibodies (TgAb) as well as laboratory testing of thyroid hormone therapy. Patients are also given the opportunity to express their tumor-related concerns and receive competent answers.

6.2 How should follow-up care be provided for proven differentiated and poorly differentiated thyroid cancer?

Follow-up care for differentiated thyroid carcinoma depends on the risk stratification and is initially based on the initial risk category; later it depends on the progression and response to the initial therapy/therapies. Ideally, this is carried out by appropriately specialized physicians.

A multi-center study [380], which compared 1,624 unifocal papillary carcinomas (PTC) with 1,000 multifocal PTC, described a significantly higher rate of local recurrence for multifocal carcinomas after a median follow-up of 56 months (19.8%, $p < 0.001$) compared to unifocal carcinomas (13.6%). Thyroidectomy and radioiodine therapy were performed in 83.6% of multifocal and 74.0% of unifocal carcinomas.

An analysis of the American National Cancer Database (NCDB) and the National Cancer Institute's SEER registry of 47,902 patients who underwent surgery for papillary thyroid carcinoma between 1988 and 2006 at the age of < 45 revealed a significant influence of lymph node metastases on overall survival.

In patients who were >45 years old at the time of surgery for papillary thyroid carcinoma, Zaydfudim et al. [790], also in an analysis of the SEER registry of 30,504 patients, found a 46% higher risk of dying from this carcinoma if lymph node metastases were detected than in patients without lymph node involvement.

In a literature analysis by Randolph et al. [600], the frequency of recurrent lymph node metastases in PTC correlates with the histopathological lymph node status at the time of initial surgery. In stage pN0, local recurrence occurred in 2% of patients, whereas in stage pN1 it occurred in 22%. The risk of local recurrence also correlated with the number of tumor-infiltrated lymph nodes at the time of initial surgery (< 5 infiltrated lymph nodes: 4% tumor recurrence, > 5 infiltrated lymph nodes: 19% recurrence).

Two meta-analyses [791], [792] also showed an increased risk of local recurrence in PTC in correlation with the extent of the initial procedure. For patients who underwent thyroidectomy and prophylactic cervicocentral lymph node dissection, the risk of recurrence was reduced by 35% compared to patients who underwent thyroidectomy alone. It must be added that postoperative radioiodine therapy was more frequent in the group with lymph node dissection (71% with versus 53% without lymph node dissection).

6.1	**Consensus-based Recommendation**	**2025**
EK	Follow-up care for differentiated thyroid carcinoma shall be organized depending on the risk stratification, initially according to the initial risk category, and later depending on the progression, in particular the response to the initial therapy/therapies.	
	Strong Consensus	

The initial classification of thyroid carcinomas according to the TNM classification is important for the indication of initial therapies and for monitoring the success of the therapies [105], [24]. However, the TNM classification does not allow any statement to be made regarding progression-free survival and overall survival after the treatment(s) [793], [794], [795], [796], [797], [798], [799].

Furthermore, neither surgical outcome, response to radioiodine therapy, nor molecular markers such as BRAF V600E, TERT and TP53 are included in the TNM classification or in other classifications proposed to date.

For example, it was shown that a TERT mutation is an independent factor for increased mortality (hazard ratio [HR]: 10.35; 95% confidence interval: 2.01-53.24) for all differentiated carcinomas. For papillary thyroid carcinoma alone, the risk is even more pronounced (HR: 23.8; 95% confidence interval: 1.36-415.8) [800].

Verburg et al. were able to show that after completion of radioiodine therapy, an inconspicuous success control with diagnostic ^{131}I whole-body scintigraphy in combination with a non-measurable stimulated Tg value levels the initial risk of recurrence regardless of the TNM stage and that patients in this constellation only have a very low recurrence rate of 3% regardless of the initial risk classification. The long-term mortality rate with a follow-up period of 25 years was 3.4% ± 1.3% in the low-risk arm and 3.7% ± 1.7% in the high-risk arm (p = n.s.) [732].

6.3 Terminology of treatment response and risk assessment for recurrence of DTC

6.2	Consensus-based Recommendation	2025
EK	The response to treatment shall be classified as excellent, good or acceptable, biochemically incomplete or structurally incomplete, taking into account clinical, laboratory and imaging findings.	
	Strong Consensus	

Table 19: Risk groups after RIT and a follow-up period of 2 years

Category	Definition	Course of the disease/risks	Follow-up care or therapy
Excellent response to therapy (excellent response)	No tumor is visible on imaging and either Tg value under TSH suppression is < 0.2 ng/ml or	96 - 99 % of patients remain disease-free 1 - 4 % of patients develop a recurrence within a period of 5 to 10 years, less than 1 % will die from thyroid cancer.	The intensity and frequency of follow-up should be reduced early and TSH suppression discontinued.

Category	Definition	Course of the disease/risks	Follow-up care or therapy
	TSH-stimulated Tg value is <1 ng/ml		
Good/acceptable response to therapy (indeterminate response)	- There is no evidence of a local tumor or metastasis of the thyroid carcinoma in the follow-up imaging or there is weak radioiodine storage in the thyroid bed - Tg value under TSH suppression is ≥ 0.2 ng/ml and < 1ng/ml - TSH-stimulated Tg value ≥ 1.0 ng/ml and < 10 ng/ml or - TgAb values are stable or falling, and nothing pathological is seen on imaging	In 80 - 85% of patients, this condition remains stable or evolves towards excellent response. In 15 - 20%, a tumor is found in follow-up over a period of 5 to 10 years. Risk of dying from this cancer below 1%	Patients should continue to receive follow-up care with repeated imaging. If non-specific tumors become specific, they should be investigated with further imaging or biopsy.
Biochemically incomplete response (biochemical incomplete response)	There is no evidence of a local tumor or metastasis of the thyroid carcinoma in the follow-up imaging and - Tg value under TSH suppression is ≥ 1ng/ml or - TSH-stimulated Tg value ≥ 10 ng/ml or - Rising TgAb values	At least 30% will spontaneously become patients who have no signs that they have thyroid cancer; another 20% will become so after additional therapy. In 30%, the condition remains unchanged. 20% percent develop a recurrence, i.e. a tumor is found on imaging. Risk of dying from this cancer is less than 1%	If the Tg value is stable or falling, patients should continue to be monitored and the TSH value should be suppressed in most patients. Rising Tg values or TgAb values should be investigated with further diagnostic methods and possible further treatment.
Structurally incomplete response	In imaging, there are structural or functional masses (uptake of iodine in RIT or [^{18}F]FDG in PET/CT) that can be assigned	In 15 - 50% of cases, further therapies are successful and the patients can be reclassified. In 50 - 85% of	Patients in this group require further therapy or further observation depending on the clinical and pathological findings,

Category	Definition	Course of the disease/risks	Follow-up care or therapy
	to thyroid cancer. This is independent of the Tg value or whether TgAb is detectable.	patients, the disease persists despite additional therapies. Around 10% of patients with metastases in the neck and around 50% of patients with distant metastases die from this cancer.	the size and localization, the growth rate, the ability to take up iodine or the uptake of [^{18}F]FDG in PET/CT.

Although the initial tumor stage, differentiated histological factors and possibly additional molecular pathological markers influence the initial risk profile and thus the extent of the initial therapy/therapies, the outcome after completion of the initial therapy is decisive for the risk of recurrence (so-called dynamic risk assessment). Several retrospective studies with a total of >5,000 patients have shown that the outcome after completion of initial therapy is a significantly more reliable predictor of recurrence risk than the initial risk classification [732], [538], [539], [801], [802], [803], [804]. Systematic prospective data are lacking. The response to the initial therapy (surgery + RIT) has a direct influence on the risk of recurrence; this has been documented in retrospective studies [732].

There are 4 references in the ATA guideline that describe the risk of recurrence after surgery and RIT as a function of the response achieved to the initial therapy; all of these patients underwent both thyroidectomy and radioiodine therapy [538], [540], [539], [541] - the problem is the transfer to German conditions, as treatment in the USA is usually with only 1.1 GBq ^{131}I, which is possible on an outpatient basis there. In retrospective studies, the risk of recurrence over a follow-up period of 5-10 years was between 1% and 4% (median 1.8%) in patients who showed an excellent response to therapy 6-18 months after total thyroidectomy. In patients with initial low-risk disease, the recurrence rate was <1% [804], [718], [805], with initial intermediate-risk disease 1-2% [539], [804] and even with initial high-risk disease, a recurrence rate of up to 5% was observed in the majority of studies. Recurrence rates of 14% were only described in individual studies [538], [806]. A reliable indication of the risk of recurrence in initial high-risk patients according to the TNM classification cannot be made with certainty, as these patients only achieved full remission in approx. 20-40% of cases and persistent disease was observed more frequently [538], [539], [807], [541], [540], which was often not consistently differentiated from disease progression requiring treatment in the above-mentioned studies during further follow-up.

In the German study by Verburg et al., the risk of recurrence after thyroidectomy and RIT with 3.7 GBq ^{131}I and a subsequent excellent response was < 4%, regardless of the initial risk classification, with a median follow-up duration of 60 months, range 4-306 months [732].

A biochemically incomplete response is observed in approx. 10-20% of patients after thyroidectomy and radioiodine therapy, without a significantly different frequency in the various initial risk groups [538], [539], [541], [808]. The majority of these patients

show a complete remission or stable elevated thyroglobulin levels during further follow-up [538], [540], [808], [809]. The risk of these patients developing a structural (i.e. image-detectable) disease in the following years has been described as 0-17% [538], [808], [809].

If, on the other hand, only a structurally incomplete remission is achieved after thyroidectomy and radioiodine therapy, this detectable finding persists in around 70% of cases in the following years [538], [539], [804]. The available studies usually only allow a differentiation of a stable, persistent, structurally detectable finding from a progressive finding requiring treatment to a limited extent, as these distinct endpoints were rarely systematically differentiated. When this was differentiated, a variable risk of progressive disease on imaging of <5% [539] to 50% [803], [806], [808] was observed. In addition, a significantly shorter overall survival of patients with structurally incomplete remission compared to patients with only biochemical persistence was reported [806], [540], [808].

The presence of image-detectable distant metastases is a predictor of a less favorable outcome compared to only cervical lesions [808]. Whether patients with an initially high risk and subsequent structurally incomplete response have a higher risk of progression requiring treatment than patients with an initially intermediate risk cannot be answered with the help of the existing literature, as generally either only the initial risk category was differentiated with regard to subsequent progression or only the degree of remission, but not both risk classifiers in combination.

In the patient group classified as "indeterminate response" according to ATA [24] and as "good/acceptable response" in this guideline (suppressed Tg 0.2-1.0 ng/ml; stimulated Tg 1-10 ng/ml; stable/regressingTgAb, possibly unspecific imaging findings), the risk of developing structurally detectable disease within a period of 5 to 10 years is approx. 10-20% [810], [811], [812].

The assessment of the risk of recurrence does not end with the completion of the initial therapy, but is constantly reviewed and, if necessary, adjusted during the entire follow-up, taking into account the dynamics of the findings. For example, the risk of recurrence can be downgraded for patients with an initially biochemically incomplete response who fulfill the criteria for full remission during the course of treatment [538], [540], [808], [809].

Patient age >55 years is well documented as an independent, prognostically unfavorable factor in the initial risk assessment [804]. However, the independent prognostic significance against the background of post-therapeutic dynamic risk stratification has not yet been sufficiently investigated or has not yet been shown to have any independent prognostic significance [804]. The additional prognostic benefit of the BRAF mutation has also not been investigated. Additional prognostic information of the TERT promoter mutation status in addition to dynamic risk stratification was derived based on retrospective data [813], but has not been validated.

6.4 What role do medical history and clinical examination play in the follow-up of patients with differentiated thyroid carcinoma?

6.3	Consensus-based Recommendation	2025
EK	A symptom-oriented medical history and physical examination shall be fundamental components of aftercare.	
	Strong Consensus	

There are no controlled studies to answer this question. Both measures are part of the general medical standard.

New onset of cervical tenderness or lymph node swelling may indicate local recurrence or lymph node metastasis.

New focal bone pain may be an indication of skeletal metastasis. In the case of differentiated thyroid carcinomas, however, this is a rare coexistence. Regional or distant metastases are usually asymptomatic at first and are more likely to be diagnosed during imaging examinations, which are initiated when the thyroglobulin level rises.

As part of the follow-up examination, the question of tolerability of thyroid hormone replacement is relevant. To this end, it is important to record hypothyroid and especially hyperthyroid symptoms, including increased sweating, sleep disorders, palpitations and cardiac arrhythmia, unwanted weight changes or digestive problems. Corresponding complaints may be cause for a dose adjustment (see Chapter 5.4).

Specific side effects and sequelae of individual therapies are described in the corresponding therapy chapters. Possible side effects of the initial therapy (recurrent paresis, hypoparathyroidism with chronic need for therapy) shall be known or investigated. Reference should be made here to the relevant chapters (see Chapter 6.13 and Chapter 6.14).

Aspects of quality of life and psychological well-being are described in Chapter 12.
How should the TSH value be adjusted in the long-term course of patients with differentiated thyroid carcinoma?

6.4	Consensus-based Recommendation	2025
EK	The TSH setting shall be adjusted depending on the risk of recurrence or progression, taking into account the individual tolerance of the medication, including the patient's condition, state of health and concomitant diseases (osteopenia/osteoporosis, cardiac arrhythmia, etc.).	
	Strong Consensus	

6.5	Consensus-based Recommendation	2025
EK	Follow-up care also includes monitoring thyroid hormone levels. If the course of the disease is stable, it should be checked annually.	
	Strong Consensus	

The recommendations mentioned in this chapter are based on current international consensus [24], [814]. In principle, there is insufficient data available for specific TSH target ranges with regard to the risk of recurrence and overall or disease-related survival for specific patient groups, so that targets with regard to TSH adjustment must always be weighed up in terms of tolerability and individual (especially cardiovascular) risk, particularly if TSH suppression is used. Unfavorable effects with regard to the cardiovascular system and bone metabolism must be taken into account.

Adjustment of thyroid hormone replacement both in terms of TSH setting and combination therapy of LT4 and LT3 can improve quality of life and should be carried out in accordance with international guidelines for the treatment of hypothyroidism [815]

In patients with TSH-suppressive thyroid hormone settings who develop hyperthyroid symptoms, the dose of thyroid hormones should first be reduced slightly with the help of specialists and after weighing up the risks. If this does not alleviate the symptoms, taking thyroid hormones in the evening can be tried on an experimental basis in order to achieve a better quality of life [816], [817].

According to a recent meta-analysis, TSH-suppressive medication in post-menopausal women favors lower bone surface density in the lumbar spine compared to a healthy control group. TSH suppression generally meant a TSH value of <0.3 mU/l, in the majority of studies <0.1 mU/l. The duration of TSH suppression was 5-15 years in each case. In contrast, there was no significant difference in bone density in the femur in postmenopausal women and in bone density in the lumbar spine or femur in men. In premenopausal women, bone density in the lumbar spine and femoral neck was significantly increased under TSH suppression [818]. A second recent meta-analysis found significantly lower bone density in postmenopausal women with TSH suppression <0.1 mU/l, but not with a TSH value of 0.1-0.5 mU/l [819]. It must be taken into account that the category "TSH < 0.1 mU/l" also includes all patients with excessive thyroxine administration (individual hyperthyroidism factitia). In a prospective observational study of 686 women >65 years of age, the risk of femoral neck and vertebral body fractures was 3 or 4 times higher with a TSH suppression ≤0.1 mU/l compared to patients with a TSH of 0.5-5.5 mU/l. The risk with a TSH value between 0.1-0.5 mU/l was not clearly increased [820]. Another observational study showed that in women (90% of whom were postmenopausal) on TSH-suppressive medication, a significant decrease in the trabecular bone score (TBS) was observed after 5-10 years at a TSH value of <0.1 mU/l, but not at a TSH value between 0.1-0.5 mU/l [821]. These studies emphasize that long-term TSH suppression in postmenopausal patients <0.1 mU/l should only be carried out with special consideration of the increased risk of osteoporosis.

In a comprehensive observational study (17,684 patients), TSH suppression <0.03 mU/l was significantly associated with increased cardiovascular events (cardiac

arrhythmias, morbidity, mortality) after adjustment for age, gender, previous cardiovascular disease, and diabetes. However, this risk was not increased with a TSH value between 0.04-0.4 mU/l compared to patients with TSH 0.4-4.0 mU/l [822]. In a placebo-controlled study in 25 patients with differentiated thyroid carcinoma and normal left ventricular ejection fraction, L-thyroxine-induced subclinical hyperthyroidism (median TSH value 0.015 mU/l, fT4 23.1 pmol/l) led to diastolic dysfunction, which was at least partially reversible after euthyroidism was restored [823]. Another interventional study (18 patients) also showed echocardiographic abnormalities and limitations in physical performance in patients on a fixed dose of L-thyroxine with a median TSH value of 0.05 mU/l compared to a euthyroid control group. These differences were reduced or normalized after individual titration of the L-thyroxine dose with a TSH target value of 0.1 mU/l [824].

In summary, these studies show that side effects of hormone replacement are only observed significantly more frequently in patients with a TSH value <<0.1 mU/l, but not with a TSH value around 0.1 mU/l.

In order to improve the tolerability of thyroid hormone replacement, it is recommended to use the lowest possible dose that allows the respective TSH target range. The respective TSH target ranges shall be aimed for, but do not necessarily have to be achieved, especially if the patient feels understandably more comfortable at a different dose. Frequent dose changes with the aim of reaching the TSH target range should also be avoided if there is otherwise a risk of jeopardizing patient compliance or acceptance. If a dose change is necessary, it should generally be made in small steps.

6.6	Consensus-based Recommendation	2025
EK	The TSH ranges mentioned below are target values that should be approximately achieved. Frequent changes in thyroid hormone dosage should be avoided. The following recommendations are summarized in the following two tables Table 20 and Table 21. **Initial situation (surgery +/- RIT) until response evaluation** *Very low risk* In the case of lobectomy, thyroid hormone replacement can be carried out with the aim of achieving a TSH value within the normal range. In the case of a complete thyroidectomy, a TSH value within the normal range should be aimed for. TSH-suppressive therapy shall not be used. *Low risk* In patients with a low risk of recurrence, a TSH value of 0.5-2 mU/l shall be aimed for in patients with an excellent response (non-stimulated Tg < 0.2 ng/ml) and a TSH of 0.1-0.5 mU/l in patients with an incomplete response (non-stimulated Tg ≥ 0.2 ng/ml). *Medium risk* In patients with a medium risk of recurrence, a TSH value of 0.1-0.5 mU/l shall be aimed for postoperatively. *High risk* In patients with a high risk of recurrence, a TSH of < 0.1 mU/l shall be aimed for postoperatively. **From response evaluation 6-12 months after initial therapy** *Excellent response* A TSH value of 0.5 - 2.0 mU/l should be aimed for in patients with an excellent response. *Good/acceptable response* A TSH value of 0.1 - 0.5 mU/l should be aimed for in patients with a good/acceptable response, taking into account possible risk factors. *Biochemically incomplete response* In patients with a biochemically incomplete response, a TSH value of 0.1 - 0.5 mU/l should be aimed for, taking into account possible risk factors. *Structurally incomplete response* In patients with a structurally incomplete response, a TSH value of <0.1 mU/l should be aimed for, taking into account possible risk factors.	
	Strong Consensus	

The only meta-analysis from 2002 [825] with 10 evaluable, predominantly retrospective studies (a total of 4,174 patients with differentiated thyroid carcinoma) showed an advantage of TSH suppression for recurrence-free survival or overall survival (relative risk: 0.73; 95% confidence interval: 0.6-0.88; p<0.05). It was not possible to differentiate between different risk groups or treatment strategies (extent of surgery, with/without radioiodine therapy) on the basis of the individual studies. The authors of the meta-analysis defined TSH-suppressive medication as a TSH value <0.5 mU/l without hyperthyroid symptoms and with free thyroid hormones in the upper normal range or slightly elevated. In the individual studies, however, the suppression

achieved was usually not stated or uniformly defined and did not necessarily correspond to the current definition of TSH suppression due to less sensitive TSH assays. Furthermore, due to the retrospective database, it cannot be ruled out that a bias may exist due to possibly different risk profiles of patient groups with and without TSH-suppressive therapy [825].

It is therefore recommended that the TSH setting be risk-adapted. In an observational study with 366 patients, a TSH threshold value of 2 mU/l was best suited to differentiate between patients who remained tumor-free and those with a recurrence or tumor-associated mortality [826]. There are no valid data to justify TSH suppression below the normal range in patients with a very low risk of recurrence, which is why a TSH value between 0.5 and 2.0 mU/l is recommended. Since the data on the risk of recurrence is not consistent for patients with an excellent response but initially high risk (see background text to Chapter 5.2), it may be considered to aim for a TSH target range of 0.1-0.5 mU/l in the first 5 years of follow-up. If the good/acceptable response remains unchanged or the biochemical response is incomplete, a TSH value in the lower reference range can be aimed for after 5 years

In patients with a biochemically incomplete response, the risk of recurrence is variable, but on average increased (Chapter 5.2), which is why a TSH target of 0.1-0.5 mU/l is recommended. If the patient achieves an excellent response in the further course of follow-up, the TSH setting could be adjusted accordingly.

In the case of structurally incomplete response, the risk of recurrence is sometimes significantly increased, and disease-related mortality is also increased on average (Chapter 5.2). For this reason, TSH-suppressive therapy with a target value of around 0.1 mU/l is recommended. Retrospective data suggest that an even significantly lower TSH value (<0.03 mU/l) does not improve disease-specific survival [827].

For patients without radioiodine therapy, a randomized controlled trial on the influence of TSH suppression on disease-free survival of 433 patients with papillary thyroid carcinoma is available. The patients underwent surgery (>80% no total thyroidectomy), no patient received radioiodine therapy. Approximately 90% of the patients were assigned to the low-risk group according to the AMES classification [828]; however, patients with microcarcinomas or distant metastases were excluded. Thus, a selected patient collective was available. In this collective, disease-free survival after 5 years was comparable between patients with TSH-suppressive therapy (median TSH: 0.07) and patients without suppression (median TSH: 3.2) at 91 vs. 89% and was not different even after a maximum of 12 years of follow-up [829]. In this respect, a TSH target range of ≤0.5 mU/l or ≤0.1 mU/l is only recommended for patients without radioiodine therapy if there is an incomplete response.

There are no dedicated data for the subgroup of patients with lobectomy that justify a different recommendation.

Provided there are no contraindications, suppressive thyroid hormone treatment appears appropriate until the first post-therapeutic follow-up. The risk assessment is subject to continuous reassessment during the course of treatment. In particular, the initial risk can be downgraded if the findings of a biochemically or morphologically incomplete response remain constant over the long term.

Table 20: Recommended TSH target ranges in the period after inital therapy until response evaluation after 6 months

	TSH target range			
	Very low risk	**Low risk***	**Medium risk***	**High risk***
Excellent response** (non-stimulated Tg <0.2 ng/ml)	0.5 - 2.0 mU/l	0.5 - 2.0 mU/l	0.1 - 0.5 mU/l	<0.1 mU/l
Incomplete response** (non-stimulated Tg >0.2 ng/ml)		0.1 - 0.5 mU/l		

* after total thyroidectomy

** in addition to the biochemical response, the structural response is also relevant

Table 21: Recommended TSH target ranges according to the response after inital response evaluation after 6-12 months

TSH target range			
excellent	**good/acceptable***	**biochemically incomplete****	**structurally incomplete*****
0.5 - 2.0 mU/l	0.1 - 0.5 mU/l	0.1 - 0.5 mU/l	<0.1 mU/l

* at age > 60 years, osteoporosis or atrial fibrillation: TSH target ranges 0.5 - 2.0 mU/l

** in addition to the biochemical response, the structural response is also relevant without risk factors such as postmenopause, tachycardia, osteopenia/osteoporosis, age > 60 years: TSH target range <0.1 mU/l

*** for atrial fibrillation: TSH target range 0.1- 0.5 mU/l

6.5 Laboratory diagnostics (thyroglobulin)

6.7	Consensus-based Recommendation	2025
EK	The determination of the thyroglobulin (Tg) value in combination with the determination of thyroglobulin antibodies (TgAb) shall be carried out as part of follow-up care using a quality-assured, highly sensitive assay. If TgAb is elevated, a negative Tg shall not be considered diagnostically usable. This applies in particular to a Tg that cannot be detected with an immunometric assay.	
	Strong Consensus	

6.8	Evidence-based Recommendation	2025
GoR **B**	Once therapy evaluation has been completed, no further tumor diagnostics should be performed if the serum Tg concentration is below 0.1-0.2 ng/ml (depending on the functional assay sensitivity) and the neck sonography is normal, given the high negative predictive value.	
LoE **2a**	2a: NPV [730]	
	Strong Consensus	

6.9	Evidence-based Recommendation	2025
GoR **A**	Endogenous or exogenous TSH stimulation alone for Tg determination shall not be performed in tumor aftercare.	
LoE **2a**	2a: NPV [730]	
	Strong Consensus	

The protein thyroglobulin (Tg) is synthesized exclusively by thyrocytes and can be detected as a tumor marker in serum. However, it is not possible to differentiate between malignant and benign thyroid tissue as the source of Tg. The use of Tg as a sensitive tumor marker therefore requires the complete removal of the thyroid gland, which is usually achieved by total thyroidectomy and adjuvant radioiodine therapy. The detection of Tg in serum can be disturbed by anti-Tg antibodies. These must therefore also be determined in parallel with the Tg determination. If TgAb is detectable, the validity of the Tg determination (in terms of reflecting the tumor burden) cannot be guaranteed. Otherwise, Tg is a very sensitive tumor marker in the tumor follow-up of differentiated thyroid carcinomas. Reliable sensitive Tg tests are commercially available and have a limit of quantification (LoQ) of 0.1 to 0.2 ng/ml, sometimes even lower.

After a lobectomy, Tg can be measured due to the residual thyroid tissue, but its significance as a tumor marker is then limited. After a lobectomy, the Tg value alone is therefore not suitable for detecting a recurrence [830], [831], [832].

After the systematic literature search, the evidence assessment was based on the meta-analysis by Giovanella [730]. Eight publications with a total of 1,568 patients were included. The result of the determination of thyroglobulin serum concentration (Tg value) under thyroid hormone medication was compared with various imaging procedures, sonography, chest X-ray, CT, MRI, fine needle aspiration cytology,

99mTc-MIBI scintigraphy and FDG-PET/CT. The overall sensitivity was 83.4% (73.4 - 90.1), the specificity 79.9% (63.0% - 90.3%). The positive predictive value was only 21.3% (11.9 - 30.7), while the negative predictive value was extremely high at 99.4% (89.9% - 99.9%). The sole use of the Tg determination under thyroid hormone medication can therefore largely rule out a recurrence, provided the Tg determination is valid. Despite the low to moderate confidence in the quality of the evidence, the two strong negative recommendations can therefore be issued.

The above evidence-based recommendations make no statement on the value of Tg determination for the detection of recurrence. There is a consensus among the experts that the absolute Tg values are of less importance than the progressive increase in Tg values. The mostly retrospective studies provide only very weak evidence on the question of how a progressively increasing Tg value should be defined and what diagnostic and/or therapeutic consequences should be drawn when. The PPVs range from 8% [833] to 40% [834] and depend on the previous therapies, the selected criteria and not least on the quality of the Tg determination.

6.6 What role does neck sonography play in the follow-up of patients with differentiated thyroid carcinoma?

6.10	Consensus-based Recommendation	2025
EK	Neck sonography shall be part of every follow-up examination and shall include a systematic examination of the thyroid bed and the central and lateral lymph drainage areas of the thyroid region.	
	Strong Consensus	

Sonography is one of the central examination methods in the aftercare of thyroid cancer. It is largely risk-free and inexpensive. In both older [793] and more recent studies [671], [835], sonography has demonstrated its diagnostic value for detecting persistence or recurrence in various situations in the follow-up of thyroid cancer.

There are three scenarios for sonography in the follow-up of thyroid cancer: timely postoperative sonography, postoperative sonography for sonomorphological characterization of treatment response and risk stratification, and long-term follow-up.

A timely postoperative sonography (i.e. within the first 3 months postoperatively) is not generally useful, as the assessability and informative value are limited. Exceptions may be [836]: There is no preoperative sonography and the diagnosis was made incidentally by histology, the preoperative sonography is not conclusive or not complete with regard to possible lymph node metastases, activity outside the thyroid bed is seen in the scintigraphy after RIT following total thyroidectomy or there are discrepantly high Tg values compared to the accumulation in the thyroid bed in the postablative scintigraphy. For patients who have initially received radioiodine therapy, cervical sonography is already described in Chapter 5.8.4 as part of the imaging preparation for radioiodine therapy.

Postoperative sonography is an important examination for the sonomorphological characterization of the response to therapy. Although prospective studies on the question of the best time for sonography checks are lacking, they are recommended 6-12 months postoperatively [105], [24]. Retrospective studies have found evidence that too early risk stratification after total thyroidectomy and radioiodine therapy has no advantage for this assessment [539], [803].

A separate situation with an early need for monitoring after 3 months arises for findings that may indicate renewed surgical therapy [24], [836]. These include organ-transcending growth (pT3/pT4), R1/R2 resections and histological evidence of lymph node metastases. In practice, the latter results from the fact that suspicious lymph nodes detected preoperatively by sonography often cannot be reliably assigned to the corresponding histological findings. Postoperative sonography 3 - 4 months after surgery was also the most sensitive method for detecting cervical tumor manifestation in a study [671].

Postoperative sonographic findings can only be interpreted with precise knowledge of the clinical, laboratory, histopathological and other imaging findings.

Standardized protocols and documentation of sonography are quality criteria for medical findings. They standardize sonographic findings and improve comparability. A complete sonography must include the examination of the thyroid bed [796], [797] as well as the cervical and lateral lymph node stations [105], [24].

After thyroidectomy, echo-rich scar tissue in the thyroid bed is typically observed on sonography as a result of the connective tissue reaction following surgery [796]. After successful radioiodine therapy of residual thyroid tissue, this may subsequently remain as inhomogeneously hypoechoic tissue, which is typically without detectable perfusion in color-coded duplex ultrasonography [796], [837]. Criteria for suspicious lesions in the thyroid bed after thyroidectomy are comparable to the general malignancy criteria for thyroid lesions (details in the "Diagnostics" chapter). In summary, these include hypoechogenic, nodular lesions (especially those that are larger in anteroposterior diameter than in lateral diameter ("taller than wide" [796]) or cystic or blurred or more vascularized or size-progressive lesions or those with calcifications [796], [838], [839].

Patients with initially low or intermediate risk and excellent as well as good and acceptable response to primary therapy occupy a special position here. The risk of recurrence is very low at <1%, meaning that abnormal findings in sonographic follow-up are more often false positives [839], [840], [841], [842]. It is therefore justified to dispense with further routine sonographic checks in these patients after 5 years of inconspicuous follow-up care [843]

The sonography of lymph nodes in the drainage area of the thyroid gland is also described in detail in the "Diagnostics" chapter (Chapter 3.4.6), also with regard to technical aspects. In summary, it makes sense to classify lymph nodes into the categories normal, indeterminate or suspected malignancy using evaluated sonomorphological criteria (cystic changes, echogenic foci, loss of the hilar sign, atypical peripheral vascularization [87], [84]). In addition, the localization of the lymph nodes in the central and lateral compartments according to an evaluated classification is necessary to ensure the reproducibility of the findings.

6.7 How often should outpatient or inpatient follow-up examinations take place?

6.11	Consensus-based Recommendation	2025
EK	Patients who have undergone surgery and radioiodine therapy should be followed up every 6 months for the first 5 years to determine the Tg and TgAb values, and have a neck sonography scan. After 5 years, the follow-up should take place every 12 months, after 10 years every 12-24 months.	
	Strong Consensus	

6.12	Consensus-based Recommendation	2025
EK	Patients who have undergone surgery without radioiodine therapy should always undergo sonography in addition to the determination of Tg and TgAb. Depending on the risk of recurrence, the follow-up intervals should be individualized.	
	Strong Consensus	

6.13	Consensus-based Recommendation	2025
EK	In the case of unclear or suspicious findings in the routine follow-up examinations, individualized, shorter examination intervals should be defined.	
	Strong Consensus	

The majority of recurrences of differentiated thyroid carcinomas are observed within the first 5 years of follow-up [844], [845], [846][846], so that consistent follow-up examinations are particularly important during this period. However, studies with longer follow-up periods show that there is no follow-up period after which subsequent recurrences can be reliably ruled out. Extensive retrospective data [847], [848] and prospective long-term data from the HiLo study [849] show that even in low-risk patients, recurrences continue to occur after >5 years and the recurrence rate is steadily increasing. However, these long-term surveys lacked additional information on the response achieved by these patients at risk of recurrence after initial therapy.

As shown in detail in Chapter 6.8.1, the risk of recurrence is clearly determined by the response achieved after completion of the initial therapy in addition to the initial risk category (low, intermediate, high risk) [850], [845], so that adjusted follow-up intervals according to the initial risk category and the response achieved are justified [835]. For all other patients (i.e. initial high risk or incomplete response), ongoing sonographic follow-up examinations are recommended even after 5 years of follow-up,

whereby the examination intervals can be extended with increasing follow-up duration.

In patients with total thyroidectomy without radioiodine therapy, the unstimulated Tg value often falls into the unmeasurable range [851] over the course of the follow-up years and can be considered a reliable indicator of normal follow-up in these cases. Nevertheless, sonographic follow-up examinations [794][794] help to detect cervical recurrences and should therefore be performed routinely. The data on "correct examination intervals" is insufficient, so that the above-mentioned examination intervals are based on clinical experience.

In patients who have undergone lobectomy, the Tg value is an unreliable follow-up parameter and is only partially sensitive for the detection of recurrences or carcinoma lesions in the remaining thyroid lobe [830]. At the same time, recurrences are also observed more frequently in small carcinomas after lobectomy than after total thyroidectomy [848], which is why regular sonographic follow-up examinations are important.

6.8 Diagnostic ^{131}I whole-body scintigraphy

^{131}I whole-body scintigraphy with a usual activity of 350 - 400 MBq, if necessary carried out with higher, also therapeutic activity depending on weight, is used in follow-up care to detect or exclude iodine-storing recurrences and/or metastases in all forms of differentiated and poorly differentiated thyroid carcinoma [852]. The individual indication for the administration of ^{131}I must be given by a doctor with the appropriate specialist knowledge (Radiation Protection Act, Guidelines on Radiation Protection in Medicine). For contraindications, see Chapter 5.8.6

The following indications are explicitly not considered in this chapter, as they have been assigned to the chapter on radioiodine therapy.

6.8.1 Patients with complete treatment success after initial adjuvant radioiodine therapy

6.14	Consensus-based Recommendation	2025
EK	If the success check shows negative findings ≥ 6-12 months after the initial RIT, no further diagnostic ^{131}I whole-body scintigraphy shall be performed if the follow-up is normal.	
	Strong Consensus	

Irrespective of the initial TNM tumor classification of thyroid carcinomas, the probability of recurrence is very low in the case of an unremarkable success control of radioiodine therapy (no evidence of residual thyroid tissue or metastases). The disease-related mortality rate is <1 % [804], [718], [805] and the probability of recurrence is <5 % [732], [539], [802], [804], [835]. To avoid radiation exposure without subsequent clinical consequences, further diagnostic ^{131}I whole-body scintigraphy shall therefore be avoided.

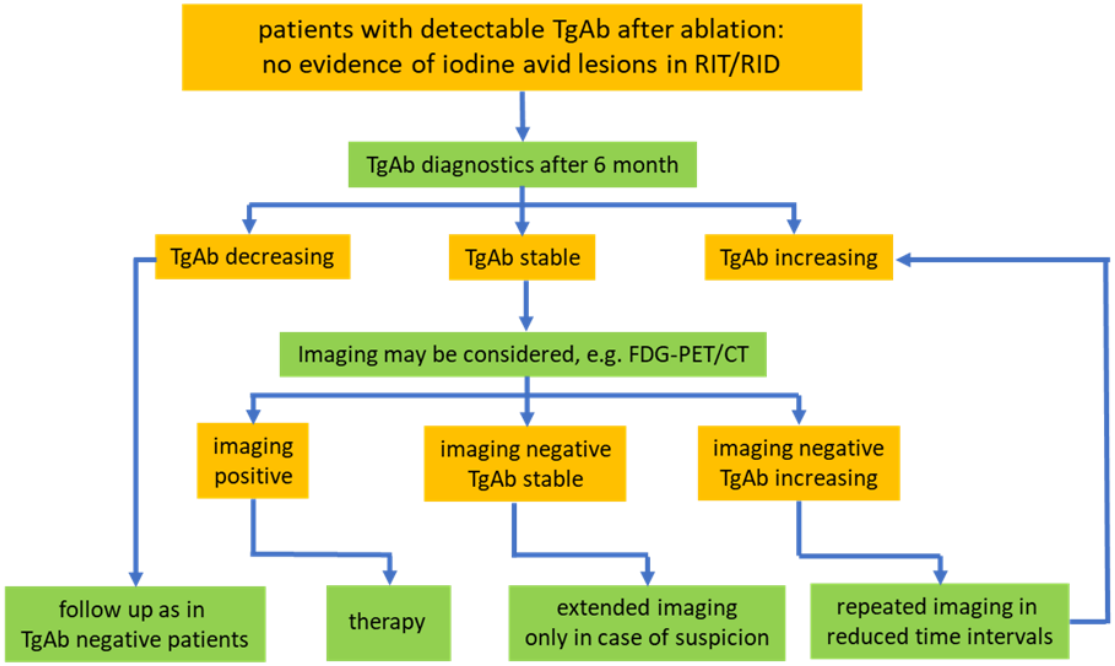
According to the dynamic risk stratification, patients with persistent iodine storage in the thyroid gland in the sense of residual thyroid tissue are also classified in the group of full remission in the absence of imaging evidence of tumor lesions and an undetectable tumor marker. This does not result in an indication for further radioiodine whole-body scintigraphy or radioiodine therapy [732], [853]. If there is a clinical suspicion of tumor recurrence (e.g. clinic, increase in thyroglobulin, imaging), a ^{131}I whole-body scintigraphy for staging and clarification of a possible indication for surgery is advisable, provided that metastases that are primarily accessible to radioiodine therapy are unlikely.

6.8.2 Patients with increased TgAb or impaired recovery

6.15	Consensus-based Recommendation	2025
EK	In the case of persistently elevated or increasing TgAb, a ^{131}I whole-body scintigraphy can be performed even if the Tg is negative.	
	Strong Consensus	

In immunometric assays, TgAb can lead to falsely low Tg values. An elevated Tg level indicates tumor persistence regardless of interfering TgAb or impaired recovery. However, if TgAb is detected, the level of the Tg serum concentration can no longer be used for follow-up and a negative Tg is not proof of a complete remission [854], [855]. Antigen presence should be assumed in the case of increasing or newly occurring TgAb during the course [856]. In the case of complete thyroid ablation, persistence/recurrence is therefore suspected. According to a recent meta-analysis, persistently elevated TgAb is also associated with an increased risk of persistent or recurrent tumor disease [857]. Therefore, if TgAb or impaired recovery is detected, an individualized approach is necessary and diagnostic ^{131}I whole-body scintigraphy may be indicated as part of follow-up care due to the inability to assess the course of Tg. TgAb levels that fall significantly (by >50%) over the course of treatment indicate a good/acceptable response to therapy, even if a plateau develops [858].

The following diagram shows the procedure for detecting TgAb as recommended in this guideline:



TgAb: thyroglobulin antibodies, RIT: radioiodine therapy, RID: radioiodine diagnostics, FDG PET: fluorodeoxyglucose Positron Emitting Tomography

Figure 3: Diagnostic concept for iodine-negative patients after adjuvant radioiodine therapy and detectable TgAb

6.8.3 Patients with suspected recurrence

6.16	Consensus-based Recommendation	2025
EK	Diagnostic ^{131}I whole-body scintigraphy shall not be performed to assess therapeutically useful iodine storage in cases of suspected recurrence; radioiodine diagnostics with therapeutic activity is the preferred procedure here.	
	Strong Consensus	

6.17	Consensus-based Recommendation	2025
EK	A diagnostic ^{131}I whole-body scintigraphy incl. SPECT/CT for metastasis localization shall only be performed if the possibility of local therapy is discussed in the tumor board.	
	Consensus	

6.18	Consensus-based Recommendation	2025
EK	After therapeutic measures (surgery, further RIT, percutaneous RTx), a diagnostic ^{131}I whole-body scintigraphy may be indicated for control purposes in the case of previously iodine-positive metastases.	
	Strong Consensus	

Patients who are suspected of having a recurrence after complete remission should undergo comprehensive diagnostics. Due to the unfavorable effect of a metastasis search with ^{131}I on a subsequent RIT [721], [859], [860], this should be omitted and RIT should be performed directly. In addition to the beneficial therapeutic effect, the sensitivity for the detection of iodine-storing metastases is also higher when using a therapeutic activity [861].

The collection of pre-therapeutic dosimetric data can enable an individualized therapy concept for subsequent radioiodine therapies (blood dosimetry with small amounts of ^{131}I, lesion dosimetry with ^{124}I, see Chapter 6.8.3), especially in patients with recurrence [862].

In the context of an individual indication, diagnostic ^{131}I whole-body scintigraphy to search for metastases as part of re-staging to clarify an indication for surgery, possibly with intraoperative use of a gamma probe [863], may be useful. The use of diagnostic ^{131}I whole-body scintigraphy to monitor the therapeutic measures can also serve to monitor success in individual cases.

6.8.4 TSH stimulation

6.19	Consensus-based Recommendation	2025
EK	The TSH stimulation required for radioiodine diagnostics can be exogenous (preferred) or endogenous.	
	Strong Consensus	

In preparation for a diagnostic ^{131}I whole-body scintigraphy, exogenous or endogenous TSH stimulation is required. Prospective comparative studies for the stimulation methods in the specific context of diagnostic ^{131}I whole-body scintigraphy in follow-up care do not exist. The two methods of TSH stimulation are described in Chapter 6.8.4 of the current guideline on radioiodine therapy. The aim is to induce a high TSH serum concentration. It is not known exactly what influence the duration of the hypofunction has, nor the level of the maximum TSH concentration. According to convention - based on radioiodine therapy - a basal TSH serum concentration >30 mU/l is required. However, with regard to the diagnostic accuracy of a diagnostic ^{131}I whole-body scintigraphy, there are no reliable data available to justify a specific threshold [864]. In the case of endogenous stimulation, a serum TSH concentration >30 mU/l is generally considered desirable and sufficient. However, this threshold is based on

observations from a single study with only 7 patients. Alternatively, exogenous stimulation with recombinant TSH has been established [865].

In the case of contraindications to endogenous stimulation, exogenous stimulation is the method of choice. Other concomitant circumstances and concomitant diseases that may also argue in favor of exogenous stimulation are listed in Chapter 6.8.4.

6.9 PET/CT in the follow-up of differentiated and poorly differentiated thyroid carcinoma

6.9.1 PET/CT with [^{18}F]FDG

6.20	Consensus-based Recommendation	2025
EK	A [^{18}F]FDG-PET/CT should be performed if Tg or TgAb is elevated, if morphological recurrence is suspected, or if the tumor is Tg-negative.	
	Strong Consensus	

A meta-analysis of 17 studies with 1,195 patients showed a high diagnostic accuracy of [^{18}F]FDG-PET/CT in the detection of recurrent and/or metastatic disease in DTC patients with hTg elevation (usually stimulated >2 ng/ml) and negative ^{131}I whole-body scintigraphy. The pooled sensitivity was 86% (95% confidence interval: 0.79-0.91), the specificity 84% (95% confidence interval: 0.72-0.91), whereby no significant advantage for previous TSH stimulation could be evaluated in the analysis [866]. In contrast, a meta-analysis of seven prospective studies with 168 patients on [^{18}F]FDG-PET/CT with and without rhTSH stimulation showed that significantly more patients with rhTSH stimulation had true positive lesions detected than without TSH stimulation (odds ratio: 4.92, 95% confidence interval: 2.70-8.95). This changed the clinical management in 9% of patients compared to [^{18}F]FDG-PET/CT without rhTSH stimulation [867]. However, the individual studies included only a few patients and the results have not yet been confirmed. It is therefore not possible to derive a recommendation that [^{18}F]FDG-PET/CT examinations should always be performed under TSH stimulation.

In a meta-analysis of 9 studies ([^{18}F]FDG-PET: 3 studies; [^{18}F]FDG-PET/CT: 6 studies) with 515 patients, the pooled sensitivity was 84% (95% confidence interval: 0.77-0.89), the specificity 78% (95% confidence interval; 0.67-0.86) [868].

^{18}F]FDG-PET/CT is more sensitive in patients with an aggressive histologic subtype, including poorly differentiated thyroid carcinoma, the tall cell variant and Hürthle cell tumor [869], [241], [240]. ^{18}F]FDG PET/CT in patients with metastatic DTC is an important negative predictor of response to radioiodine therapy and an independent prognostic factor for survival [870], [871]. PET/CT is able to identify lesions with high [^{18}F]FDG accumulation (quantification by SUV), which may correspond to a more aggressive subtype and should be treated specifically or monitored more closely. Even if ^{131}I-enrichment is detectable in metastases, [^{18}F]FDG-PET/CT is valuable as a complementary cross-sectional diagnostic, as it can detect neoplastic foci that do not show ^{131}I-enrichment.

6.9.2 PET/CT with ^{124}I

6.21	**Consensus-based Recommendation**	**2025**
EK	^{124}I-PET/CT imaging with or without dosimetry can be performed as an alternative to ^{131}I whole-body scintigraphy as part of the diagnostic procedure.	
	Strong Consensus	

^{124}I emits positrons and thus enables PET/CT imaging in patients with DTC. ^{124}I PET/CT can be used both as a dosimetric and diagnostic tool for localizing iodine-avid lesions. However, ^{124}I is neither available for purchase as an approved radiopharmaceutical nor is it widely available. According to two prospective studies with a total of 45 patients, the diagnostic sensitivity of ^{124}I-PET/CT under rhTSH stimulation is significantly higher at 78-99% than that of diagnostic planar ^{131}I whole-body scintigraphy with low activity of 37-74 MBq ^{131}I (22-49%) [861], [872], [873]. According to several prospective studies, the sensitivity of ^{124}I-PET/CT under rhTSH stimulation or hormone deprivation (57-100%) is also comparable to post-therapeutic ^{131}I whole-body scintigraphy with 3.7-11.1 GBq (70-100%) [861], [872], [874], [875], [876]. One exception is disseminated or micronodular lung metastasis, which frequently leads to false negative results of ^{124}I-PET/CT compared to post-therapeutic ^{131}I whole-body scintigraphy [875]. Simplified imaging protocols have been developed and feasibility evaluated for ^{124}I-PET/CT for lesion dosimetry prior to radioiodine therapy [877], [878], [879], [880].

6.9.3 PET/CT with somatostatin receptor-affine radiopharmaceuticals

6.22	**Consensus-based Recommendation**	**2025**
EK	PET/CT with somatostatin receptor-affine radiopharmaceuticals ^{68}Ga-DOTA-NOC/DOTATOC/DOTATATE etc.) can be performed in cases of increased Tg or TgAb in the search for metastases of a differentiated thyroid carcinoma in the absence of detection with other nuclear medicine or morphological imaging methods.	
	Strong Consensus	

Differentiated thyroid carcinomas express somatostatin receptors (SSTR) to varying degrees, predominantly SSTR 2, 3 and 5 [881], [882] and can therefore potentially be detected with SSTR-affine radiopharmaceuticals. In a prospective pilot study, metastases were detected in 14 of 15 patients with PTC (60% of whom had aggressive subtypes) and hTg increase with negative ^{131}I whole-body scintigraphy using ^{68}Ga-DOTA-TATE-PET/CT both under TSH suppression and after endogenous TSH stimulation with a sensitivity of 91% and 100% respectively. The other available imaging (CT/MRI, [^{18}F]FDG-PET/CT) served as a reference. Under endogenous stimulation conditions, more cervical and distant lymph node metastases tended to be detected, but with

lower specificity due to a higher detection rate of false positive lymph nodes (an inflammatory genesis was postulated). It can therefore be assumed that the higher sensitivity is the result of a more aggressive diagnosis with correspondingly lower specificity. There was no difference to suppressed TSH in the detection of local recurrence or lung or skeletal metastases [883].

Another prospective study compared ^{68}Ga-DOTANOC-PET/CT with [^{18}F]FDG-PET/CT in patients with differentiated thyroid carcinoma and negative ^{131}I whole-body scintigraphy despite elevated Tg values. Patient-related sensitivity and specificity were comparable at 78% and 100% (^{68}Ga-DOTANOC) and 86% and 91% ([^{18}F]FDG), respectively, but [^{18}F]FDG-PET/CT detected more lesions (168/186) than ^{68}Ga-DOTANOC-PET/CT (121/186). Only 55% of all lesions (103/186) were concordant, so that ^{68}Ga-DOTANOC-PET/CT partly provided supplementary information compared to [^{18}F]FDG-PET/CT [884].

PET/CT with DOTA-conjugated peptide radioreceptors can also be considered against the background of a theranostic approach with optional specific and systemic DOTA-conjugated peptide radioreceptor therapy.

6.10 Functional cross-sectional imaging diagnostics

6.23	Consensus-based Recommendation	2025
EK	If the sonography diagnosis is inconclusive, the ^{131}I storage is negative and the [^{18}F]FDG-PET is unremarkable and the Tg serum level or TgAb value continues to rise, additional morphological localization diagnostics should be performed using diagnostic CT or MRI.	
	Strong Consensus	

The use of PET/CT for the localization of non-iodine-storing tumor parts (Chapter 6.9) and iodine whole-body scintigraphy of iodine-storing tumor parts has been discussed in Chapter 6.8. Computed tomography (CT) and magnetic resonance imaging (MRI) are complementary morphological methods to [^{18}F]FDG-PET/CT. However, after performing a PET/CT with diagnostic CT, an additional CT would be redundant and not necessary.

The question of which of these two procedures, CT or MRI, should be preferred for an individual patient cannot be adequately answered, as comparative and tumor-specific studies are lacking. Instead, the decision shall be made on an individual basis, taking into account the suspected tumor location.

Due to the higher soft tissue contrast, MRI shows advantages over CT in tumor detection of deep cervical lymph nodes as well as liver and brain metastases [885]. This contrasts with the higher spatial resolution, speed and lower susceptibility to artifacts of CT, which leads to better detection rates for small lung metastases [886].

An indication for CA-supported CT is only given if radioiodine therapy is not planned or foreseeable in the next few months.

6.11 Further procedures

6.24	**Consensus-based Recommendation**	**2025**
EK	A chest X-ray shall not be performed as a routine follow-up examination.	
	Strong Consensus	

The chest X-ray examination is not sensitive enough as a search method for the detection of lung metastases in the context of follow-up care and is clearly inferior to Tg determination. If there is a concrete suspicion of lung metastases, chest X-ray is also not recommended, as it is considerably inferior to CT even in low-dose mode (here detection of lung foci < 3mm is possible [887]).

6.25	**Consensus-based Recommendation**	**2025**
EK	If pulmonary filiae are suspected, a diagnostic CT of the thorax should be performed (with contrast medium if necessary, after ruling out the possibility of radioiodine therapy).	
	Strong Consensus	

If pulmonary filiae are suspected, diagnostic CT of the thorax is the most sensitive method of assessment. Pulmonary foci with a size of 2 mm and less can be detected here if performed adequately [887]. Before the examination, it should be checked in detail whether the administration of a contrast agent can be expected to provide relevant additional information (e.g. for the assessment of vascular and mediastinal structures), as this interferes with any radioiodine therapy that may be required. In many cases, a native CT without contrast agent is sufficient.

6.26	**Consensus-based Recommendation**	**2025**
EK	Skeletal scintigraphy (incl. SPECT or SPECT/CT) shall not be used to search for metastases of DTC.	
	Strong Consensus	

To date, there are no clear recommendations as to when skeletal scintigraphy can or should be performed in cases of osseous filiae. 17 studies on skeletal scintigraphy were analyzed in comparison to other methods for the detection of bone metastases.

The data analysis showed that planar skeletal scintigraphy without the use of SPECT has a significantly lower sensitivity and specificity [245], [244], [888], [889], [890], [891], [892], [893], [894], [895], [896] compared to other methods (^{131}I whole-body

scintigraphy with SPECT, whole-body MRI, [^{18}F]fluoride PET/CT and [^{18}F]FDG PET/CT). Without additional SPECT images, the probability of detecting osseous metastases is significantly limited, especially in the more osteolytic filiae typical of differentiated thyroid carcinoma [245], [897]. The specificity and diagnostic accuracy increase in relation to planar skeletal scintigraphy and also in comparison to SPECT when hybrid SPECT/CT imaging is used [890], [892], [896], [898], [899], [900], [901]. Osteo-CT is the superior procedure for this issue.

There is no routine indication for skeletal scintigraphy as part of follow-up care [902]. As extra-osseous metastases may be present in addition to osseous filiae, [^{18}F]FDG-PET/CT examination is the diagnostic method of choice in this situation.

6.12 Should a fine needle aspiration be performed for suspicious cervical lesions discovered during follow-up care?

6.27	**Consensus-based Recommendation**	**2025**
EK	In patients with a suspicious cervical lesion, fine-needle aspiration cytology with Tg determination from the punctate can be performed if therapeutically appropriate.	
	Consensus	

There are no controlled studies regarding the value of fine-needle aspiration in suspected recurrence of known differentiated thyroid carcinoma. Retrospective surveys with small numbers of cases showed a diagnostic sensitivity of between 75-85% for fine needle aspiration with cytologic examination of suspicious cervical lymph nodes alone [903], [904], [905]. Fine-needle aspiration of suspicious cervical lymph nodes or lesions can therefore be considered if the result is of potential therapeutic consequence (e.g. decision on surgery). Several retrospective studies have shown that the determination of Tg from the aspirate improves the diagnostic sensitivity on average compared to cytological assessment of the material alone [904], [906], [211], [907], [908]. A meta-analysis of a total of 1,007 lymph nodes in patients after thyroidectomy for differentiated thyroid carcinoma showed a pooled sensitivity of 97% (95% confidence interval: 95-98%) and a specificity of 94% (92-96%) for Tg determination from the aspirate [909].

The determination of Tg from the aspirate requires special calibration and quality control of the kit used with regard to this specific question.

6.13 How should postoperative hypoparathyroidism be treated?

6.28	Consensus-based Recommendation	2025
EK	Postoperative hypoparathyroidism shall be monitored and treated as required.	
	Strong Consensus	

Postoperative hypoparathyroidism can occur both temporarily and persist permanently. In this context, timely recognition and initiation of therapy during the inpatient stay with adequate treatment are important. Subsequent determination of serum calcium and parathyroid hormone is required; medication with calcium and highly active vitamin D analogs should be reduced or discontinued if the serum calcium value is in the lower normal range or PTH > 15 pg/ml. The management of hypoparathyroidism in the postoperative setting is illustrated in the S2k guideline "Operative therapy of benign thyroid diseases" [910].

Patients with long-standing hypoparathyroidism have a significantly increased risk of developing kidney stones (nephrocalcinosis/nephrolithiasis) and cataracts as well as neurological symptoms (e.g. depression etc.) and neuromuscular symptoms (e.g. paresthesia, cramps etc.). Therefore, an optimal setting is necessary. To date, there are no data on optimal serum calcium levels in the treatment of hypoparathyroidism. In order to minimize renal calcium excretion, a serum calcium level in the lower normal range or slightly lower should therefore be aimed for. However, some patients require higher values in order to achieve freedom from symptoms. As long as calcium in the 24-hour urine remains within the normal range, serum calcium can be increased until the patient is symptom-free.

Few studies exist on endpoints such as mortality, quality of life, risk of hypercalcemia, kidney stones, tetany and cardiovascular events. An improvement in quality of life under treatment with a recombinant parathyroid hormone [911] could not be reproduced in comparison with a placebo preparation in a randomized controlled trial [912]. With regard to cardiovascular risk under recombinant parathyroid hormone, 2 studies were published [913], [914], in each of which a serious cardiovascular event was described in the recombinant parathyroid hormone group (122 patients in total) compared with no serious cardiovascular event in the placebo group. Convulsions and tetany were not quantitatively evaluated in the majority of studies. Although nephrocalcinosis/kidney stones have been frequently described in hypoparathyroidism, different treatment regimens have not yet been compared in terms of frequency.

With regard to the treatment of chronic hypoparathyroidism in adults, reference is made to published recommendations [915], [916], [917]. There are also several statements from American expert groups [915], [918][918], [919].

6.14 Diagnosis of vocal fold function and management of vocal fold dysfunction

6.29	Consensus-based Recommendation	2025
EK	Before and after each thyroid surgery, a laryngoscopic check of the respiratory mobility of the vocal folds shall be carried out and subjective vocal, breathing and swallowing difficulties shall be recorded.	
	Strong Consensus	

6.30	Consensus-based Recommendation	2025
EK	If postoperative vocal fold mobility is restricted, a phoniatric examination should be performed.	
	Strong Consensus	

6.31	Consensus-based Recommendation	2025
EK	In the case of a voice disorder, the indication for voice function therapy should be checked.	
	Strong Consensus	

6.32	Consensus-based Recommendation	2025
EK	The indication for phonosurgical treatment should be examined in the case of persistent voice disorders or dyspnoea. When phonosurgical procedures are indicated in cases of insufficient vocal fold closure or dyspnoea, it shall be considered whether respiratory mobility can still be expected to return.	
	Strong Consensus	

Dysphonia, i.e. impaired vocal tone or vocal performance, can be caused by unilateral or bilateral paresis of the two laryngeal nerves (recurrent/inferior laryngeal nerve or superior laryngeal nerve) or impaired function of the straight neck muscles following thyroid surgery. In 2-12% of patients with thyroid carcinoma, a voice disorder is already present pre-therapeutically, usually due to paresis of the recurrent/inferior laryngeal nerve [920]. As 20-30% of patients with unilateral paresis do not experience a voice disorder [921], [922], [923], the motility of the vocal folds should be checked preoperatively [924]. Pre-existing, previously asymptomatic functional dysphonia can

be unmasked by surgical interventions on the neck organs. Damage to the superior laryngeal nerve or the straight neck muscles can be further causes of voice disorders and can be observed in 27% of patients with preserved respiratory mobility of the vocal folds [925]. For this reason, not only shall a laryngoscopic check of the respiratory mobility of the vocal folds be performed after every thyroid surgery, but subjective voice complaints (preferably using the standardized Voice Handicap Index, VHI), breathing and swallowing difficulties should also be recorded [924], [926]. If there are limitations in vocal function, breathing or swallowing, a phoniatric examination should be carried out and the next steps determined.

According to two reviews, early recurrent paresis after thyroid surgery is found in 5-8% and 0.8-10.5% respectively, permanent paresis in 0.3-3% and 0-1.5% [927], [928].

In the case of dysphonia, voice function therapy is usually indicated. Direct therapy methods focus on voice and speech technique in order to optimize breathing, resonance, phonation and articulation. Indirect therapies focus on those factors that can cause and maintain a voice disorder, e.g. unfavorable room acoustics, dehydration, laryngo-pharyngeal reflux as well as stress and strain factors [929], [930], [931], [932]. Disorders of vocal fold movement with incorrect position and/or tension of the vocal folds can also be treated by phonosurgery [933], [934], [935], [936], [937]. The indication should be based on extensive phonosurgical experience and the timing should be determined according to the prognosis [938].

6.15 Other side effects/long-term consequences

6.33	Consensus-based Recommendation	2025
EK	In the treatment and aftercare of patients with thyroid cancer, aspects of quality of life, as well as physical, social and psychological well-being should be recognized and addressed in the interaction with the patient.	
	Strong Consensus	

Several surveys on quality of life in patients with thyroid cancer have shown that, compared to the general population, a reduced quality of life was reported on average after adjustment for important covariates [939], [940], [941], [942], with these impairments covering various dimensions. These included impairments in psychological well-being (e.g. fatigue, anxiety and depression), in physical functioning [942] and role functions as well as in the general perception of health. In addition, specific somatic complaints such as musculoskeletal or neurological symptoms, e.g. migraine-like headaches, were reported [943] as well as signs of thyroid dysfunction (e.g. dry skin, hair loss, concentration problems, sleep disorders, heat/cold intolerance, palpitations, digestive problems and weight changes) [943]. Patients also complain about the trivializing categorization of thyroid cancer as a "good cancer" in the face of psychological, social and physical stress [944].

In several surveys, fatigue was reported as one of the primary symptoms by approx. 40% of patients with thyroid cancer [945], [946], [947] and thus as frequently as by patients with other cancers [945]. In a single randomized controlled trial with 36

patients, fatigue was reduced by physical exercises under supervision (aerobic training and stretching exercises) [948] (see alsoChapter 12 and Chapter 13).

7 Treatment of primary metastatic DTC and PDTC - Management of persistence and recurrence of DTC

Tumor persistence is present if vital tumor is still detectable after initial surgery and adjuvant or curative radioiodine therapy. This can be considered certain if extrathyroidal iodine storage and/or tumor-suspicious lesions are detected using [^{18}F]FDG-PET/CT with a significantly increased Tg serum concentration. This must be distinguished from recurrence, in which full remission was initially diagnosed after surgery with or without radioiodine therapy.

7.1 Therapy of tumor persistence, recurrence and/or metastases - principles

7.1	Consensus-based Recommendation	2025
EK	In the relapsed or metastatic situation, the treatment concept shall be determined in an interdisciplinary tumor board: whether and how a remission or improvement or maintenance of quality of life can be achieved by using individual or a combination of treatment modalities.	
	Strong Consensus	

The recurrence/persistence situation is too complex to make a general treatment recommendation. This must take into account the patient's general condition, age, treatment preference and ability to undergo treatment. The biology of the primary tumor, the extent of the primary surgical intervention, the location of the metastases, the extent of metastasis and known or suspected iodine avidity must be taken into account. Radioiodine therapy prior to a new operation enables the metastasis/local recurrence to be classified as iodine-avid or iodine-refractory, which is important in terms of prognosis and for any therapies that may be required later.

7.1.1 Locoregional persistence or locoregional recurrence

7.2	Consensus-based Recommendation	2025
EK	Locoregionally persistent or recurrent DTC, cervical soft tissue infiltrates and persistent or recurrent lymph node metastases should be treated surgically. The individual treatment plan should be recommended in the interdisciplinary tumor board in order to weigh up alternative, concomitant or subsequent treatment options, or monitoring observation for the individual patient.	
	Strong Consensus	

The presence of lymph node metastases is an unfavorable predictor: Ricarte-Filho et al. analyzed the recurrence-free survival of patients with lymph node metastases. 246 patients in the period from 1980 to 2002 met the inclusion criteria. The presence of more than 3 lymph node metastases was a predictor of poorer recurrence-free survival. The combined presence of a BRAF mutation together with extranodal tumor spread was a predictor of disease-specific survival [949].

With the increasing use of hybrid imaging (SPECT/CT), small iodine-avid lymph node metastases are seen more frequently after RIT, which would have escaped detection by overlaying the iodine-storing residual thyroid tissue when using the planar technique. Lee et al. reported iodine-avid lymph node metastases in 4/61 patients (7%) in the low-risk group and 31/231 patients (13.4%) in the intermediate-risk group [165].

Ronga et al. reported on the benefit of RIT for the treatment of lymph node metastases: RIT is an effective treatment method for iodine-avid lymph node metastases if they are up to 10 mm in diameter [950][950]. These data confirmed earlier data from Trybek et al. according to which radioiodine was able to achieve a cure in 82.6% of patients (n=57 patients) using radioiodine when lymph node metastases (TxN1M0) were present [951]. Cao et al. also reported successful RIT of iodine-avid lymph node metastases [952]. Small lymph node metastases can thus be eliminated by adjuvant RIT. If small iodine-avid lymph node metastases are still detected after surgery and RIT, the result of the subsequent diagnostic ^{131}I whole-body scintigraphy can usually be awaited. This measure and measurements of the Tg serum concentration during the course allow a decision to be made on how to proceed.

Ilhan et al. were able to show that small lymph node metastases could be successfully treated with radioiodine (activities used 2.0 - 7.0 GBq). In 65 patients, 67 of 70 lymph node metastases with a volume of less than 0.9 ml were successfully treated with radioiodine, whereas only 6 of 14 lymph node metastases with a volume greater than 0.9 ml were successfully treated. The sensitivity and specificity as well as the positive and negative predictive value for predicting treatment success using this cut-off value were 92% and 73% and 96% and 57% respectively. The results of the short-axis diameter with a cut-off value of less than 1.0 cm yielded values of 90%, 69%, 94% and 56%. The majority, i.e. 88% of ^{131}I-positive lymph node metastases were thus successfully treated by RIT. Ilhan et al. were thus able to show that small iodine-avid lymph node metastases in particular respond well to radioiodine therapy (tumor volume < 0.9 ml and short-axis diameter < 1 cm). Over a mean follow-up period of 64 months, 56/65 patients (86%) did not have an elevated thyroglobulin level. Volume and short-axis diameter were predictors of treatment success [953].

Wu et al. confirm these data: in their collective of 118 patients with iodine-avid LN metastases and exclusion of distant metastases, radioiodine achieved complete remissions in 33/118 patients (28%) and partial remissions in 62/118 patients (53%). Serial RIT achieved an efficacy of 80.5% (95/118 patients), with up to three RITs with cumulative administration of 3.7-16.7 GBq radioiodine [954]. He et al. also confirm the efficacy of RIT for the treatment of lymph node metastases with a success rate of 88% in 218 patients. The response rate to RIT was 88% (including a cure rate of 20.6% and an improvement rate of 67.4%). Of the total of 406 lymph nodes from 218 patients, 319 lymph nodes (78.6%) were judged to be effectively cured, including 133 (32.8%) lymph nodes that completely disappeared and 186 (45.8%) lymph nodes that shrank. 87 (21.4%) of the 406 lymph nodes showed no obvious morphological changes [955].

If lymph node metastases cannot be successfully treated with RIT, surgery or external radiation may be considered.

Local recurrences of follicular thyroid carcinomas usually manifest as tumor infiltration of the perithyroid soft tissue and less frequently in the form of lymph node metastases. If a resectable soft tissue recurrence is detected in the imaging procedures, this should be extirpated by a systematic compartment-oriented neck dissection. If this has already been performed in a previous procedure, a focused tumor extirpation can also be performed with a sufficient safety margin. If the findings are unclear, the diagnosis can be confirmed preoperatively using an FNAC.

Extensive resection of the trachea and/or esophagus should only be performed in well-differentiated, minimally invasive FTC, taking into account the possibility of distant metastasis, and is only indicated in exceptional cases of grossly invasive FTC.
In terms of possible complications and the oncological radicality to be achieved, recurrent FTC surgery is a very demanding procedure that should only be performed in clinics with the appropriate expertise.
As with all other recurrent thyroid cancer surgery, the procedure should be performed using intraoperative neuromonitoring [956], [957].

7.3	Consensus-based Recommendation	2025
EK	In a palliative situation, metastases that are threatening and/or impair the quality of life (e.g. skeletal metastases that threaten stability with imminent paraplegic symptoms, metastases with nerve infiltration or vascular erosion, brain metastases) should be treated specifically.	
	Strong Consensus	

7.4	Consensus-based Recommendation	2025
EK	In the case of progressive radioiodine-refractory extensive disease with no other treatment option, the indication for systemic drug therapy shall be examined and discussed with the patient rather than a wait-and-see approach.	
	Strong Consensus	

Most patients with a differentiated thyroid carcinoma can be cured by the initial therapy (surgery, possibly with subsequent radioiodine therapy). Figures on the frequency and localization of recurrence as well as the frequency and localization of metastasis already present at the time of diagnosis are heterogeneous. In about 1 - 4% of PTC patients and in about 7 - 28% of FTC patients, distant metastases are already detected initially [958]. Prompt targeted therapy is necessary here. In patients with distant metastases, a delay in RIT of more than 6 months means poorer overall survival, which has already been demonstrated in a follow-up period of only 5-6 years [959].

Shokoohi et al. reported on Canadian data showing that 87% of primary metastatic DTC patients achieve complete remission. However, 136 patients (13%) in their

collective had a recurrence, of which 37 patients (3%) had distant metastases, predominantly localized in the lungs (76%) or skeleton (30%) [960].

Carvalho et al. analyzed 4,085 patients in the period from 1996 to 2015. Patients with extrathyroidal infiltration or cervical lymph node metastases or a higher risk of recurrence received radioiodine therapy after surgery. After a median follow-up period of only 58.7 months, 176 patients were found to have a recurrence (4.3%), mostly in lymph nodes. Distant metastases were found in 18 patients (0.4%). The recurrence rate in the low-risk arm was 1.6%, in the intermediate stages 7.4% and 22.7% in the high-risk patients. Distant metastases were found in 18 patients (0.4%) [961].

Goffredo et al. reported 2.2% of DTC patients in the SEER registry (n = 1,291) with metastases at diagnosis; 5-year survival in this metastatic group was 59%, which was significantly worse compared to non-metastatic patients [647].

Data on survival are heterogeneous, with Chow et al. reporting a 10-year survival rate of 85% and a 20-year survival rate of 71% in 164 metastatic patients [962]. Sampson et al. published that the 3-year survival of metastatic FTC patients was 62% worse than that of metastatic PTC patients [963].

Nixon et al. published worse data on long-term survival. Around half of metastatic patients died within the next 5 years if distant metastases were present at the time of diagnosis [964]. Lin et al. also confirm the reduced prognosis of patients with distant metastases: of 70 PTC patients with distant metastases, 70% had died of their disease after a median follow-up period of 10.1 years [965]. Metachronous metastases also have a poor prognosis with a 10-year survival rate of only 57% [966].

According to Li et al., radioiodine treatment is an effective treatment for metastatic patients, with metastatic patients receiving 22 GBq (600 mCi) or more of radioiodine [967].

Generally recognized oncological principles also apply to DTC. The more advanced the disease, the more rapidly it progresses and the more poorly differentiated the tumor, the worse the prognosis. In the case of DTC, however, the special feature is that better differentiation is associated with the preservation of iodine metabolism. The resulting radioiodine therapy can be curative even in the case of extensive metastasis.

The procedure for the individual metastatic localizations will be discussed below. Multiple factors are taken into account when making an individual treatment decision. In addition to the number and location of metastases (tumor burden), tumor dynamics are important. Patient age, co-morbidities, life expectancy and patient wishes play an important role.

The following structured procedure applies to persistent tumor burden or recurrence:

A curative approach uses the treatment options of surgery and/or RIT and/or percutaneous radiotherapy alone or in combination. If metastases are considered inoperable, it must be checked whether a cure can still be achieved with radioiodine therapy, possibly in combination with percutaneous radiotherapy. Otherwise, the curative concept has been exhausted.

If the intention is palliative, surgery/RIT/radiotherapy or a combination may be considered first. If these measures are not indicated or are unsuccessful, controlled waiting or systemic drug therapy may be considered. In addition, redifferentiation therapy

(with a low probability of success) can be discussed with the patient; please refer to the relevant chapter.

As long as sufficient iodine storage of the metastases is proven or can be assumed, and if the tumor burden cannot be treated surgically, RIT is usually the treatment of choice. The associated scintigraphy provides information about the radioiodine storage capacity of the metastases and thus also their degree of differentiation. Depending on this result, [^{18}F]FDG-PET/CT should be planned, especially if the metastases are no longer iodine-avid but de-differentiated.

In the case of localized metastasis, the possibility of resection should be considered as the primary treatment option. The smaller the tumor mass and the higher the degree of differentiation, the better the results of RIT. Especially in the case of lung metastases - including disseminated metastases - RIT can be considered as the sole therapeutic measure. In the case of inoperable tumors and tumors that cannot be completely removed by surgery, radioiodine therapy is carried out if a relevant radioiodine storage is proven or can be assumed.

This approach is supported by a number of retrospective studies reporting on the results of RIT in metastases:
Schlumberger published in 1996 on the benefits of RIT in patients with lung and bone metastases. Patients with a very good response to RIT in the sense of a complete response had a significantly better 15-year overall survival than those who did not (89% versus 8%) [968]. Durante et al. reported on 444 metastatic PTC and FTC patients from 1953 to 1994 with lung (n = 223), bone (n = 115), lung and bone metastases (n = 82), or other metastatic sites. Serial therapies were given at 3-9 month intervals in hypothyroidism for the first two years and then at annual intervals. 43% of patients achieved complete remission on the ^{131}I whole-body scintigram [969].

Ito et al. (Japan) evaluated 5,969 PTC patients, of whom 71 (1.2%, period 1987 - 2004) had distant metastases at the time of initial diagnosis, predominantly with exclusive lung metastasis (n = 60), or otherwise exclusive bone metastasis (n = 5), lung and bone metastases (n = 5) and 1 pt. with brain metastases. Patients with iodine-avid metastases received one or repeated RIT. 15 patients died at a median follow-up of 7 years and 10 months. The 5- and 10-year survival rates were 78.8 ± 5.2 % and 76.3 ± 5.7 %, respectively [970], [606].

Li et al. analyzed the benefit of RIT in 1,608 patients with distant metastases using the SEER database, including 521 patients (32.4 %) with bone metastases, 90 patients (5.6 %) with brain metastases, 158 patients (9.8 %) with liver metastases, 995 patients (61.9 %) with lung metastases and 50 patients (3.1 %) with other metastases. Distant metastatic patients under 45 years of age who underwent RIT had a 5-year survival rate of 91.7%, while those who underwent percutaneous radiotherapy had a rate of only 45.5%, which was significantly lower than RIT (external beam radiotherapy versus radioiodine therapy), adjusted hazard ratio [HR]: 5.5; 95%CI: 1.672-18.804, p < 0.005). In patients older than 45 years, the 5-year survival rate was 69.1%, compared to 20.0% in patients who underwent EBRT [971].

Overall, metastatic disease often requires an individualized approach that includes a combination of therapeutic options (surgery, radioiodine therapy, radiation, etc.). Shokoohi et al. published their experiences on recurrence therapy and achieved a very good treatment outcome in 67% of patients with multimodal therapy concepts [960]. Different collectives and different treatment concepts also result in variable

survival rates. Kim et al. reported on 242 patients with a 5-year survival rate of 85% and a 10-year survival rate of 68% [972].

In addition to the most common metastatic sites (lymph node, lung, skeleton), Madani et al. published on rare metastatic sites [973]. Mihailovic et al. confirm that the radioiodine avidity of metastases or the possibility of treating metastases with radioiodine is associated with a better prognosis than if this is not the case [974]. Patients with metastases in three or more organ systems have a particularly poor survival. Zhang et al. reported on 37/717 patients (5.2%) with metastases in three or more organ systems. The 5-year and 10-year survival was 45.9% and 37.8%, respectively, for patients with distant metastases in three or more organ systems versus 74.5% and 64.9%, respectively, for patients with distant metastases in one or two organ systems.

Radioiodine accumulation in the metastases was the main factor for longer survival [975]. Zunino et al. focused on the occurrence of rare organ metastases and described metastases in 36/3,982 patients (0.9 %), predominantly localized in the CNS. These patients with rare organ metastases often had a poor prognosis: after a median follow-up period of 13 months, 21/36 (58.3 %) patients had died as a result of DTC [976].

7.2 Therapy of tumor persistence, recurrence and/or metastases

7.2.1 Lung metastases

7.5	Consensus-based Recommendation	2025
EK	Unless the metastases are known to be radioiodine-refractory, RIT should be performed in the case of multilocular or disseminated lung metastases.	
	Strong Consensus	

7.6	Consensus-based Recommendation	2025
EK	Local therapeutic procedures (surgical resection or external radiotherapy) or "watch and wait" can be used for low grade, oligofocal lung metastasis, especially in radioiodine-refractory tumors. An individual treatment plan should be recommended in the interdisciplinary tumor board.	
	Consensus	

Sabra et al. presented data on the course of patients with lung metastases who were treated only with TSH-suppressive levothyroxine therapy after thyroidectomy and RIT. The median overall survival of the 199 patients was 10.5 years, the median progression-free survival 3.7 years. At the time of the last follow-up (median 6.9 years after

diagnosis of lung metastases), 68% of patients had tumor progression and 46% of patients had died. This collective can be regarded as a reference collective for the spontaneous course of DTC patients with lung metastases [977].

In the case of lung metastasis, a distinction must be made between miliary seeding and multiple single or multiple well-defined metastases [978]. In the former case, it is not possible to determine the size of the metastases or perform a morphological check. The success of radioiodine therapy is good. A cure is possible. When planning the treatment of lung metastases using RIT, the patient's age, the number and distribution pattern of the lung metastases (micro- versus macronodular lung metastases and multilocular-disseminated versus oligofocal tumor burden) and - if preliminary images are available for comparison - the growth dynamics must be taken into account. An increase in the size of lung metastases and the loss of radioiodine accumulation are the cause of different clinical courses and differences in prognosis [979].

Song et al. reported on 256 patients with radioiodine-avid lung metastases (256/372, 68.8 %). Of these patients, 156 patients (156/256, 60.9%) showed a significant decrease in serum thyroglobulin levels after RIT and 138 patients (138/229, 60.3%) showed a morphologic decrease in lung metastases on follow-up CT. Song et al. reported a cure in 62/256 patients (24%) by RIT [980]. Multivariate analysis showed that age, the presence of multiple distant metastases and the size of lung metastases were significant independent variables between the radioiodine-avid and non-radioiodine-avid groups. Patients under 40 years of age, lung metastases up to 1 cm in diameter and possibly also lymph node metastases had a better survival than patients over 40 years of age, lung metastases over 1 cm in diameter and other organ metastases, for example in the skeleton [980]. Yang et al. also reported favorable treatment effects with radioiodine: Of 151 patients with lung metastases, 17 patients achieved a complete response with RIT and 71 patients a partial response. 63 patients had no response. Survival was 72.2% after 5 years, 55.2% after 10 years and 51.3% after 15 years [561].

These data are confirmed by Wang et al. in an evaluation of 20 patients and a meta-analysis. Wang et al. reported a response rate to RIT of 40%, but 58% in the meta-analysis, which had its reasons in the composition of the therapy collectives [981]. In a recent publication, Wang et al. report on the benefits of RIT for the treatment of patients with lung metastases: 83/117 patients (71%) responded to the therapy, documented by a decreasing thyroglobulin level [982]. High cumulative therapy activities were used. Yang et al. report a mean cumulative activity of 19.6 GBq (530 mCi) (range 3.7 - 61 GBq (100 to 1650 mCi)) ^{131}I. The effectiveness in the group receiving up to 14.8 GBq (400 mCi) cumulative radioiodine was lower (10-year survival rate 38%) than in the group receiving at least 33.3 GBq (900 mCi) (10-year survival rate 80%) [983]. In their meta-analysis, Zang et al. report a pooled effectiveness of RIT for pulmonary metastases of 58% [981].

Kim et al. point to prognostic differences between micrometastasis (lung metastases < 1 cm) and macrometastasis (lung metastases ≥ 1 cm). Macronodular metastases were found in 27/112 patients (24%). These patients had a significantly poorer response to therapy and poorer progression-free survival. Radioiodine avidity had a significant prognostic impact in the group with micronodular lung metastases [984].

Lin et al. reported on lung metastases in FTC patients: 70/272 patients (25.7%) had lung metastases, the 10-year survival rate was 54%. Tumor size and cumulative

radioiodine activity had an impact on survival, with a cumulative average of 14.2 ± 1.8 GBq (383 ± 48 mCi) ^{131}I administered to these patients [985].

Zhu et al. refer to the prognostically unfavorable group of de-differentiated, [^{18}F]FDG-avid lung metastases [554]. Identifying a prognostically unfavorable group with a short tumor doubling time of less than 1 year can guide the decision to treat with kinase inhibitors [986]. Demarcated lung metastases, on the other hand, can be morphologically monitored and this information can be taken into account when determining the indication for RIT. The younger the patient and the more extensive the lung metastasis, the more generous the indication for RIT. The older the patient and the slower the tumor growth or the Tg doubling time (> 6 - 12 months), the more likely it is that a wait-and-see approach will be chosen [986].

Micronodular, iodine-storing lung metastases (not always visible on CT, often not visible on conventional chest X-ray) can be treated with ^{131}I at intervals of 6 - 12 months if necessary. The RIT can be repeated as long as there is a relevant ^{131}I storage. A further RIT is made dependent on the response to the previous RIT. Usually you want to see a (significant) drop in the tumor marker thyroglobulin. There is a treatment corridor with a few high-dose cycles with the longest possible treatment-free intervals versus a higher number of treatment cycles with careful dosing of radioiodine. The former approach is preferable.

The subgroup with micronodular or miliary metastasis has the best prospects of achieving a complete remission. Kim et al. confirmed that complete remissions were found in the group with micronodular metastases [987]. A good response to therapy in micronodular metastases is also reported by Long et al. with a response rate of 95.2 % (20/21 patients) in whom the lung metastases were only visible on iodine imaging but not on CT [988].

If there was initially extensive micronodular lung metastasis, a still measurable Tg level is often present after repeated RIT and decreasing iodine storage of the lung metastases. The indication for a further RIT is then based on the intensity of ^{131}I storage in the previous ^{131}I whole-body scintigraphy and the bone marrow reserve (neutrophils, platelets). ^{124}I-PET is not very suitable for ruling out disseminated lung metastases; in this situation, a ^{131}I post-therapy whole-body scintigraphy is superior. The level of therapy activity (standard activity, weight-adapted for children if necessary and the number of RIT depends on the response to previous treatments. When planning repeated radioiodine therapy, possible side effects must be taken into account. If the situation is stable, it may be possible to wait for years and only plan a new RIT if there is clear biochemical or morphological progress. The prognosis is very good, especially in children and adolescents under TSH suppression with levothyroxine [614].

Radiation pneumonitis or radiation fibrosis are rare complications after repeated high-dose ^{131}I therapies for disseminated lung metastasis. Corticosteroids may also be considered as an adjunctive medication in RIT of disseminated lung metastases to prevent pulmonary fibrosis, but the evidence for this approach is low.

Macronodular, iodine-storing lung metastases should also be treated with ^{131}I in the event of iodine storage. Treatment activity and the number of RITs depend on the response to previous treatments, disease progression, patient age, metastasis size, the absence/detection of other metastases and the prospects of success of other treatment options. A response to therapy speaks in favor of repeating radioiodine therapy.

In the case of lung metastases without iodine storage, the indication for surgical or ablative procedures should be reviewed. The possibility of atypical, tissue-sparing resection or local therapeutic alternative procedures such as radiofrequency ablation can be used.

In a review (9 studies with 112 children), Pawelczak et al. analyzed the treatment response of lung metastases in children and young adults < 21 years. A complete response was achieved in 47.3% of patients, a partial response in 38.4% and no response in 14.3%. The disease-specific mortality rate was 2.7%. Treatment-associated morbidity was low: only one patient had a secondary malignancy, one of eleven patients examined developed pulmonary fibrosis [989]. Wang et al. also investigated the efficacy of RIT for pulmonary metastases in children: RIT was effective in 55.9% (38 of 68) of patients, disease was stable in 26.5% (18 of 68) and ineffective in 17.6% (12 of 68 children) [990].

7.2.2 Skeletal metastases

7.7	Consensus-based Recommendation	2025
EK	Radioiodine therapy for the treatment of iodine-avid bone metastases shall only be used in consideration of the number and distribution pattern of the metastases and patient-specific factors. Depending on the extent (e.g. risk of fracture) of the osseous metastases, further therapeutic measures shall be planned.	
	Consensus	

Skeletal metastases occur in about 4% of DTC patients and are mainly localized in the spine, pelvis and ribs [991]. Qui et al. reported a lower frequency of 244/67,176 patients (0.36%) of the SEER database with synchronous skeletal metastases, the median survival of these patients was 22 months [992].

Skeletal metastases imply a worse prognosis: at a median follow-up of 11 +/- 9.6 years after diagnosis of DTC, 55% of the 64 patients followed up in this study died [991]. In their review article, Iñiguez-Ariza et al. reported a median survival of 4 years for DTC patients with skeletal metastases [993].

One of the rare localizations of skeletal metastases is the cranial skeleton. Varadarajan et al. reported on 59 patients with metastases in the cranial skeleton based on a review of the published literature. The treatment options are resection, radiotherapy and/or administration of radioiodine [994]. A rare but dramatic complication for the patient is paraplegia due to vertebral fractures of osteolytic metastases [995].

The treatment concept for skeletal metastases must be interdisciplinary. A cure is unlikely. Ramadan et al. specifically investigated the management of metastases in the spine and found a lack of an established treatment concept [996]. There is a spectrum of treatment options that includes surgery, local embolizing procedures, RIT, external radiation and drug therapy options (biphosphonates, VEGF receptor targets, etc.). Patient survival is better if the skeletal metastases can be completely removed or treated with radioiodine [996].

The therapy aims to achieve a high quality of life and avoid pathological fractures. Criteria for selecting a suitable treatment strategy for bone metastases are the risk of pathological fracture (metastases in weight-bearing skeletal segments), the risk of neurological complications (spine), pain symptoms, the storage behavior for ^{131}I and the radiosensitivity of adjacent organs (percutaneous radiotherapy). Complete surgical resection of isolated bone metastases leads to an improved outcome [996]. Symptomatic bone metastases that cannot be resected or can only be resected incompletely can be treated with a combination of different therapy methods (radioiodine therapy, percutaneous radiotherapy, local interventional therapy, systemic therapy).

Califano et al. reported on 52 DTC patients in a multicenter retrospective evaluation from Argentina, two thirds of whom had multiple skeletal metastases. FTC patients metastasized to the skeleton more frequently (7 - 28%) than PTC patients (1.4 - 7%). The spine is often the site of skeletal metastasis. Skeletal pain was the initial symptom in half of the patients. 42/52 patients were treated with radioiodine, of these 30 patients received a cumulative activity of more than 22.2 GBq (600 mCi) ^{131}I. 2- and 5-year survival rates were 64 and 38% respectively. At a median follow-up of 34 months, half of the patients died, a quarter in direct connection with the tumor disease [997].

Small bone metastases without abnormalities on morphological imaging are most likely to be cured with a few radioiodine therapies, especially in young patients [998], [999]. In contrast, only a few patients with large and multiple metastases were cured with radioiodine; 5-year survival in these patients was around 60 % [969].

Kondraciuk et al. reported on 74 patients with bone metastases. Those treated with external beam radiotherapy had a better survival: 5-year survival was 59%, median survival 92 months. TERT or BRAF mutations had no unfavorable effect on survival [1000]. Wu et al. report on a retrospective analysis of 77 patients with skeletal metastases, of whom 23/77 patients had received a single therapy and 54/77 multiple therapies; the median survival in the first group was 3.9 years and 7.7 years in the second group. Patients treated with radioiodine within 6 months and those who received radiotherapy had better survival [62].

Mazziotti et al. reported on the Italian MOSCATI study (**M**etastases **O**f the **S**keleton from **CA**rcinoma of the **T**hyro**I**d). 131 patients with skeletal metastases were included in this study. Overall mortality was significantly reduced by RIT (HR 0.10; p = 0.02), while drugs interfering with bone metabolism (p = 0.36), external radiotherapy (p = 0.54) and surgical interventions (p = 0.43) had no significant effect on skeletal metastases [1001].

In a recent review, Kato et al. describe the range of treatment options including surgical resection [1002]. Rare localizations such as skeletal metastases of the facial skull may require special surgical interventions [1003], [1004].

Deandreis et al. found no advantages in the comparison of an empirical versus dosimetric approach in the treatment of skeletal metastases using radioiodine [1005].

7.2.3 Brain/CNS metastases

7.8	Consensus-based Recommendation	2025
EK	When planning the treatment of brain and spinal canal metastases, surgical resection or external radiotherapy shall be considered first. Radioiodine therapy can be used for brain or CNS metastases, but is less effective than the former procedure.	
	Strong Consensus	

7.9	Consensus-based Recommendation	2025
EK	In the case of cerebral or spinal metastases with a risk of compression, glucocorticoids can be administered with the aim of edema prophylaxis or edema reduction.	
	Strong Consensus	

Brain metastases are rare. Hong et al. found brain metastases in 25/4,683 DTC patients (0.5%), of these 24 patients had further metastases outside the CNS. 20/24 patients underwent surgery, 4 received radiotherapy and one patient received "best supportive care". The median survival after diagnosis of brain metastases was 27 months [1006]. Osborne et al. reported on 79 DTC patients with brain metastases. The median survival of these patients was only 18 months, which was comparable to the 17.5 months reported in a publication by Wu et al. [1007]. A maximum of 3 brain metastases and surgical resection improved survival [1000]. Even less favorable are the data from Simões-Pereira et al., who reported on 27 patients with brain metastases with a median survival of only 5 months; only the patients who were offered surgery had a slightly better survival [1008]. Wu et al. published 22/2,013 DTC patients with brain metastases (1.1%) from 2000-2020 with a median survival of 17.5 months. Only neurosurgical measures had a favorable impact on survival [1007]. Slutzky-Shraga et al. confirm these statements [1009].

Surgical resection is therefore the primary treatment option for brain metastases, regardless of radioiodine storage. If the CNS metastases are not amenable to a surgical procedure, percutaneous or stereotactic radiotherapy is recommended. If ^{131}I therapy of iodine-avid CNS metastases is considered, concomitant glucocorticoid administration should be recommended to minimize the potential swelling of metastases or the risk of concomitant peritumoral edema due to TSH stimulation and β-radiation of RIT. RIT is less effective than surgery or external beam radiotherapy for the treatment of brain metastases and is therefore usually a third choice treatment. The benefit of glucocorticoid therapy to reduce pressure symptoms in RIT is not well established, but clinical experience shows that corticosteroids work well for pre-existing symptoms.

Gomes-Lima published on 24 patients with brain metastases. Patients who underwent surgery had a longer median survival time than those who did not undergo surgery (27.3 months versus 6.8 months; P = 0.15). Patients who underwent stereotactic radiosurgery had a longer median survival time than those who did not receive such

therapy (52.5 months vs. 6.7 months; P = 0.11). Twelve patients (50%) were treated with tyrosine kinase inhibitors (TKIs), and these had better survival than those who did not receive TKIs (median survival 27.2 months vs. 4.7 months; P , 0.05) [1010].

Although patients with brain metastases have a poorer prognosis, long-term survivors have been reported in individual cases [1011], [1012].

7.3 When is systemic therapy indicated? And which medication should be used?

7.10	Consensus-based Recommendation	2025
EK	Patients with radioiodine-refractory metastatic DTC that is asymptomatic, stable or minimally progressive, with a low probability of developing rapid progression with clinically significant complications and no indication for local therapy, shall be observed under TSH-suppressive therapy. Regular imaging checks (every 3-12 months) are recommended with evaluation in the interdisciplinary tumor board in the event of clinically significant progression.	
	Strong Consensus	

Patients with radioiodine-refractory metastatic DTC often have indolent clinical courses for years without any impairment of their quality of life. Despite the great progress made in the systemic treatment of radioiodine-refractory DTC, it must be borne in mind that complete remissions have only been described in a few individual cases to date and there is insufficient data on the prolongation of overall survival [1013], [24], [60], [1014], [1015]. It also remains unclear on the basis of the current data whether starting treatment earlier improves therapeutic efficacy. This must be carefully weighed up against the high quality of life of patients with advanced radioiodine-refractory DTC, who often have very long stable courses. In view of the sometimes not insignificant side effect profiles of systemic therapy options with a low but clinically relevant mortality risk (1.5-2%) [1016], the motto "less is more" therefore still applies today in line with the current international guidelines [24], [60], [1014], [1015]. The use of molecularly targeted therapies is only indicated if there is significant progression with a high tumor burden, local therapy measures are no longer useful and a Watch & Wait strategy can no longer be justified. The extent of the metastasis, the symptoms caused by the tumor disease, the co-morbidities and the growth dynamics of the radiologically evident lesions are taken into account.

No studies are available to determine adequate intervals for staging examinations as part of the Watch & Wait strategy. Staging intervals of 3-12 months are reasonable, taking into account the tumor burden, growth dynamics and the location of the metastases. Significant progression is assumed according to RECIST criteria if there is an increase of at least 20% in the sum of the longest diameters of the target lesion, if significant new metastatic lesions occur or if tumor-induced symptoms occur. An increase in the tumor marker thyroglobulin alone without morphological progression is not a basis for starting systemic therapy [24].

7.11	Evidence-based Recommendation	2025
GoR **A**	Systemic therapy with the approved multityrosine kinase inhibitors sorafenib, lenvatinib, or cabozantinib (from second-line) shall be considered as part of an evaluation in the interdisciplinary tumor board in patients with radioiodine-refractory DTC/PDTC if metastatic, rapidly progressive (according to RECIST), symptomatic and/or locally immediately threatening disease is present without meaningful local treatment options.	
LoE ⊕⊕⊕⊖ - ⊕⊕⊖⊖	⊕⊕⊕⊖: Sorafenib: OS [Brose, MS et al. 2014], Lenvatinib: PFS [Schlumberger, M et al. 2015], Cabozantinib: OS [Brose, MS et al. 2021], [Brose, MS et al. 2022] ⊕⊕⊖⊖: Sorafenib: PFS [Brose, MS et al. 2014] ⊕⊕⊕⊕: Lenvatinib: OS [Schlumberger, M et al. 2015], Cabozantinib: OS [Brose, MS et al. 2021], [Brose, MS et al. 2022] [1017], [1018], [1019], [1020]	
	Strong Consensus	

There are 3 randomized controlled phase 3 studies on the approved multityrosine kinase inhibitors (MKI) sorafenib (DECISION Trial) [1017], lenvatinib (SELECT Trial) [1018] and the recently approved cabozantinib in second-line therapy (COSMIC-311) [1019]. An update on the latter study has been published [1020].

Based on a randomized, placebo-controlled multicenter phase 3 study (DECISION study) in patients with radioiodine-refractory DTC (sorafenib n=207; placebo n=210), sorafenib was approved in 2014 for the treatment of progressive locally advanced or metastatic radioiodine-refractory DTC. Progression-free survival (PFS) was prolonged to 10.8 months in the treatment arm vs. 5.8 months in the placebo arm, with tumor stabilization in 42% of patients and partial remission in 12.2%; there were no complete remissions. Adverse events were more common in the sorafenib arm (98.6%) than in the placebo arm (87.6%), requiring treatment interruption in 66.2%, dose reduction in 64.3% and treatment discontinuation in 18.8%, with hand-foot syndrome (76.3% vs. 9.6%), diarrhea (68.6% vs. 15.3%), alopecia (67.1% vs. 7.7%) and rash (50.2% vs. 11.5%) reported most frequently [1017].

Lenvatinib was approved as a further oral MKI on the basis of an international, randomized, multicenter phase 3 study (SELECT) for patients with progressive radioiodine-refractory DTC (lenvatinib n=261; placebo n=131) in 2015. It showed a PFS extension of 14.7 months to 18.3 months in the lenvatinib arm versus 3.6 months in the placebo arm, with an objective response rate (ORR) in the lenvatinib group of a remarkable 64.8%, which also included 4 complete remissions. Tumor stabilization was achieved in an additional 23% of patients in the lenvatinib arm. A PFS extension was seen both in treatment-naïve patients (PFS 16.7 months) and in patients who had already received prior therapy with an MKI (PFS 15.1 months), demonstrating the efficacy of lenvatinib in second-line therapy as well. A significant prolongation of OS was not observed for the overall study population, but could be demonstrated for the subgroup of older patients (> 65 years) [1021]. Adverse events occurred in 97.3% of patients in the lenvatinib arm vs. 59.5% of patients in the placebo arm, requiring dose reduction in 67.8%, treatment interruption in 82.4% and treatment discontinuation in 14.2% of patients, with hypertension (67.8% vs. 9.2%), diarrhea (59.4% vs. 8.4%),

fatigue syndrome (59% vs. 27.5%), loss of appetite (50.2% vs. 11.5%) and weight loss (46.4% vs. 9.2%) were most frequently reported [1018].

On the basis of convincing data with very good efficacy of cabozantinib in the second- or third-line setting in all histologic DTC subtypes, including poorly differentiated DTC (PDTC), an international multicenter phase 3 study of cabozantinib was conducted in patients with radioiodine-refractory DTC after progression on up to two prior antiangiogenic MKI therapies (COSMIC-311) (cabozantinib n=170; placebo n=88). PFS was 11 months in the treatment arm vs. 1.9 months in the placebo arm (PFS 16.6 months for pretreatment with sorafenib without lenvatinib; PFS 5.8 months for pretreatment with lenvatinib without sorafenib; PFS 7.6 months for pretreatment with sorafenib and lenvatinib). The ORR was 11% for cabozantinib, which included complete remissions (1%), vs. 0% in the placebo arm. Adverse events were more common in the cabozantinib arm (98%) than the placebo arm (85%), requiring dose reduction in 67% and leading to treatment discontinuation in 9%, with diarrhea (62% vs. 3%), hand-foot syndrome (47% vs. 1%) and hypertension (32% vs. 3%) reported most frequently [1019], [1020]. Based on these data, cabozantinib was approved in 2022 for the treatment of adults with locally advanced or metastatic radioiodine-refractory DTC who have experienced progression during or after prior systemic therapy.

None of the studies showed an overall survival benefit with the limitation of the crossover design. For lenvatinib, a significant prolongation of overall survival was demonstrated in a subgroup analysis for older patients (> 65 y.), who at the same time had significantly more severe side effects (grade ≥3) (89 vs. 67%) and required dose modification more frequently [1021].

In the presence of contraindications or failure of the approved MKI, a number of substances based on efficacy data in phase 2 trials are also available for use in individual treatment trials or optimally - if available - as part of trials, including everolimus [1022], pazopanib [1023], vandetanib [1024], [1025], sunitib [1026], [1027] and axitinib [1028], [1029] (National Comprehensive Cancer Network Guidelines, Thyroid Carcinoma, 2022).

7.12	**Consensus-based Recommendation**	**2025**
EK	In patients with metastatic radioiodine-refractory DTC/PDTC, a molecular genetic analysis of the tumor, including gene fusions, shall be carried out before deciding on the type of systemic therapy so that the use of selective inhibitors can be discussed in the interdisciplinary tumor board.	
	Strong Consensus	

Due to the increasing characterization of molecular alterations, at least some of which have been identified as oncogenic drivers, selective inhibitors have also become the focus of interest in radioiodine-refractory DTC in recent years. Based on the current data, a molecular genetic analysis of the tumor is therefore recommended for all patients with radioiodine-refractory progressive DTC so that the use of selective inhibitors can be discussed in an interdisciplinary team. Selective inhibitors are not only used for contraindications to the use of VEGFR-targeted MKI (relative contraindications include, in particular, poor cardiac function, recent myocardial infarction,

poorly controlled hypertension, colitis, diverticulitis, ulcer disease, large or poorly healing wounds, intestinal perforations, tumors with invasion of the trachea/esophagus/large vessels, hemoptysis, anticoagulant therapy, very low body weight), but should also be discussed in the interdisciplinary tumor board as alternatives to MKI with a lower side effect rate and convincing effectiveness [1030].

7.13	Consensus-based Recommendation	2025
EK	In patients with radioiodine-refractory DTC/PDTC who have RET fusion, with metastatic, rapidly progressive (according to RECIST), symptomatic, and/or locally immediately threatening disease without meaningful local treatment options, treatment with a selective RET inhibitor represents an alternative treatment approach with a low side effect rate and high treatment response and should be used.	
	Strong Consensus	

DTC can exhibit a number of gene fusions, such as RET, NTRK and ALK fusions, which can be therapeutically targeted with the available selective inhibitors.
The single-arm LIBRETTO-001 phase 1/2 study of the selective RET inhibitor selpercatinib included 22 pre-treated and 12 treatment-naïve patients with RET fusion-positive thyroid carcinomas, which resulted in complete remission in 2 and 4 patients, respectively, and partial remission in 15 and 7 patients, respectively, while the remaining patients showed tumor stabilization (ORR 77% and 92%, respectively). 4 patients achieved complete remission and 15 and 7 patients achieved partial remission, respectively, while the remaining patients showed tumor stabilization (ORR 77% and 92%, respectively) [1031], [1032]. The most common side effects of selpercatinib are dry mouth (39%), hypertension (30%), diarrhea (17%), fatigue (25%), increased liver enzymes (28%).
The long-term course of the patients in the LIBRETTO-001 Phase 1/2 study was published by Wirth [1033]. A total of 66 patients were followed up with regard to the RET fusion-positive tumors. The objective response rate was 85.8% (of non-pretreated patients). The median follow-up time was 24.9 and 30.4 months in the non-pretreated and pretreated groups, respectively. The median progression-free survival was not yet reached in the non-pretreated group. The overall survival rate at median follow-up was 94.4% in the non-pretreated group and 65.5% in the pretreated group. The safety profile was comparable to the initially published LIBRETTO-001 study.
Selpercatinib is now approved for RET fusion-positive thyroid carcinoma in first-line therapy (see bundesanzeiger.de; BAnz AT 10.12.2024 B3).
Similar efficacy was shown in the ARROW phase 2 study of the selective RET inhibitor pralsetinib, for which no approval for thyroid carcinoma is currently being pursued in Europe. The study included 9 patients with RET fusion-positive thyroid carcinoma, of whom 8 patients showed partial remission and one patient showed tumor stabilization. This shows a similar ORR of 89% [1034].

The most common side effects with pralsetinib were increased liver enzymes (34%), constipation (28%), leukopenia (34%), asthenia (26%), neutropenia (34%), anemia (29%). In contrast to the approved MKI therapies, both substances are associated with a relatively mild side effect potential with predominantly grade 1-3 side effects. Due to the documented efficacy and better tolerability, therapy with a selective RET inhibitor is recommended if RET fusions are detected.

7.14	Evidence-based Recommendation	2025
GoR **B**	In patients with radioiodine-refractory DTC/PDTC who have an NTRK fusion, with metastatic, rapidly progressive (according to RECIST), symptomatic, and/or locally immediately threatening disease without meaningful local treatment options, treatment with a selective TRK inhibitor represents an alternative treatment approach with a low side effect rate and high treatment response and should therefore be used.	
LoE ⊕⊖⊖⊖, ⊕⊖⊖⊖	⊕⊖⊖⊖: Larotrectinib: OS, Larotrectinib: PFS [1035]	
	Strong Consensus	

NTRK fusion-positive thyroid carcinomas were investigated in basket trials for the TRK inhibitors larotrectinib and entrectinib.
Larotrectinib showed an ORR of 86% in 22 patients with DTC, with 2 complete remissions, 16 partial remissions and 3 stabilizations. In the 13 patients with prior systemic therapies, the ORR was 92%. The PFS rates at 12 and 24 months were 100% and 84%, respectively, and the OS rates at 12, 24, 36 months were 100%, 92% and 79%, respectively. Side effects were predominantly mild (grade 1-2) [1035]. Current data from the basket studies on entrectinib were presented at ESMO 2021, including 13 patients with NTRK fusion-positive thyroid cancer who showed an ORR of 53.85% [1036]. Overall, it is recommended to look for NTRK fusions in radioiodine-refractory DTC, as an effective therapy is available with the selective TRK inhibitors that are tumor-agnostically approved for NTRK fusion-positive solid tumors. Despite the very low confidence in the quality of the evidence, the positive recommendation is made for the life-threatened patient group with NTRK.

7.15	Consensus-based Recommendation	2025
EK	In patients with radioiodine-refractory DTC/PDTC with metastatic, rapidly progressive (according to RECIST), symptomatic, and/or locally immediately threatening disease without meaningful local treatment options, an individual treatment attempt with a selective ALK inhibitor can be discussed in the interdisciplinary tumor board if ALK fusion is detected.	
	Strong Consensus	

In DTC with proven ALK fusion, promising use of ALK inhibitors, such as crizotinib [1037], [1038], [1039], has been shown in individual case reports. To date, there are no systematic clinical studies on ALK inhibitors in ALK fusion-positive thyroid carcinomas, but in individual cases an individualized treatment trial with an ALK inhibitor should be examined.

7.16	Evidence-based Recommendation	2025
GoR **B**	In patients with radioiodine-refractory DTC/PDTC with metastatic, rapidly progressive (according to RECIST), symptomatic, and/or locally immediately threatening disease without meaningful local treatment options, an individual treatment attempt with a selective BRAF inhibitor ± trametinib should be discussed in the interdisciplinary tumor board if a BRAF V600E mutation is detected.	
LoE ⊕⊕⊖⊖, ⊕⊖⊖⊖	⊕⊕⊖⊖: OS ⊕⊖⊖⊖: PFS [1040]	
	Strong Consensus	

Due to the frequent detection of the BRAF V600E mutation in radioiodine-refractory DTC, the efficacy of selective BRAF inhibitors was investigated both as monotherapy and in combination with MEK inhibitors in advanced, radioiodine-refractory DTC. In a phase 1 study of the BRAF inhibitor dabrafenib, 14 patients with BRAF V600E-positive PTC showed partial remission in 29%, stabilization in 43% and a total tumor volume reduction of at least 10% in 64%. The PFS was 11.3 months [1041]. In a phase 2 study, 53 patients with progressive BRAF V600E-positive DTC were randomized into 2 treatment arms: BRAF inhibitor dabrafenib alone (arm A; n=26) vs. combination dabrafenib with the MEK inhibitor trametinib (arm B; n=27). Partial remission was observed in 9 patients in arm A and in 8 patients in arm B with an objective response rate of 35% and 30% respectively and a PFS of 10.7 months and 15.1 months respectively without statistically significant differences in the two treatment arms. Interestingly, by crossover of patients who showed progression under dabrafenib monotherapy into the dabrafenib + trametinib arm (n=14), tumor stabilization or partial remission was achieved in 12 patients (disease control rate 86%) with an extension of PFS by 7.5 months [1040]. The side effects are relatively moderate overall (predominantly grade1/2), in the dabrafenib arm at 65% (most frequently fever (50%), hyperglycemia (46%), anemia (42%), hand-foot syndrome (42%), nausea (42%), alopecia (42%), chills (42%)), in the dabrafenib/trametinib arm 33% (most frequently fever (59%), nausea (52%), chills (52%), fatigue (52%), hypophosphatemia (41%)).

With low confidence in the quality of evidence, a response of dabrafenib has been shown, but also a superiority of combination therapy with trametinib, which is why the recommendation is made for the life-threatened patient group with a BRAF V600E mutation.

The BRAF inhibitor vemurafenib was investigated in a further Phase 2 study with 2 cohorts: Cohort 1 comprised patients without prior MKI therapy (n=26), Cohort 2 patients who had already been pre-treated with an MKI (n=25). Partial remission was observed in 38.4% of patients in cohort 1, in 27.3% in cohort 2, and stabilization in 57.7% and 63.6% respectively. Most striking was a significantly longer PFS of 18.2 months in cohort 1 vs. 8.9 months in cohort 2. These results indicate that vemurafenib is a very effective therapy for BRAF-positive PTC, especially in first-line therapy. Side effects were predominantly grade 1/2, most commonly rash (73%), fatigue (77%), dysgeusia (54%), creatinine increase (50%), weight loss (54%), joint pain (46%), loss of appetite (52%), nausea (52%), skin papillomas (52%), diarrhea (46%) [1042].

The BRAF inhibitors therefore represent an effective therapy with fewer side effects for BRAF V600E-positive DTC and should be discussed as an alternative to the approved substances in the context of an individualized treatment trial.

Treatment with the selective inhibitors listed above not only shows good antiproliferative efficacy in radioiodine-refractory DTC with corresponding genetic alterations, but can also have a redifferentiating effect with a significant re-induction of radioiodine storage capacity in the tumors, as is known from smaller pilot studies and individual case reports [1043], [1044], [1045], [1046], [1047], [1048], [1049]. It is therefore recommended to check radioiodine storage during ongoing therapy with these selective inhibitors by means of a diagnostic radioiodine scan and to carry out radioiodine therapy if radioiodine storage is sufficient. This so-called redifferentiation therapy should be considered at an early stage, taking into account tumor and radiobiological aspects, if possible in first-line therapy, which requires a detailed explanation with a critical risk-benefit assessment together with the patient, as long as there is no approval for this. Of course, the possibility of study inclusion should always be examined and given preference. In the absence of established protocols, this should be carried out at highly specialized centers.

7.17	**Consensus-based Recommendation**	**2025**
EK	In patients with radioiodine-refractory PDTC with metastatic, rapidly progressive (according to RECIST), symptomatic, and/or locally immediately threatening disease without meaningful local treatment options, an individual treatment attempt with a combination therapy with lenvatinib and pembrolizumab can be discussed at the interdisciplinary tumor board.	
	Strong Consensus	

In recent years, immunotherapeutic approaches have also been pursued in advanced, radioiodine-refractory DTC/PDTC, as in ATC. An initial phase 1 basket study of pembrolizumab showed disappointing results for monotherapy with pembrolizumab in 22 enrolled DTC patients with a partial remission of only 9% [1050]. A pilot study (n=8) led by Prof. Dr. Christine Dierks at the University Medical Center Freiburg on pembrolizumab in combination with lenvatinib (6 ATC, 2 PDTC) showed an excellent response in the ATC patients as well as a partial remission in both PDTC patients [1051], [1052]. Internationally, a phase 2 study initiated by the International Thyroid Oncology Group was conducted on this combination therapy in advanced radioiodine-refractory DTC. Cohort 1 (n= 29, combination of lenvatinib and pembrolizumab from the beginning) showed a partial response in 62% and additional tumor stabilization in 35% with a clinical benefit rate of 97% [1053] vs. 88%, which was described for lenvatinib monotherapy in the SELECT trial [1018]. Median progression-free survival was not yet reached, PFS at 12 months was 74%. In cohort 2 (n=25), in which lenvatinib monotherapy was started and pembrolizumab was only added at progression, partial remission was seen in 15% and tumor stabilization in 85% (clinical benefit rate 100%), median PFS was 12.6 months [1054]. This add-on therapy with pembrolizumab at progression under lenvatinib therefore appears to be the more effective approach.

7.18	Consensus-based Recommendation	2025
EK	Bisphosphonates or denosumab should be considered in patients with diffuse and/or symptomatic bone metastasis, taking into account renal function and monitoring of calcium levels, as well as prior dental evaluation.	
	Strong Consensus	

Bone metastasis represents a particular challenge in the management of patients with radioiodine-refractory DTC [1055]. Kinase inhibitor therapy alone is often not sufficient to control bone metastasis, as the efficacy of kinase inhibitors in bone metastases is limited compared to other metastases, such as pulmonary or lymphogenous metastases. In the case of isolated bone metastases, especially symptomatic bone metastases, local therapies, especially radiotherapy, are preferred. In cases of disseminated bone metastasis, the use of bisphosphonates or denosumab is recommended, primarily based on studies in other tumor entities, but also smaller studies in DTC that have shown a delay in the occurrence of skeletal complications [1056], [1057], [1058], [1059].

7.19	Consensus-based Recommendation	2025
EK	Patients who are eligible for kinase inhibitor therapy shall be informed in detail with individual risk-benefit assessment and information on alternative therapies including best supportive care.	
	Strong Consensus	

When deciding on systemic therapy, it must be taken into account that there is insufficient data from randomized clinical trials on a number of critical questions in connection with systemic molecularly targeted therapy for radioiodine-refractory DTC, such as the effect of systemic therapy on overall survival and quality of life, optimal patient selection, optimal timing for starting therapy.

Overall, based on the current state of the data, the treatment decision is based on expert opinion and patient preference/philosophy with individual risk-benefit assessment on both sides.

In order to ensure optimal individual treatment planning while exhausting all possible treatment options, including inclusion in controlled clinical trials, these patients should be urgently cared for by an interdisciplinary team of experts at specialized centers.

8 Medullary thyroid carcinoma (MTC)

Medullary thyroid carcinoma (MTC) affects around 5 % of all thyroid carcinomas and is characterized by a number of special features:

- it is a malignant degeneration of the C-cells of the thyroid gland,
- it is not involved in iodine turnover and does not store iodine, which is why radioiodine therapy is not possible [1060],
- it secretes calcitonin (Ctn) and carcinoembryonic antigen (CEA)
- it can only be cured by surgery,
- overall it has a relatively good prognosis with a relatively good quality of life,
- it occurs sporadically in approx. 75% and hereditarily in approx. 25% as part of multiple endocrine neoplasia type 2 (MEN2) in association with pheochromocytomas and/or primary hyperparathyroidism,
- a pathogenic germline variant in the RET protooncogene is the cause of MEN2, a somatic variant in the RET protooncogene in tumor tissue is often detectable in sporadic MTC.

8.1 Preoperative diagnostics

The preoperative suspected diagnosis of MTC is confirmed by the joint assessment of the clinic, sonography of the thyroid gland (suspected malignancy) and the cervical region (suspected lymph node (LN) metastases), the Ctn level (elevated) and, in individual cases, by fine needle aspiration (suspected malignancy/ suspected MTC). The results of these examinations determine the extent of surgical resection and are prognostically significant.

8.1.1 Clinical examination

8.1	Consensus-based Recommendation	2025
EK	The general anamnestic and clinical criteria for thyroid carcinoma: palpable, growing nodule in the thyroid gland and/or cervical lymph node swelling also apply to MTC; if this is suspected, further clarification shall be carried out to rule out or confirm MTC.	
	Strong Consensus	

8.2	Consensus-based Recommendation	2025
EK	MTC-specific anamnestic and clinical indications can be: an elevated Ctn and possibly elevated CEA level, therapy-resistant diarrhea, usually in the advanced, metastatic stage, are indicative. A positive personal history of pheochromocytoma and/or primary hyperparathyroidism and/or a family history of first-degree relatives with MTC and/or pheochromocytoma and/or primary hyperparathyroidism suggest MEN2.	
	Strong Consensus	

Sporadic MTC usually manifests itself in the fourth to fifth decade of life. Of the MTC diagnosed via a palpable thyroid nodule, 70% already have cervical lymph node metastases and 13% have distant metastases in the liver, lungs or bones [1061], [1062], [1063], [1064]. The 10-year survival is approx. 61-81% [1065], [1066], depending on the tumor stage at diagnosis, age, gender and pre- and postoperative Ctn levels. In the last decade, due to increasingly earlier diagnosis, more favorable tumor stages and improved surgical strategies, survival has increased overall, but also in the higher tumor stages [1065] , [1067].

8.1.2 Laboratory

8.3	Consensus-based Recommendation	2025
EK	In the case of suspected MTC and before any thyroid surgery for nodules, a Ctn determination shall be performed; an elevated Ctn is indicative of MTC. If MTC is suspected in the context of MEN2, a germline analysis of the RET gene shall be performed; molecular genetic evidence of an activating pathogenic germline variant of the RET gene is indicative of MEN2 syndrome. If MEN2 is suspected, appropriate diagnostics (plasma and urine metanephrines or serum calcium, parathyroid hormone) shall be performed before surgery to exclude or detect a pheochromocytoma or hyperparathyroidism.	
	Consensus	

The most important laboratory test leading to the diagnosis of MTC is Ctn. The molecular genetic detection of an activating pathogenic germline variant in the RET gene proves the familial variant of MTC. If a hereditary form of MTC (MEN2) is suspected, molecular genetic germline diagnostics should be performed preoperatively (see Chapter 8.5). If an activating pathogenic germline variant in the RET gene is present or there is a history of MEN2, a pheochromocytoma and primary hyperparathyroidism must first be excluded or confirmed biochemically before a thyroidectomy. If a pheochromocytoma is detected, it should be operated on first to avoid hypertensive crises during thyroidectomy (see Chapter 8.5).

8.1.2.1 Calcitonin

8.4	Consensus-based Recommendation	2025
EK	1. A basal Ctn determination should be performed to clarify thyroid nodules, at least preoperatively before thyroid surgery and in the case of sonographically suspicious findings. 2. The Ctn determination shall be carried out using a double antibody immunoassay, taking into account the pre-analytical requirements. The values shall be interpreted taking into account the gender- and age-specific reference values. 3. If MTC is suspected, surgical treatment should be carried out in a center with proven experience in thyroid cancer surgery.	
	Strong Consensus	

Ctn is a specific and sensitive tumor marker of MTC and is used for early detection, progression monitoring and prognosis assessment. It is also secreted by normal C cells, the level of serum concentration correlates with the tumor mass. Rarely (< 0.7%) is an MTC found without Ctn secretion [1068]. As early detection of MTC improves the prognosis [1069], [1070] and medullary microcarcinomas cannot be ruled out with certainty even by sonography examination or fine needle aspiration [1071], preoperative determination of Ctn is recommended at the latest before thyroid surgery due to sonographically suspicious thyroid nodules [1069], [1072], [1073], [1074].

Calcitonin determination: The new fully automated double antibody immunoassays for Ctn allow a reliable determination of gender-specific upper reference values (men up to 10 pg/ml, women up to 7.5 pg/ml, depending on the assay) and age-dependent reference values for children [1075], [1076], [1077], [1078]. During pre-analysis, it must be ensured that the blood sample is centrifuged within 60 minutes and the serum frozen, as the Ctn can degrade by 20% within 2 hours at room temperature [1077]. If correct pre-treatment of the sample is not ensured, a Ctn determination must not be carried out.

Calcitonin elevation: Ctn levels above 100 pg/ml indicate an MTC in almost 100% of cases, whereas Ctn levels between 10-20 pg/ml (women) and 20-50 pg/ml (men) result in a diagnosis of MTC in only 5 and 8.3% respectively [1073], [1079]. The newer assays reliably and reproducibly detect the range between 10 and 100 pg/ml, which is important for the diagnosis of micro-MTC. Slightly elevated Ctn levels are also found in C-cell hyperplasia, which can be found as a precursor of hereditary MTC, but also as a concomitant phenomenon in other benign thyroid diseases [1080]. The gray area with unspecifically elevated Ctn levels due to other diseases or medications can now be better defined. The non-specific increases in basal serum Ctn levels seen more frequently with the earlier assays in autoimmune thyroiditis, renal insufficiency, use of proton pump inhibitors, alcohol consumption, smokers, etc. now only occur in a gender-specific gray area of up to 20 pg/ml in women and up to 30 pg/ml in men with the new assays [1078]. Rare exceptions are heterophilic antibodies, ingestion of biotin and the paraneoplastic secretion of Ctn in neuroendocrine tumors [1081][1081], [1082].

Calcitonin screening in thyroid nodules: The prevalence of MTC in a population with nodular goiter is approximately 0.31-0.4% [1069], [1083], ranging from 0.14 to 7.6% [1084] in autopsy series depending on geographic region. Routine determination of Ctn in the investigation of thyroid nodules enables early diagnosis and thus an improvement in prognosis. Ctn screening for thyroid nodules is endorsed by the German Society of Endocrinology [1085], the Surgical Association of Endocrinology (CAEK), the European Thyroid Association [1086], [1087] and the European Society of Medical Oncology (ESMO) [1088]. The American Thyroid Association Thyroid Nodule and Cancer Guideline [1089], [24] and the American Thyroid Association guidelines for the Management of Medullary Thyroid Carcinoma [335] leave the recommendation open, the British Thyroid Association [60] does not recommend it due to a lack of evidence.

A Cochrane analysis on the significance of Ctn determination for the detection of MTC in patients with thyroid nodules found a prevalence of MTC of 0.32% in 16 studies with a total of 72,368 patients. A sensitivity of 100% (95%CI: 99.7-100) was found at a cut-off value of 10 pg/ml. Due to the low prevalence and the high rate of false positive results at a cut-off value of 10 pg/ml with a positive predictive value of only 7.7% (95%: 4.9-12.1), Ctn screening remains controversial [1090]. For the goiter and thyroid nodule endemic area of Germany, there is a lack of data on the cost-benefit/(cost-harm) analysis of such screening. Due to the rarity of MTC, the diagnostic uncertainty with only slightly elevated Ctn levels, the non-comparability of old Ctn assays with different reference ranges, and the lack of binding threshold values in the past, basal Ctn determination has not been generally accepted. In the case of only slightly elevated Ctn values, attempts were made to achieve better diagnostic certainty by stimulating Ctn with the aid of pentagastrin or calcium. If the threshold values for a pathological stimulation test are poorly defined, it is not possible to reliably differentiate between C-cell hyperplasia and microcarcinoma [1072] and this can result in overtreatment [1091], [1092]. The lack of availability of pentagastrin and the occasional cardiac side effects associated with calcium stimulation [1093] have increasingly pushed stimulation tests into the background. A comparison between Ctn stimulation with pentagastrin or calcium and the determination of Ctn basal levels with modern measuring systems did not show any superiority of Ctn stimulation [1079], [1094], [1091].

8.5	**Consensus-based Recommendation**	**2025**
EK	1.a. From a limit value of ≥ 30 pg/ml Ctn for women and ≥ 60 pg/ml for men, a MTC can be expected with high probability. 1.b. Ctn levels in the gray area between the upper reference value and 30 pg/ml (women) or 60 pg/ml (men) shall be monitored. If elevated Ctn levels above the limit of ≥ 30 pg/ml Ctn for women and ≥ 60 pg/ml for men are confirmed, surgery shall be performed. These limits do not apply to children and adolescents. 1.c. Stimulation tests for Ctn only provide greater certainty in the early diagnosis of MTC in individual cases and shall therefore not be performed routinely.	
	Strong Consensus	

By selecting the above-mentioned threshold values for recommending surgery, 6-13% of micro-MTCs are overlooked in the range up to approx. 30 pg/ml in women and approx. 60 pg/ml in men, but just as often only C-cell hyperplasia not worthy of surgery or non-specific, sometimes persistent Ctn elevations are found [1079], [1095], [1096]. In the literature, the positive predictive value for detecting an MTC is given as 95/100% for threshold values above 26/35 pg/ml in women and correspondingly 95/100% above threshold values of 46/68 pg/ml in men [1079], [1095]. The threshold values achieve a good balance between overtreatment, i.e. thyroid surgery in the case of elevated Ctn and benign histology (C-cell hyperplasia/no MTC) and the risk of overlooking an early-stage micro-MTC. Ctn values > 100 pg/ml usually indicate an MTC. In patients with thyroid nodules and Ctn values in the gray range (up to 30 pg/ml in women and up to 60 pg/ml in men), Ctn should be checked every 3-6 months and surgery should be performed if the limit values are exceeded. If one also considers the fact that an almost 100% cure rate can be achieved with Ctn values < 100 pg/ml [1071], this leads to a further improvement in the reliability of the use of basal values in Ctn screening for nodular goiter. Ctn screening should also be performed for all nodules smaller than 1 cm. MTC of size 0.4 to 0.6 cm have Ctn levels between 20 and 100 pg/ml [1071].

8.1.2.2 CEA and other markers

8.6	**Consensus-based Recommendation**	**2025**
EK	The carcinoembryonic antigen (CEA) is the second tumor marker in MTC. It shall not be used for preoperative diagnosis. It is a more stable marker compared to Ctn for tumor monitoring and can be used in the follow-up of metastatic MTC (see Recommendation 8.15).	
	Consensus	

In addition to Ctn, other substances such as CEA, pro-calcitonin, ACTH, chromogranin A and other neuroendocrine markers can be secreted by the MTC. CEA is of particular importance, as MTC is occasionally present in patients with a gastroenterologically clarified but persistent unclear CEA elevation. CEA is the less sensitive marker and often only rises when Ctn is clearly elevated (often only at Ctn levels above 100 pg/ml). Like Ctn, CEA correlates with the tumor mass. During the course of the disease, CEA is important as a tumor marker alongside Ctn, the fluctuation range of CEA values is smaller than for Ctn, and the rate of degradation in the blood is significantly longer. Paraneoplastic ACTH production can trigger ectopic Cushing's syndrome in MTC [1097].

8.1.3 Preoperative imaging

8.1.3.1 Sonography

8.7	Consensus-based Recommendation	2025
EK	A sonography of the neck of the thyroid gland and cervical lymph nodes shall be performed preoperatively. It serves as an indication of suspicious thyroid nodules and locoregional lymph node metastases.	
	Consensus	

Sonography is the method of choice for evaluating thyroid nodules due to its widespread use and ease of performance. The experience of the examiner influences the risk assessment of a nodule. The data on sonographic characteristics that indicate thyroid carcinoma is extensive, but due to the high prevalence, it is primarily based on the analysis of papillary thyroid carcinomas. The sonographic criteria for an MTC do not differ significantly from papillary thyroid carcinoma: hypoechogenicity, microcalcification, blurred borders, hypervascularity. These are indicators of a possible malignancy and in principle represent an indication for fine needle aspiration (FNA) [1098], [51], [1099]; in the case of suspected MTC, the result of the Ctn determination should be awaited first and, if the Ctn is elevated, FNA should be dispensed with in order to be able to reliably assess the desmoplasization reaction in the intraoperative frozen section (see Chapter 8.1.3.1).

Wolinski et al. investigated the sonographic characteristics of medullary thyroid carcinomas [1100]. Six exclusively retrospective studies with a total of 169 MTC patients were included. Common sonographic features were absent or irregular halo sign (89.9%), hypoechogenicity (83.4%), marked hypoechogenicity (32.7%) and a solid nodule (79%). Microcalcifications were seen in 35.5% and macrocalcifications in 27% of MTCs. An irregular margin was present in 38% of MTCs and a "taller-than-wide" form in 14.4%.

Kim et al. investigated the frequency of suspicious sonographic features in MTC compared to papillary thyroid carcinoma [1101]. MTCs were significantly more likely to be oval or round in shape and less likely to be irregular or "taller-than-wide" compared with PTCs. No significant differences were found for echogenicity, composition, margin and calcifications. In a similar, also retrospective study, cystic portions [1102] or mixed echogenicity [1103] were significantly more common in MTC than in PTC. Trimboli et al. were able to show in a retrospective comparison that PTC had significantly more suspicious sonographic features than MTC [1099]. In contrast to the previously mentioned studies, the feature of microcalcification was present more frequently in MTC than in PTC.

Cho et al. investigated whether sonographic features correlate with the likelihood of biochemical healing and found small size, round or oval shape, smooth margin and absence of microcalcification to be predictive factors for biochemical healing [1104]. Oh et al. investigated whether sonographic features are predictive of the presence of cervical lymph node metastases in the lateral compartment [1105]. In addition to size, an irregular shape, a spiculated margin and a subcapsular location were

identified as risk factors. In a retrospective multicenter study, Trimboli et al. showed that MTCs that appear as sonographically suspicious nodes are more likely to have lymph node metastasis and extrathyroidal spread than MTCs that do not appear suspicious according to sonographic criteria [1106][1106].

Two working groups investigated the applicability of a standardized reporting system or the sonographic patterns proposed by the ATA and were able to show that 95% of MTC fell into an intermediate or high risk class (TIRADS 4-5) and that the interobserver variance was acceptable [1107], [1108].

Focal autonomies, which often have an intermediate or high TIRADS risk class, can be ruled out by thyroid scintigraphy.

If sonography and Ctn determination confirm the presence of locally advanced MTC (invasion, lymph node metastases), computed tomography (CT) or magnetic resonance imaging (MRI) of the neck and especially the mediastinum may be useful for surgical planning.

8.1.3.2 Advanced preoperative imaging

8.8	Consensus-based Recommendation	2025
EK	An extended cross-sectional imaging examination (CT neck/thorax/abdomen and/or MRI abdomen (liver) shall be performed as part of the initial staging if Ctn levels exceed 500 pg/ml and distant metastasis (lung, liver, bone) is clinically suspected. PET/CT with suitable radiopharmaceuticals (preferably ^{18}F-DOPA) can be used for initial staging.	
	Majority Vote	

If Ctn levels exceed 1,000 pg/ml and cervical LN metastases are present, locoregional metastasis/distant metastasis should be assumed [1071]. A CT or MRI scan of the neck and mediastinum/thorax can be helpful for surgical planning. The role of functional radionuclide imaging in preoperative diagnostics is currently limited, as only a few studies are available [1109]. The use of positron emission tomography/computed tomography (PET/CT) with the tracer ^{18}F-DOPA showed a higher detection rate for cervical lymph nodes than sonography in the central or lateral compartment. Additive detection of mediastinal lymph node metastases or distant metastases by ^{18}F-DOPA-PET/CT influenced surgical planning in 6% of patients in each case [1110]. Additive detection of mediastinal lymph node metastases or distant metastases by ^{18}F-DOPA-PET/CT influenced surgical planning in 6% of patients in each case. Detailed staging with known distant metastasis is not necessary preoperatively. Lateral LN dissection is performed systematically regardless of distant metastasis and is used for cervical tumor removal. There are not yet enough studies on the use of PET/CT prior to primary surgery in cases of suspected metastasis [1109].

8.1.4 Cytology, pathology

8.9	Consensus-based Recommendation	2025
EK	Ctn determination is superior to cytology. Due to the particular importance of calcitonin screening, FNA is generally not required for the preoperative diagnosis of MTC. The assessment of a desmoplastic stromal reaction in histology is no longer possible with certainty after FNA, which is why FNA should not be performed in cases of suspected MTC as long as there is no normal Ctn level.	
	Majority Vote	

The histomorphological findings of a fully diagnosed MTC in the context of a thyroidectomy or lobectomy are classified by pathology with a corresponding pTNM classification (see also Chapter 4.1). The TNM classification differs for MTC only with regard to the clinical stages; the T, N and M categories are identical.
The 5th edition of the WHO classification provides for a new group of high-grade MTC with a correspondingly poorer clinical prognosis. This new category is defined on the basis of histological parameters such as proliferation and necrosis [1111], [1112], [1113].

Table 22: Histomorphologic criteria for the diagnosis of high-grade MTC according to the 5th edition of the WHO classification. A high-grade MTC is to be diagnosed if at least one of the three characteristics is positive.

		low-gradellow-grade MTC	high-grade MTC
1.	Number of mitoses per 2 mm²	< 5	≥ 5
2.	Ki-67 index	< 5 %	≥ 5%
3.	Necrosis	not present	present

Desmoplasia is generally defined as a neoplastic-induced and thus tumor-associated new formation of collagenous connective tissue, which is mainly found in carcinomas. Desmoplasia must be distinguished from reactive new connective tissue formation in the context of physiological scarring as a result of tissue injury and/or inflammation. In the case of a histomorphological assessment of malignant neoplasia, it is not always possible to distinguish with certainty whether the intra- or peritumoral fibrosis is desmoplastic or regenerative connective tissue formation.

Fine needle aspiration, which is frequently performed when a suspicious nodule of the thyroid gland is clinically diagnosed, leads to histologically detectable regenerative effects in thyroid and tumor tissue. In everyday practice, the histopathologist recognizes such areas in the tumor on the basis of tumor capsule defects, focal fibrosis with residual bleeding, fibroblastic stromal reaction and sometimes radially arranged tumor epithelial strands with regenerative changes [1114], [1115], [1116]. Pandit et

al. were able to demonstrate reparative effects in a study of 265 thyroid specimens after fine needle aspiration. In 38% of cases, suspicious changes such as regenerative tumor cell changes with nuclear atypia, capsular pseudoinvasion and metaplastic changes were also described [1115]. Bolat et al. compared 150 thyroid specimens with a condition after fine needle aspiration with 150 thyroid specimens without prior aspiration. As a result, significantly increased signs of hemorrhages, bleeding residuals, granulation tissue, pseudopapillary hyperplasia, fibrosis, calcification, capsular defects, cholesterol crystal clefts and focal microthrombus formation were detected [1116]. Against this background, the clinical information of a previous fine needle aspiration to the pathologist is necessary to allow a correct assessment of the intratumoral changes including fibrosis/desmoplasia.

The significance of stromal desmoplasia in MTC as a predictive marker of lymphonodal spread has been described several times and is also mentioned in the current version of the WHO classification for tumors of the endocrine organs [172]. In a retrospective study of a cohort of 50 hereditary and sporadic MTC, Kaserer et al. 2001 described for the first time the absence of tumor desmoplasia as a statistically significant histological marker against lymphonodal tumor spread [1117]. The same working group published further retrospective studies on 120 sporadic and 196 hereditary and sporadic MTC [175], [176]. Both studies supported the role of the lack of tumor desmoplasia as a strong positive prognostic marker and discussed the possibility of intraoperative frozen section diagnostics to avoid lateral lymph node dissection. In an extended and partly prospective study of this group, this thesis was further supported in a total of 360 hereditary and sporadic MTC. In the analysis, 17.8 % of the MTC showed no tumor desmoplasia. The patients who did not receive lateral lymph node dissection due to the diagnosis of no tumor desmoplasia made in the intraoperative frozen section nevertheless all achieved biochemical healing in the course of the procedure [178]. An independent study by another working group was able to collect similar data. Aubert et al. also showed the positive prognostic value of the absence of tumor desmoplasia in 54 sporadic MTC. A threshold value of desmoplasia of 20% of the tumor area was defined as predictive for the absence of lymphonodal spread [1118]. Only recently, a German working group was able to support these statements in a study of 139 retrospectively reviewed cases of MTC with a diameter of ≤ 25 mm. Tumors with a desmoplasia of < 10 % showed no lymph node metastases [179]. The intraoperative assessment of desmoplasia in MTC requires a high degree of experience with regard to the percentage classification of fibrosis based on the differentiation of true desmoplasia as opposed to perivascular intratumoral fibrosis in vascularized parts and amyoid deposits.

8.1.5 Molecular genetic diagnostics

8.10	Consensus-based Recommendation	2025
EK	If MTC is suspected (clearly elevated Ctn, women ≥ 30 pg/ml, men ≥ 60 pg/ml), a germline analysis of the RET gene from whole blood should be carried out, as in approx. 25% a hereditary MTC, possibly with pheochromocytoma and/or primary hyperparathyroidism, may be present (see also Chapter 8.5.2). If a negative result of a germline analysis of the RET gene is not available preoperatively, a pheochromocytoma and primary hyperparathyroidism shall be excluded biochemically preoperatively.	
	Consensus	

If the RET analysis is not available, a pheochromocytoma and primary hyperparathyroidism must be ruled out before surgery for MTC. Since a familial MTC cannot be ruled out or proven on the basis of family history alone, molecular genetic diagnostics are recommended for all MTCs. In approx. 3-7% of apparently "sporadic" MTC with an unremarkable family history, a pathogenic germline variant is surprisingly detectable, either as a de novo variant or as a pathogenic variant in the RET gene with low penetrance of the MTC [1119]. Molecular diagnostics for the presence of an activating pathogenic germline variant in the RET gene must be initiated at the latest after histological detection of an MTC (see Recommendation 8.15 / Chapter 8.3.1).

8.2 Initial surgical therapy

8.2.1 Surgical indication

8.11	Consensus-based Recommendation	2025
EK	If MTC is highly suspected biochemically, molecularly and clinically, surgery shall be performed as it is the only curative treatment option. Patients with thyroid nodules and a Ctn ≥ 30 pg/ml (women) or Ctn ≥ 60 pg/ml (men) are very likely to have MTC and shall undergo surgery (see Chapter **Fehler! Verweisquelle konnte nicht gefunden werden.**). In the presence of thyroid nodules and slightly elevated Ctn above the reference range of up to 30 pg/ml in women and up to 60 pg/ml in men, the value should first be checked after 3 months at the latest; if the values are reproducibly rising and approaching the limit value, surgery can be discussed. Micro-MTC (< 10mm) is found in a small percentage of patients, and lymph node involvement is very rare in these patients.	
	Consensus	

The aim of MTC surgery is to cure the tumor by completely removing the primary tumor and any affected lymph nodes.

Clinically detectable MTCs almost always already have more than 10 lymph nodes and often distant metastases and cannot usually be cured by surgery.

In the case of grossly invasive tumors, highly metastatic tumors or distant metastases, the goal is local tumor control to avoid local complications from the tumor.

For early diagnosis of MTC, basal Ctn values shall be determined in patients with thyroid nodules [1120]. MTC is considered highly probable with Ctn values above the limit of 30 pg/ml in women and above 60 pg/ml in men (seeChapter **Fehler! Verweisquelle konnte nicht gefunden werden.**).

For Ctn values above the reference value of up to 30 pg/ml in women and up to 60 pg/ml in men (gray zone), there is only a relative indication for surgery, as a micro-MTC (pT1a) is only rarely found, but C-cell hyperplasia with questionable precancerous significance is found far more frequently. Lymph node involvement is rarely observed here. If surgery is not decided upon, Ctn checks are recommended every 3-6 months and later annually. An increase of more than 30 pg/ml in women and more than 60 pg/ml in men is an indication for surgery. With basal Ctn values of up to 100 pg/ml, a cure is possible in almost all cases [1071].

8.2.2 Extent of surgery according to calcitonin level and desmoplasia

8.12	Consensus-based Recommendation	2025
EK	Surgical treatment of MTC: 1. A thyroidectomy shall be performed, as hereditary MTC and also 10% of sporadic MTC occur multifocally (on both sides), 2. Thyroidectomy shall be supplemented by central and possibly lateral cervical LN dissection, as early local/regional metastasis can occur, 3. A transsternal mediastinal lymphadenectomy is indicated if LN metastases are seen on imaging and curative surgery appears possible, or if LN resection is indicated to avoid local problems. 4. In advanced organ-spanning MTC with infiltration of the trachea and/or esophagus, resection may be advisable in individual cases to improve the prognosis. Exceptions in the surgical treatment of MTC: • In the absence of a desmoplastic stromal reaction in the frozen section, a **one-stage** cervical LN dissection should primarily be avoided. • If the preoperative Ctn values are slightly elevated (up to 30 pg/ml in women, up to 60 pg/ml in men), cervical lateral LN dissection can be primarily dispensed with. • Cervical lateral LN dissection can also be performed as part of a second operation if the Ctn value is **not** below the detection limit 6-12 weeks postoperatively.	
	Consensus	

In the case of biochemically proven MTC, thyroidectomy with bilateral central LN dissection is recommended, as 10% of sporadic MTCs also occur multifocally (bilaterally) and micro-MTCs are also associated with lymph node metastases (exception: lack of desmoplasia detection in frozen section) [1121], [1122]. It has been shown that in women with basal Ctn ≥ 85 pg/ml and men ≥ 100 pg/ml, at least 40% of women and 53% of men have lateral lymph node metastases [1091]. The authors therefore recommend performing a (unilateral) lateral LN dissection on the tumor side in addition to thyroidectomy and bilateral central LN dissection in the initial procedure. If the basal Ctn is >200pg/ml at the latest, a contralateral lateral LN dissection shall also be performed, as contralateral LN involvement has been described [1071].

Systematic lateral (unilateral) LN dissection as a compartment dissection can also be performed in individual cases as part of a second operation [1123]. Due to the early tendency to micrometastasize, central LN dissection is an important part of the initial procedure. The associated morbidity risk is estimated to be lower than the deterioration in prognosis or local complications arising during the course of the disease due to potentially affected but retained lymph nodes. In addition, the risk of morbidity is increased in the case of central re-intervention.

A systematic, en bloc compartment dissection with quantitative lymph node analysis (ratio of removed to affected lymph nodes) should always be performed. Selective, i.e. non-systematic lymph node removal ("berry picking" of enlarged lymph nodes) should be avoided. It reduces the chance of a cure, as the surgical conditions are more difficult in the second or completion operation that is then often necessary due to the scarring, which significantly increases morbidity [1124]. Re-surgery may be necessary in special individual cases after previous adequate compartment resection.

A transsternal mediastinal lymph node dissection is only indicated if there is suspected involvement of the corresponding lymph nodes and no distant metastases, or in individual cases to avoid local complications.

The tissue reaction caused by the fine needle biopsy is microscopically similar to a desmoplastic stromal reaction and should therefore be avoided. The intraoperative frozen section is necessary, as this is the only way to prove the absence of a desmoplastic stromal reaction, which means that lateral LN dissection can be avoided in approx. 27% of patients [175].

The desmoplastic stromal reaction is a characteristic of invasive tumor growth. MTC without desmoplastic stromal reaction is a special form. Tumors without desmoplastic stromal reaction do not form LN metastases. Patients with MTC without desmoplastic stromal reaction were cured in the long-term even without LN dissection [175]. Thus, in the absence of a desmoplastic reaction in the intraoperative frozen section, no further LN dissection is necessary regardless of the preoperative basal Ctn level.

However, since the absence of a desmoplastic stromal reaction in the frozen section can only be demonstrated after organ removal in the frozen section of the primary tumor, but central bilateral LN dissection is technically easier as long as the thyroid gland is still in situ, some centers always perform a central bilateral LN dissection first [1125].

8.2.2.1 Indication for completion surgery

8.13	Consensus-based Recommendation	2025
EK	If a sporadic MTC is found as an incidental finding after partial thyroidectomy and the postoperative basal Ctn level is not measurably low, no completion surgery shall be performed. In the case of persistently elevated Ctn levels postoperatively after inadequate initial surgery (no total thyroidectomy, no LN dissection), completion surgery shall be performed. If there is no evidence of distant metastases, there is a chance of achieving a "biochemical" cure through completion surgery. In the case of persistently elevated Ctn levels postoperatively with evidence of distant metastases, a locoregional recurrence can be avoided through completion surgery.	
	Majority Vote	

In the case of incidentally histologically documented MTC, no completion surgery needs to be performed after partial thyroidectomy in patients without evidence of a pathogenic variant in the RET gene and with postoperatively unmeasurable Ctn levels [1126], [1127], as no tumor tissue is expected in the residual thyroid gland and in the LN. In some older Ctn determination methods with less specific assays, the postoperative Ctn level is in the lower reference range [1128]. If Ctn levels are elevated postoperatively, completion surgery (residual thyroidectomy with central and possibly lateral LN dissection) should be performed.

In the case of persistently elevated Ctn levels postoperatively without evidence of distant metastases, completion surgery can achieve a "biochemical" cure in individual cases [1129], [1130], [1131]. If distant metastases are detected, completion surgery can prevent locoregional recurrence.

If no lateral LN dissection was performed during the initial thyroidectomy with bilateral central LN dissection, lateral LN dissection can be dispensed with if the post-operative Ctn value is below the detection limit or in the lower reference range (depending on the method of determination).

8.2.2.2 Surgery for micro MTC ≤ 10 mm (mMTC, pT1a)

8.14	Consensus-based Recommendation	2025
EK	Patients with a micro-MTC (≤ 10 mm) and Ctn values **above** the gender-specific threshold (women > 30 pg/ml; men > 60 pg/ml) shall be thyroidectomized and cervical LN dissected in the same way as larger MTCs, as LN metastases are present in 18.5%. In patients with micro-MTC (≤ 10 mm) and a Ctn **below** the threshold value, lateral LN dissection can be omitted during the initial procedure (especially in the absence of a desmoplastic stromal reaction in the frozen section); lymph node metastases were only found in the central compartment in <3%.	
	Majority Vote	

Patients with Ctn values **above** the gender-specific threshold (women > 30 pg/ml; men > 60 pg/ml) have a significantly increased risk of MTC and therefore have an absolute indication for surgery.

In patients with micro-MTC (≤ 10 mm) and a Ctn above the threshold value, 18.5% have LN metastases. The surgical procedure should be the same as for a larger MTC (pT1b - pT4) [1132], [1133] (see Chapter 8.2.2.1). If lateral LN dissection was not performed during the initial operation, lateral LN dissection shall be performed subsequently depending on the postoperative Ctn level.

In patients with a micro-MTC (≤ 10 mm) and a Ctn **below** the threshold value, only <3% had lymph node metastases in the central compartment. In these patients, lateral lymph node dissection can be omitted during the initial procedure. If the Ctn level is elevated postoperatively, this can be performed as part of a second surgery [1132].

8.3 Risk-adapted follow-up care for medullary thyroid carcinoma

8.3.1 Classification according to risk groups - follow-up strategy

8.15	Consensus-based Recommendation	2025
EK	The following findings shall be available for planning risk-adapted postoperative follow-up care of a histologically and immunohistologically confirmed MTC: • pTNM classification = staging • postoperative basal Ctn and CEA levels (6-8 weeks after surgery) • molecular genetic analysis for pathogenic germline variant in the RET protooncogene	
	Strong Consensus	

Lifelong follow-up is indicated for all MTC. A prerequisite for adequate follow-up care after surgical removal of the MTC is histological confirmation of the diagnosis, if necessary with the help of immunohistology, classification according to the pTNM scheme and thus staging, a postoperative basal Ctn and CEA level and the result of molecular genetic diagnostics for the presence of a pathogenic germline variant in the RET gene for classification into sporadic or hereditary variant of the MTC. These parameters determine the intensity and frequency of biochemical and imaging examinations as part of risk-adapted follow-up care. In the further course, risk-adapted follow-up care can be adapted based on the recording of progression by means of Ctn/CEA doubling times and imaging examinations with recording of growth according to RECIST criteria (dynamic risk stratification). Depending on the response to primary therapy, 3 groups of patients can be defined: biochemically cured, biochemically incomplete and structurally incomplete [1134], which also differ in terms of their prognosis and follow-up examination intervals [1135], [1136], [1137]:

Biochemically cured, very good result of primary therapy: the Ctn level is not measurably low postoperatively, CEA in the normal range, the tumor has been completely removed microscopically (R0 resection, usually stage I and II): then the patient can be assumed to be biochemically cured provided the histology is correct (Ctn immunohistology obligatory). In the first 2 years, six-monthly follow-up examinations with sonography of the neck, Ctn and CEA determination shall be carried out [1138]. Thereafter, if there has been no increase in Ctn, annual checks or even longer intervals can be carried out. The prognosis is very good: 87% survival after 20 years [1134].

Biochemically incomplete response: The Ctn level is usually persistently low to moderately elevated (usually ≤ 1,000 pg/ml) (mostly stage II and III). It can be assumed that MTC remains but is usually undetectable on imaging (clinically occult persistent). If the previous operation was not "adequate", a completion surgery should be performed if the postoperative Ctn level is elevated, even if the cervical imaging "staging" is negative and distant metastases have been excluded (see Chapter 8.2.2.1) [1139], [1140]. In the further course, six-monthly follow-up checks are usually sufficient. The frequency of diagnostic imaging can be planned on the basis of the primary findings and the tumor marker doubling time; close-meshed maximum diagnostics without therapeutic consequences is not advisable; the diagnostic imaging serves to determine the tumor burden or for "staging" in connection with a new therapeutic option. In most cases, active surveillance is sufficient, as the survival rate in this group can be up to 82% after 20 years [1134].

Structurally incomplete response: The Ctn level is significantly elevated (usually ≥ 1,000 pg/ml): Here, locally infiltrating tumor tissue (pT4a-b) or distant metastasis (stage IV) mostly in the lungs, liver and/or bones (clinically manifest MTC) can be assumed. A curative approach is no longer possible. Despite distant metastases, many patients have a good quality of life for years, as tumor growth is often very slow. An "active surveillance" strategy is then often possible. In the case of progressive tumor growth, the indication for intervention can be assessed with the help of the Ctn doubling time and imaging during the course (e.g. RECIST criteria) (see Chapter 8.4) [1141]. All therapies in this situation are non-curative, so the indication must also take particular account of the patient's quality of life and wishes. Even with distant metastasis at the time of diagnosis, the 10-year survival rate is 44% [1142].

8.3.2 Laboratory diagnostics as part of follow-up

8.16	Consensus-based Recommendation	2025
EK	TSH-suppressive therapy is not indicated in MTC; the TSH shall be within the reference range under levothyroxine substitution.	
	Consensus	

After thyroidectomy, levothyroxine substitution should be checked at every outpatient presentation. As MTC does not grow in a TSH-dependent manner, TSH in the reference range is sufficient.

8.17	Consensus-based Recommendation	2025
EK	A postoperative Ctn determination shall be carried out 6-8 weeks after thyroidectomy.	
	Majority Vote	

Depending on the level of the preoperative basal Ctn value, the drop in the (high) Ctn value can take weeks. The same applies even more to CEA, which has a longer half-life per se. The nadir is reached 6-8 weeks postoperatively [1143]. If the basal Ctn cannot be measured or is in the low reference range, this indicates a biochemical cure with an excellent therapeutic outcome. The six-monthly checks with non-measurable Ctn confirm **biochemical healing**. If the Ctn level is persistently elevated during controls, this indicates that tumor tissue is still present; levels up to 150 pg/ml usually indicate locoregional persistence, ≥ 1,000 pg/ml often already indicate distant metastases. Imaging at Ctn ≤ 150 pg/ml is usually unsuccessful due to insufficient tumor mass; in terms of primary therapy, these patients belong to the group with a **biochemically incomplete response**.

8.18	Consensus-based Recommendation	2025
EK	If possible, the Ctn doubling time (CEA doubling time, if applicable) should be calculated with 4 values over 2 years.	
	Consensus	

The progression of the tumor disease in the further course can vary greatly and can be estimated relatively well using the Ctn and CEA doubling time (a calculation aid can be found at www.thyroid.org/professionals/calculators/CDTC.php, [1144]. At least 4 Ctn/CEA values over 2 years are a prerequisite for a good statement. Patients with tumor marker doubling times ≤ 24 months also had image morphological

progression in 94% of cases; if the tumor marker doubling times were ≥ 24 months, 86% of patients had no detectable tumor growth [1145]. In favorable cases (no or long tumor marker doubling time > 2 years), further checks every 12 months are sufficient, treatment of asymptomatic metastases is not necessary, "active surveillance" is appropriate. The same applies to higher Ctn values and slow progression in the group with a **structurally incomplete response** to primary therapy. On the other hand, if Ctn and CEA doubling times are ≤ 1 year, monitoring of Ctn, CEA and also imaging at 3-month intervals is appropriate for treatment decisions (e.g. tyrosine kinase inhibitors).

8.3.3 Molecular genetic diagnostics in follow-up

8.19	Consensus-based Recommendation	2025
EK	In sporadic MTC, RET analysis of tumor tissue for somatic pathogenic variants may be useful for prognosis assessment and future treatment planning (e.g. selective RET kinase inhibitors).	
	Strong Consensus	

In sporadic MTC, a somatic RET variant can be detected in up to 90% of tumor tissue, most frequently the pathogenic variant M918T with high inter- and intra-tumoral heterogeneity [1146]. Somatic RET variants are rarely found in small primary tumors, whereas the prevalence increases in large primary tumors and lymph node metastases, and somatic RET variants are most frequently found in distant metastases [1147], [1148]. This has prognostic and therapeutic significance. Patients with a somatic RET M918T variant have a more aggressive course of disease and a poorer prognosis. The detection of a pathogenic RET variant is necessary for the treatment decision, especially for the selective RET kinase inhibitors that will be available in the future.

8.3.4 Postoperative imaging

8.20	Consensus-based Recommendation	2025
EK	In patients with postoperative persistently elevated Ctn (> 150 pg/ml), metastases of the MTC shall be localized by imaging and tumor growth shall be monitored over time. Methods, interval and extent shall be determined depending on the initial risk profile, the localization of metastases, and the course of the disease.	
	Consensus	

Depending on the location of the suspected metastases or the locoregional recurrence, imaging procedures that may be considered include sonography of the neck and abdomen, CT with contrast agent, magnetic resonance imaging (MRI) with liver-specific contrast agent if necessary, bone scintigram, DOPA-PET/CT, [^{18}F]FDG-PET/CT or SSTR-PET [1149]. The intervals of the examination, every 6 months to once a year, depend on the Ctn and CEA values and their doubling time, the size and location of the residual tumor/metastases and the extent of the progression of the tumor, the

patient's symptoms and, if applicable, the planned palliative therapy [1150]. Imaging only makes sense from a Ctn level of >150 pg/ml [335]. In patients who have only undergone lobectomy (Ctn not measurably low), examinations at yearly intervals and with sonography examination of the neck if Ctn is elevated up to 150 pg/ml are sufficient for long-term observation. This also applies to biochemically incomplete response to primary therapy including recurrence/completion surgery and long Ctn/CEA doubling time (> 2 years).

8.3.4.1 Sonographic diagnostics (see also Chapter 8.1.3.1)

8.21	Consensus-based Recommendation	2025
EK	A sonographic examination of the neck shall be performed 3 months after surgery to assess locoregional recurrence and the presence of cervical lymph node metastases; thereafter, sonographic examinations of the neck shall be performed depending on the initial risk profile, the localization of metastases and the course of the disease.	
	Consensus	

With the help of cervical sonography, locoregional recurrences with increased Ctn can be easily detected and the growth documented over the course of the disease. Sonographic examination of the neck is easy to perform and is a sensitive method for detecting local recurrence [1151]. Sonography can be helpful for the assessment of liver metastases, while other imaging modalities are also required in the case of distant metastases.

8.3.4.2 CT/MRI, skeletal scintigram

8.22	Consensus-based Recommendation	2025
EK	For the diagnosis and follow-up of MTC metastases outside the neck region, morphological cross-sectional imaging techniques should be used first: CT and/or MRI examinations (CT thorax/abdomen, MRI abdomen, dedicated MRI depending on the localization of MTC metastases). Sonography of the abdomen can be used to localize and assess the progression of liver metastases. Bone scintigraphy can be performed in individual cases, but is nowadays largely replaced by the methods mentioned above. The time intervals for imaging shall depend on the initial risk profile, the location of metastases and the course of the disease (doubling time of the tumor marker).	
	Majority Vote	

If distant metastasis is suspected, a contrast-enhanced CT of the thorax (for lung metastases and mediastinal LN) and MRI of the liver (liver metastases) and possibly a bone scintigram are useful; alternatively, a ^{18}F-DOPA-PET/CT can be performed if available.

8.3.4.3 Molecular (functional) imaging

8.23	Evidence-based Recommendation	2025
GoR **B**	For the diagnosis and follow-up of MTC metastases outside the liver, a PET/CT with a suitable radiopharmaceutical should be performed, as well as a corresponding regional MRI in the case of liver or brain metastases.	
LoE **3a**	[1152]	
	Consensus	

8.24	Evidence-based Recommendation	2025
GoR **B**	^{18}F-DOPA should preferably be used as a PET radiopharmaceutical, alternatively a DOTA-SSTR radiopharmaceutical. In the case of poorly differentiated or rapidly progressive MTC (tumor marker doubling time usually ≤ 12 months), [^{18}F]FDG can also be considered.	
LoE **3a**	[1152]	
	Strong Consensus	

The publications on PET examinations in metastatic MTC for diagnostic purposes examine various tracers, preferably [^{18}F]Fluor-DOPA, ^{68}Ga-DOTATOC and [^{18}F]FDG. The results are heterogeneous. Due to the rarity of the clinical picture, the original studies usually include around 20 patients.

Treglia et al. [1152] carried out a meta-analysis taking into account eight publications and evaluated the results of fluor-DOPA and FDG-PET/CT, also depending on the calcitonin (Ctn) or CEA serum concentration, which can be seen as an indicator of tumor burden and aggressiveness. With a Ctn > 1,000 ng/l the sensitivity was determined to be 86% (73% to 95%), with Ctn< 150 ng/l 39% (20% - 61%) In comparison across all lesions, the sensitivity for DOPA was slightly higher than for FDG; 71% versus 66%. Furthermore, PET diagnostics were reported to be more sensitive with shorter calcitonin doubling time, with a CTn doubling time below 2 years 86% independent of the level of serum CTn. The results of the studies considered are heterogeneous. The studies [1153] and [1154], which are included in the above-mentioned meta-analysis, point to the complementarity of the two tracers FDG and DOPA, whereby the sensitivity for FDG increases with increasing aggressiveness of the MTC. In [1154], a direct comparison between DOPA, FDG and a ^{68}Ga DOTATOC was also carried out in 18 patients; the sensitivities were 72%, 17% and 33% respectively.

In a prospective study, Terroir et al. [1155] compared the examination results (CT, MRI, DOPA-PET/CT and FDG-PET/CT) of 36 patients with a total of 74 metastases of MTC. They found PET/CT examinations to be superior to morphological imaging, with the exception of the liver. In this organ, MRI was able to detect all 11 filiae, whereas DOPA and FDG were unable to detect any. DOPA was superior to FDG for smaller lesions. Quantitative analysis on a lesion basis showed the following sensitivities; DOPA-PET/CT 84 % (75 % – 100 %); FDG-PET/CT 45 % (34 % – 57 %), whole body MRI 32 % (21 % – 44 %), whole body CT 32 % (21 % – 44 %). Although SSTR-PET/CT is inferior to the DOPA examination offered by only a few centers, it has the advantage of being widespread and available in Germany. In addition, SSTR examination offers the option of deciding on SSTR radionuclide therapy if the findings are positive. Consideration of all the above-mentioned aspects leads to the differentiated recommendation.

8.25	**Consensus-based Recommendation**	**2025**
EK	If radionuclide therapy is being considered, the prospects of success of [^{131}I]-mIBG therapy shall be evaluated using [^{123}I]-mIBG SPECT or SPECT/CT or the prospects of success of radio-DOTA-SSTR therapy with DOTA-SSTR-PET/CT.	
	Strong Consensus	

8.4 Treatment of metastatic MTC (including persistence and MTC recurrence)

8.26	**Consensus-based Recommendation**	**2025**
EK	Patients with metastatic MTC that is asymptomatic, stable or less progressive are less likely to develop rapid progression later in the course of the disease. A wait-and-see approach - "active surveillance" - with regular check-ups every 6-12 months shall be adopted, as many interventions reduce quality of life without evidence of improving survival.	
	Consensus	

8.27	**Consensus-based Recommendation**	**2025**
EK	In patients with progressive metastatic MTC, the possibility of local therapy shall be examined before initiating systemic therapy.	
	Consensus	

If there is clear progression of the metastases (RECIST criteria, more than 20% increase/year), tumor marker doubling time ≤ 1 year and imminent or existing tumor-related symptoms, loss of function or complications, the possibility of local therapy should be evaluated first, e.g. palliative surgery or radiotherapy [1156]. If local therapy is not possible or does not make sense oncologically, the indication for systemic therapy with tyrosine kinase inhibitors or RET kinase inhibitors should be evaluated. Even in the case of a primary diagnosis of MTC in an advanced metastatic state, surgery on the primary tumor with LN dissection should be performed from a palliative perspective in order to avoid local complications relating to the trachea and/or esophagus.

The treatment of metastatic MTC is extremely symptom-oriented, including the consistent treatment of secretory diarrhea in the advanced tumor stage with loperamide and/or tinctura opii, which is often neglected to the detriment of quality of life or dosed too carefully.

8.4.1 Indication for (local) re-surgery

8.28	**Consensus-based Recommendation**	**2025**
EK	In the case of persistent or newly occurring and progressive local recurrence or painful lymph node metastases in the central neck area (near the trachea or esophagus/infiltration), surgery using a palliative approach may be advisable in order to avoid local complications.	
	Strong Consensus	

If Ctn levels are persistently elevated postoperatively, residual tumor tissue in the neck or distant metastases should be assumed. If primary surgery is inadequate, completion surgery (see Chapter 8.2.2.1) shall be performed [1139], [1140]. Completion surgery should be used to attempt curative surgical treatment. However, if the following limits (postoperative persistently elevated Ctn levels up to max. 1,000 pg/ml without evidence of distant metastases, less than 5-10 affected lymph nodes, only two affected lymph node compartments and absence of lymphangiosis carcinomatosa) are exceeded, a curative approach is no longer possible. Therefore, all further therapeutic measures should be considered while weighing up the risk of morbidity and quality of life in the case of a remaining tumor with a possibly favourable prognosis. If the primary operation was "adequate" (total thyroidectomy with central and lateral lymph node dissection), a re-surgery may be indicated after imaging "staging" with locoregional MTC findings.

Re-surgeries using a **palliative** approach are particularly useful in cases of progressive local recurrence or painful lymph node metastases in the central neck area (near the trachea or esophagus/infiltration) in order to reduce local complications. Automatic surgery of newly occurring cervical metastases ("berry picking") should not be performed, as this leads to numerous interventions that impair the quality of life and do not affect the prognosis, but can often lead to complications such as recurrent paresis, hypoparathyroidism and arm muscle paralysis [449].

Local radiotherapy (tumor bed irradiation) may be useful for symptomatic tumor manifestations after surgical procedures have been exhausted [1157].

8.4.2 Therapy for specific issues

8.4.2.1 Invasion of the MTC in the trachea, larynx or esophagus

8.29	Consensus-based Recommendation	2025
EK	Radical resections of the larynx, trachea or esophagus should only be carried out after an individual and very strict risk-benefit assessment.	
	Majority Vote	

In the case of locally infiltrating tumor growth in the aerodigestive tract, resection of the larynx, trachea or esophagus is possible if the local situation requires resection. In most cases, advanced tumor disease with disseminated distant metastasis is present [454]. Accordingly, the indication for extended, organ-spanning resections should be viewed critically, as they often significantly impair quality of life.

In the case of a locally inoperable MTC, radiotherapy may be indicated if local symptoms are present at the same time or to avoid complications.

8.4.3 Local therapy of distant metastases

8.30	Consensus-based Recommendation	2025
EK	Bisphosphonates or denosumab should be considered in patients with diffuse and/or symptomatic bone metastases, taking into account renal function and monitoring of calcium levels and after prior dental examination (see S3 guideline on supportive therapy).	
	Majority Vote	

Bone metastases of MTC usually occur together with other distant metastases. They are usually multifocal, most frequently localized in the spine and pelvis, and are osteolytic, osteoplastic or mixed [1158], [1159]. Their treatment poses a particular challenge. Smaller, clinically unremarkable bone metastases can be observed initially. External radiotherapy or surgical intervention is indicated for painful bone metastases and/or if there is a risk of fracture, particularly in the case of vertebral metastases at risk of fracture. Systemic therapy alone, e.g. with tyrosine kinase inhibitors in advanced MTC, is often not sufficient to control bone metastasis. The use of antiresorptive therapy (bisphosphonates/denosumab) is therefore recommended, particularly in the case of disseminated bone metastasis. There are no prospective studies on MTC itself [1087], [335]. The recommendation is therefore primarily based on studies in other tumor entities that have shown a delay in the occurrence of skeletal complications [1158], [1056], [1057], [1160], [1058], [1059]. A recent study provides evidence

that the complication rate and prognosis are less favorable in MTC with osteolytic metastases and that antiresorptive therapy may be appropriate [1159].

Liver metastases of MTC are often small and disseminated and usually cause few symptoms. Clearly progressive and painful liver metastases should be treated, especially if there is pronounced diarrhea that cannot be controlled with loperamide or tinctura opii. Single or large metastases should, if possible, be surgically removed, but in most cases the metastasis is extensive and treatment with a local ablative procedure is therefore often of limited efficacy. Systemic therapy with a tyrosine kinase inhibitor would be useful in the case of aggressive MTC (see Chapter 8.4.4).

Lung metastases of MTC are often miliary, multiple and frequently associated with mediastinal LN. Local surgical or radiotherapeutic measures can be taken if the airways are obstructed with respiratory problems, but they also represent an indication for systemic therapy.

Brain metastases of MTC are rare and usually only become manifest with clinical neurological symptoms. Surgical resection, stereotactic radiosurgery or conventional radiotherapy may be considered.

Soft tissue metastases of MTC in the skin and breast are rare and only occur at an advanced stage. If possible, they can be treated locally (resection or radiotherapy); in the case of aggressive MTC, systemic therapy is advisable.

8.4.4 Systemic drug therapy

8.31	Evidence-based Recommendation	2025
GoR **A**	Systemic therapy with the tyrosine kinase inhibitors cabozantinib or vandetanib shall be considered in patients with advanced MTC with significant tumor burden and symptomatic or clinically relevant progressive disease, whereby vandetanib shall only be used in RET-mutated MTC after re-analysis of the approval study.	
LoE **1b**	[1161], [1162], [1163]	
	Strong Consensus	

Cytotoxic chemotherapy is only partially effective in metastatic MTC, which is why new molecular-targeted therapeutic approaches are preferred [335]. Tyrosine kinase inhibitors (TKIs) have been investigated in trials for advanced thyroid cancer for more than 10 years. The tyrosine kinase inhibitor vandetanib has been available in Germany for the treatment of advanced, rapidly progressive and symptomatic MTC since February 2012, and cabozantinib since October 2014.

Vandetanib is an orally administered TKI that acts on the RET tyrosine kinase receptor, which is frequently mutated in MTC, but also on the EGF receptor and VEGF receptor. A randomized phase III study (n = 331 patients) with 300 mg vandetanib/day by Wells [1162] showed that progression-free survival was significantly extended by 11.2 months to 30.5 months with vandetanib vs. 19.3 months with placebo. The

objective response rate was 45% according to RECIST criteria. Adverse events were more common in the vandetanib arm than in the placebo arm, the most common being diarrhea (56% vs. 26%), rash (45% vs. 11%), nausea (33% vs. 16%), hypertension (32% vs. 5%) and headache (26% vs. 9%). The most common grade 3–4 adverse events were diarrhea (11% vs. 2%), hypertension (9% vs. 0%), QT time prologation (8% vs. 1%), fatigue (6% vs. 1%). Treatment discontinuation due to side effects occurred in 28% of patients vs. 3% in the placebo arm.

A recent re-analysis of patients from the vandetanib pivotal trial who were originally included with unknown mutation status, published only in the form of a red-handed letter, showed an inadequate objective response rate of 18.2% in RET mutation-negative patients compared with an objective response rate of 51.7% in patients with a RET mutation. In view of this change in data, the efficacy of vandetanib is considered insufficient to justify the risk of side effects in RET-negative patients. Therefore, the indication for vandetanib was limited in January 2023 to the treatment of aggressive and symptomatic RET-mutated medullary thyroid cancer in patients with unresectable, locally advanced or metastatic disease.

Cabozantinib is also administered orally and acts on the RET tyrosine kinase receptor, the c-Met receptor and the EGF and VEGF receptors. In the pivotal phase III trial, 330 patients with image morphologically confirmed MTC progression after RECIST were shown to have significantly longer progression-free survival (11.2 months) compared to placebo (4.0 months) with an initial dose of 140 mg cabozantinib/day [1163]. Subgroup analyses show that patients with RET mutations have the longest extension of progression-free survival and that there are also indications of an extension of overall survival in this subgroup - even if these analyses must be interpreted with caution, as they were only collected post-hoc and have not been prospectively validated. For patients with unknown RET status and RET-negative status, efficacy in terms of prolongation of progression-free survival was also demonstrated [1163]. According to RECIST, 28% of patients treated with cabozantinib showed a partial remission. Grade 3 or 4 adverse events were reported in 69% of patients in the cabozantinib arm (most frequently diarrhea (15.9%), hand-foot syndrome 12.6%, fatigue 9.3%) vs. 33% in the placebo arm. The dose had to be reduced in 79% of patients due to significant toxicity (vs. 9% in the placebo arm), treatment discontinuation due to side effects occurred in 16% of patients on cabozantinib (vs. 8% in the placebo arm).

The results of both studies are not comparable due to conceptual differences in the study design. While only patients with radiologically documented progression within a period of 14 months were included in the cabozantinib study, patients without progression were also included in the vandetanib study. In addition, in the vandetanib study, a switch to the verum arm was possible in the event of radiologically proven progression during treatment. In the cabozantinib study, cross-over was not planned. These conceptual differences, which make it impossible to compare the results obtained, are also reflected in the shorter time of progression-free survival in the verum and placebo arm of the cabozantinib study. There are no studies that directly compare the effectiveness of vandetanib and cabozantinib. Therefore, a decision must be made on the basis of the patient's medical history, physical examination, ECG and laboratory results, previous illnesses, concomitant medication and tumor characteristics as to which drug is preferred in each individual case.

To date, no TKI has been convincingly proven to prolong survival in metastatic MTC. Complete remissions have also not been described. Furthermore, there is no evidence that an early start of therapy increases its effectiveness.

As mentioned above, therapy with TKIs is often associated with side effects: Diarrhea, skin rash, nausea, hypertension, headache and also severe side effects such as ECG changes. These side effects sometimes significantly impair quality of life, but can be alleviated by symptomatic therapies. Nevertheless, it is not uncommon for a dose reduction, therapy break or discontinuation of therapy to be necessary. As there is no clear evidence of benefit in the early stages of the disease, the indication for treatment with TKIs is currently only seen with the following criteria under individual risk-benefit assessment, also based on international guidelines [1087], [1144], [335]: high tumor burden and progressive (RECIST criteria), short Ctn/CEA doubling time < 1 year and pronounced symptomatic disease when local therapy measures have been exhausted. Uncontrollable pain and treatment-resistant diarrhea can also support the indication for TKI therapy in individual cases. Since the majority of patients are only slowly progressive even in the advanced metastatic stage and have a barely impaired quality of life, the sole evidence of metastasis and progression is not an indication for therapy, nor is the sole evidence of increased or rising tumor markers Ctn and/or CEA.

The recommendation is based on the high evidence quality of the studies for the response to therapy and is aimed at patients in need of therapy.

If a patient is not a good candidate for vandetanib or cabozantinib or if there is significant progression during the course of treatment, inclusion in a clinical trial should be considered. Alternatively, other TKIs can be used that have shown positive effects in phase II trials in MTC and have been used in other tumor entities as part of an individual treatment trial due to their approval (e.g. axitinib, pazopanib, sorafenib, sunitinib, lenvatinib) [1164], [1165], [1026], [1166][1166], [1028], [1167], [1168].

8.32	**Evidence-based Recommendation**	**2025**
GoR **A**	In patients with advanced MTC with significant tumor burden and symptomatic or progressive (according to RECIST) metastatic disease and evidence of a RET variant, a selective RET inhibitor with a low side effect rate and high treatment response shall be used.	
LoE **1b**	[1032], [1169], [1170]	
	Strong Consensus	

The phase I/II study [1032] and also the phase III study [1170] on the selective RET inhibitor selpercatinib show very good response rates in progressive advanced MTC in first-line therapy and after TKI pre-treatment with a significantly lower rate of side effects compared to the TKI inhibitors cabozantinib and vandetanib.

In the completed Phase I/II study of selpercatinib [1032], 55 patients with RET-positive medullary thyroid cancer who had been pretreated with vandetanib and/or cabozantinib showed an objective response rate of 69% (complete remission 9%, partial remission 60%) and a 1-year PFS of 82%. In 88 patients with RET-positive medullary thyroid carcinoma without prior therapy, the objective response rate was 73%

(complete remission 11%, partial remission 61%) and 1-year PFS 92%. The side effects were predominantly mild (grade 1-2), the most common grade 3, 4 side effects were hypertension (21%), transaminase elevation (GPT 11%, GOT 9%), hyponatremia (8%), and diarrhea (6%). Based on these study results, selpercatinib was approved in the USA in May 2020 for adult and pediatric patients ≥ 12 years of age with advanced or metastatic RET positive medullary thyroid carcinoma who require systemic therapy. In Europe, approval was granted in March 2021 for second-line therapy after treatment with vandetanib and/or cabozantinib in patients ≥ 12 years of age with advanced RET-positive medullary thyroid cancer.

The phase III trial of selpercatinib in advanced RET-mutated medullary thyroid cancer has now been published [1170]. A total of 291 patients were included in the study. It is a first-line therapy with selpercatinib compared to vandetanib or cabozantinib. The median follow-up was 12 months. The median progression-free survival was not achieved in the selpercatinib group; in the control group it was 16.8 months. Progression-free survival after 12 months was 86.8% (95% CI, 79.8 - 91.6) in the selpercatinib group and 65.7% (95% CI, 51.9 - 76.4) in the control group. The median treatment failure-free survival was not reached in the selpercatinib group and amounted to 13.9 months in the control group. The objective response rate was 69.4% in the selpercatinib group and 38.8% in the control group. A dose reduction due to side effects was necessary in 38.9% of patients in the selpercatinib group compared to 77.3% in the control group. Treatment discontinuation was necessary in 4.7% of patients in the selpercatinib group and 26.8% in the control group. Important side effects in the selpercatinib group (grade ≥ 3) were arterial hypertension (18.7%), diarrhea (3.1%), increased liver enzymes (10.4%), etc. Based on these data, the EMA extended the approval for selpercatinib in July 2022 to include first-line treatment of RET-mutated medullary thyroid carcinoma.

The selective RET inhibitor pralsetinib is currently only approved in Germany for RET fusion-positive non-small cell lung cancer. Approval for the treatment of medullary thyroid carcinoma is not being sought. It was investigated in a Phase I/II trial in patients with RET-positive medullary thyroid carcinoma [1034]. The study included 55 patients with RET-positive medullary thyroid carcinoma who had been pretreated with vandetanib and/or cabozantinib. There was an objective response rate of 60% (complete remission 2%, partial remission 58%) and stabilization in 33% of patients, and in patients without pretreatment (n=21) an objective response rate of 71% (complete remission 5%, partial remission 67%) and stabilization in 29% of patients. The median PFS had not yet been reached. The side effects were relatively rare, predominantly grade 1-3. The most common grade 3 or higher side effects were hypertension (17%), neutropenia (13%), lymphopenia (12%) and anemia (10%) [1169]. Based on these data, approval was granted in the USA in December 2020 for adult and pediatric patients ≥12 years of age with advanced or metastatic RET-positive medullary thyroid carcinoma who require systemic therapy. Due to the lack of phase III studies, the significance of the already approved substances vandetanib and cabozantinib as well as in comparison to the selective RET inhibitor selpercatinib cannot be conclusively assessed. The positive recommendation takes into account the patients' need for treatment and the proof of efficacy of the drugs with good quality of evidence.

In summary, an RET mutation analysis (somatic mutation) of the tumor tissue is therefore recommended if medullary thyroid carcinoma is detected (with the exception of patients in whom a pathogenic RET germline variant is known). In the case of a RET mutation, a selective RET inhibitor (e.g. selpercatinib) shall be used in advanced MTC with significant tumor burden and symptomatic or progressive (according to RECIST)

metastatic disease. This is also preferable to treatment with a non-selective multi-kinase inhibitor.
In order to ensure optimal individual treatment planning while exhausting all possible treatment options, including inclusion in controlled clinical trials, it is strongly recommended that these patients be cared for by an interdisciplinary team of experts at specialized centers.

8.33	Consensus-based Recommendation	2025
EK	In patients with metastatic sporadic MTC, a molecular genetic analysis of the tumor for the presence of a somatic variant in the RET gene shall be performed before starting systemic therapy with regard to the use of selective RET inhibitors and vandetanib.	
	Strong Consensus	

8.5 Multiple endocrine neoplasia type 2 (MEN2)

8.5.1 MEN2 clinical presentation

8.34	Consensus-based Recommendation	2025
EK	If there is a family history of MTC and/or primary hyperparathyroidism and/or pheochromocytoma, multiple endocrine neoplasia type 2 should always be considered and appropriate diagnostics should be initiated. Psychosocial support should be offered to the usually young patients and their families [1057], [1160]. An exchange of experiences within suitable patient groups should be communicated.	
	Strong Consensus	

MTC occurs hereditarily in approx. 25% of cases in the context of multiple endocrine neoplasia type 2 (MEN2). MEN2 is one of the hereditary tumor syndromes in which MTC can occur in association with pheochromocytomas in up to 50% (unilateral or bilateral) and with primary hyperparathyroidism (parathyroid adenomas/hyperplasia) in up to 20% depending on the type of pathogenic RET variant [335], [1171]. MEN2 syndrome has an estimated frequency of 1:30,000 and is inherited in an autosomal dominant manner. Hereditary MTC occurs in two different phenotypic forms (MEN2A approx. 95% and MEN2B approx. 5%), which differ in terms of frequency, genetics, age at clinical manifestation, association with other tumors, aggressiveness and prognosis [335], [1172]:

MEN2A (Sipple syndrome) - characterized by an MTC, with unilateral or bilateral pheochromocytomas in up to 50%, primary hyperparathyroidism on the basis of multiglandular disease in up to 10-20%, and rarely with a skin change on the back

(cutaneous lichen amyloidosis) or, extremely rarely, Hirschsprung's disease. A rare variant must be distinguished from this: FMTC - familial MTC with the sole occurrence of MTC without pheochromocytoma or primary hyperparathyroidism.

MEN2B - associated with MTC, unilateral or bilateral pheochromocytomas and a childhood-onset phenotype with marfanoid habitus and centrofacial mucosal neuromas of the lips, tongue and eyelids and intestinal ganglioneuromatosis that can lead to episodes of constipation and diarrhea. Primary hyperparathyroidism is not observed. In most cases, the typical phenotype (bulging lips, multiple ganglioneuromas, etc.) allows a visual diagnosis of MEN2B [1173], [1174].

Hereditary MTC is the leading tumor in MEN2 and manifests earlier than in the sporadic form. In MEN2B, MTC already develops in the first year of life, in classic MEN2A usually in the first/second decade of life and in the mild MEN2A forms in the third/fourth decade of life or later, depending on the causative pathogenic variant in the RET gene. Histopathologically, hereditary MTC is often associated with "neoplastic" C-cell hyperplasia, multifocality, with occurrence in one or both thyroid lobes [1175]. Clinically, the index case presents like a sporadic MTC. The MEN2-associated tumors (pheochromocytoma or primary hyperparathyroidism) often occur after the manifestation of MTC and can be bilateral or multiglandular. Primary hyperparathyroidism often has an "asymptomatic" (mild) course.

8.5.2 Molecular genetic diagnostics

8.35	Consensus-based Recommendation	2025
EK	All patients with MTC or C-cell hyperplasia shall undergo germline diagnostics of the RET protooncogene following appropriate information and consent. If a pathogenic RET variant is detected in an index person, this person should be recommended genetic counseling. All first-degree relatives of this person should be offered predictive diagnostics as part of genetic counseling. All patients with a MEN2 shall receive risk stratification based on the pathogenic RET variant with regard to an early manifestation time of the MTC in "moderate, high, highest".	
	Strong Consensus	

8.36	Consensus-based Recommendation	2025
EK	In the case of sporadic MTC, molecular genetic testing of the tumor tissue for pathogenic variants in the RET gene should be carried out with a view to targeted systemic therapy for aggressive MTC progression.	
	Strong Consensus	

The cause of autosomal dominant hereditary MEN2 is an activating germline variant in the RET protooncogene on chromosome 10q11.2, a gene that codes for a tyrosine kinase receptor. Certain variants in the RET protooncogene lead to a permanent activation of the RET receptor and thus activation of the postreceptor signaling cascade, which is responsible for the proliferation of neuroendocrine cells, among other things. C-cell hyperplasia, defined as multifocal proliferation of C-cells within the thyroid gland, can be considered a precursor or precancerous condition of hereditary MTC.

To date, over 100 different pathogenic RET variants are known in MEN2. A list of classified RET variants can be found, for example, in the ClinVar database: https://www.ncbi.nlm.nih.gov/clinvar/?term=MEN2. In almost all families that fulfill the clinical criteria of MEN2, activating, pathogenic germline variants in the RET gene from the DNA of peripheral lymphocytes could be detected and serve as genetic markers. There is a good correlation between the genotype (type and location of the pathogenic variant in the RET protooncogene) and the phenotype (clinical appearance). The expression and penetrance of MTC and other MEN2 tumors is highly variable, from early metastatic MTC in infancy with an activating variant in codon 918 (MEN2B), to MTC occurring in adolescence with variants in codon 634 (MEN2A), to MTC occurring in adulthood associated with variants in exons 13-15 (MEN2A). Three risk groups are formed according to the age at manifestation of the MTC and the clinical course: with "highest" risk (MEN2B, RET variant M918T), with "high" risk (MEN2A, e.g. RET variants affecting codon 634) and with "moderate" risk (MEN2A, e.g. RET variants in exons 13-15) [335] (Table 23).

If a pathogenic germline variant is found in the RET protooncogene in an index patient, the familial RET variant can be identified in other family members. In these individuals with a pathogenic variant in the RET gene, further clinical, biochemical and morphological examinations are then necessary to clarify the extent and confirm the diagnosis of MTC, pheochromocytoma and pHPT. In MEN2B, "de novo" variants are often found. The predictive exclusion of a known familial RET variant exonerates these individuals, who do not require further examination for manifestations of MEN2.

8.5.3 Calcitonin screening for familial MTC

8.37	**Consensus-based Recommendation**	**2025**
EK	If the Ctn rises above the age- and sex-specific reference value, a prophylactic thyroidectomy shall be planned depending on the risk classification of the pathogenic variant in the RET gene.	
	Strong Consensus	

Ctn determination in carriers of a pathogenic RET variant in families with MEN2 is used to determine the time for prophylactic thyroidectomy. In these cases, a neoplastic precursor, C-cell hyperplasia (then prophylactic thyroidectomy), or a micro-MTC (then early thyroidectomy) is to be expected due to the significantly higher pretest probability if the Ctn rises above the upper reference range. The optimal timing of prophylactic thyroidectomy is recommended taking into account the RET variant,

the typical age at manifestation (3 risk groups: "moderate, high, highest") and the Ctn level (Table 23). It should be noted that children have higher Ctn reference values depending on their age.

8.5.4 Prophylactic thyroidectomy

8.38	Consensus-based Recommendation	2025
EK	Carriers of a pathogenic germline variant in the RET protooncogene shall be offered a prophylactic thyroidectomy in the asymptomatic stage. The optimal timing of thyroidectomy depends on the risk classification of the detected pathogenic RET variant, the age of the patient and the Ctn level (Table 23) Before operating on a hereditary MTC, a pheochromocytoma and primary hyperparathyroidism shall be excluded or confirmed.	
	Strong Consensus	

Since the lifetime risk of carriers of a pathogenic germline variant in the RET protooncogene developing MTC is over 90%, prophylactic thyroidectomy is recommended before the manifestation of a thyroid-transcending MTC. The optimal timing of prophylactic thyroidectomy of asymptomatic carriers of a pathogenic germline variant of the RET gene is recommended based on the risk classification of the specific RET variant into "moderate, high and highest" risk for early development of MTC (early or late penetrance) [335]. The Ctn level complements and individually defines the timing of prophylactic thyroidectomy. As soon as the Ctn level rises above the age- and sex-specific normal range, (mostly) neoplastic C-cell hyperplasia as a precursor of MTC can be assumed. At this stage, the MTC is unlikely to spread beyond the thyroid gland, central (prophylactic) lymph node removal is then not necessary and a thyroidectomy is sufficient. With increasing Ctn levels, a micro-MTC is to be expected, which involves a risk of LN metastases; depending on the Ctn level, a central LN dissection may then have to be discussed [1176]. The time of MTC development in the "highest" risk group is to be expected in the first year of life, possibly in the first month of life, in the "high" risk group at 3-5 years and in the "moderate" risk group after the age of 5 in early adolescence. If the Ctn level measured at this time is within the reference range, thyroidectomy can be postponed by measuring Ctn every 6 months until Ctn rises to a maximum of 30 pg/ml; this applies in particular to patients in the "moderate" risk group [1177], [1178]. With this approach, almost all children can be cured with minimal morbidity.

Index patients and later diagnosed carriers of a pathogenic RET variant with clinically manifest MTC and basally elevated Ctn receive a thyroidectomy with bilateral central and possibly lateral lymph node dissection (compartments I-III) in the same way as patients with sporadic MTC (see Chapter 8.2.2).

8.5.5 Management of pheochromocytoma and primary hyperparathyroidism in MEN2

8.39	**Consensus-based Recommendation**	**2025**
EK	In all MEN2 patients, a pheochromocytoma shall be diagnosed at an early stage by annual examination in the "highest" and "high" risk groups from the age of 11, and in the "moderate" group from the age of 16, and treated by (partial) adrenalectomy if possible.	
	Strong Consensus	

Depending on the genotype, MEN2 patients develop a **pheochromocytoma** in up to 50 % of cases in the course of their lives , often bilaterally. In most cases, MTC precedes pheochromocytoma by an average of 10 years; it is usually benign, multicentric and restricted to the adrenal gland [1179]. It is important to diagnose pheochromocytoma biochemically (plasma metanephrines, plasma normetanephrines) [1180] and, if necessary, by imaging (CT/MRI/MIBG scintigraphy or F-18-DOPA-PET/CT) before thyroidectomy in order to first operate on the pheochromocytoma and then the MTC. In early thyroidectomized MEN2 patients, annual biochemical screening for the presence of pheochromocytoma is required even in asymptomatic patients. Screening begins in the "highest" and "high" risk groups at the age of 11, and in the "moderate" group at the age of 16. For smaller pheochromocytomas and depending on the location of the tumor in the adrenal gland, subtotal adrenalectomy to preserve the adrenal cortex can be performed laparoscopically or endoscopically retroperitoneally [1181]. A further pheochromocytoma often develops in the residual tissue or on the opposite side over the next 10 years [1182]. After total adrenalectomy, lifelong glucocorticoid and mineral corticoid substitution as well as regular patient training and provision of an emergency card are necessary to prevent adrenal insufficiency.

8.40	**Consensus-based Recommendation**	**2025**
EK	All MEN2 patients shall undergo an annual examination for primary hyperparathyroidism (in the "high" risk group from the age of 11, in the "moderate" group from the age of 16) and surgery shall be performed if confirmed.	
	Strong Consensus	

Primary hyperparathyroidism also shows a genotype-phenotype correlation; it is not observed in MEN2B patients, but typically in patients with the pathogenic variants in RET codon 634 in up to 20 %, usually also only after the manifestation of MTC. Primary hyperparathyroidism is usually asymptomatic with often only slightly elevated serum calcium [1183], [1184]. It is often a single-gland disease, more rarely a multigland disease. Depending on the macroscopic findings, surgery may involve selective removal of the enlarged parathyroid gland(s), subtotal (3 ½) resection or, alternatively, total parathyroidectomy with synchronous autotransplantation of a parathyroid gland. A higher probability of recurrence with selective limited surgery must be

weighed against the higher risk of postoperative hypoparathyroidism with total thyroidectomy with autotransplantation [1185], [1186]. Examinations such as sestamibi SPECT/CT or choline PET/CT to localize the leading parathyroid gland or prior to recurrent surgery to localize the persistent/recurrent hyperactive parathyroid gland are helpful [1187].

Table 23: Risk stratification and management of patients with MEN2 depending on the pathogenic RET variant

MEN2 subtype	FMTC/MEN2A	MEN2A	MEN2B
Common pathogenic RET variant, codon	533, 609, 611, 618, 620, 630, 631, 768, 790, 804, 891	634	918
Risk group	moderate	high	highest
Occurrence of MTC (age)	mostly 5 years and older	often before the age of 5	often in the 1st year of life
Time of prophylactic thyroidectomy	as soon as Ctn rises above the upper reference value, usually in adolescence	as soon as Ctn rises above the upper reference value, usually before the age of 5	as soon as soon as possible, in the 1st year of life
Screening for pheochromocytoma	from the age of 16, annually	from the age of 11, annually	from the age of 11, annually
Screening for primary hyperparathyroidism	from the age of 16, annually	from the age of 11, annually	-

Source: [335]

9 Anaplastic thyroid carcinoma

Anaplastic thyroid carcinoma (ATC) is a very rare, highly aggressive disease that is usually presenting with rapidly growing mass in the neck often accompanied by other symptoms such as difficulty swallowing, hoarseness and dyspnea on initial presentation. The clinical suspicion is confirmed by cervical sonography. Immediately, imaging is performed to assess the extent of the disease in parallel with histological confirmation. Treatment is a challenge due to the aggressiveness of the disease and the very limited data available. A distinction can be made between resectable disease (stage IVA according to UICC) and non-resectable and/or primarily metastatic disease (stage IVB and IVC according to UICC). Treatment is multimodal and consists of surgery, radiotherapy and chemotherapy. Other therapeutic approaches include targeted therapy (e.g. BRAF and MEK, RET and NTRK inhibitors). There is also data on PDL1 inhibition, which has shown efficacy. The care of ATC patients includes experts in palliative medicine and psycho-oncology.

9.1 Preoperative diagnostics

9.1.1 Clinical examination

9.1	Consensus-based Recommendation	2025
EK	Anaplastic thyroid carcinoma (ATC) can present clinically as a rapidly progressive cervical mass with sudden hoarseness and shall be subjected to further work-up immediately.	
	Strong Consensus	

Clinical suspicion of ATC are sudden hoarseness and difficulty swallowing. Other typical symptoms are a rapidly growing cervical tumor and shortness of breath. B symptoms such as weight loss and night sweats have also been described as initial symptoms in retrospective studies [1188].

The physical examination serves to assess the general condition using ECOG (Eastern Cooperative Oncology Group) status [1189] as well as specific examinations depending on the initial symptoms. The physical examination of the neck can provide relevant information such as the extent of the tumor, palpable metastases or infiltration of the skin. Overall, the physical examination is not primarily used for diagnosis, but for further treatment planning [1190].

9.1.2 Laboratory studies

9.2	Consensus-based Recommendation	2025
EK	Laboratory diagnostics are used to assess the general health status and the functional status of the thyroid gland. If a surgical procedure is planned, the functional status of the parathyroid glands shall also be evaluated.	
	Strong Consensus	

There is no specific tumor marker for anaplastic thyroid carcinoma. Thyroglobulin, which is used as a progression parameter in differentiated and poorly differentiated thyroid carcinoma, is not useful in ATC, as there is complete dedifferentiation and this is accompanied by a loss of thyroglobulin expression, among other things [1191]. Thyroglobulin should nevertheless be determined during the initial diagnosis, as a lack of thyroglobulin production can support the diagnosis of ATC [337].

9.1.3 Sonography

Sonography examination is discussed in Chapter 9.1.4.

9.1.4 Imaging (CT, MRI, PET/CT)

9.3	Consensus-based Recommendation	2025
EK	Staging shall be performed using suitable imaging. Local tumor spread can be detected using sonography, CT or MRI. Whole-body PET/CT with [^{18}F]FDG should be performed to detect distant metastases and local tumor spread. If brain metastases are suspected, a head MRI should be performed.	
	Strong Consensus	

Accurate and rapid assessment of the extent of the histologically confirmed ATC is essential for adequate treatment planning. Immediately after initial diagnosis or histological confirmation of the ATC, the extent of the disease must be determined using suitable methods of cross-sectional imaging in order to plan next therapeutical steps (surgery and/or radiotherapy) [1192] and to predict if local resectability is feasible [1193], [49], [1194]. Local resectability is given if surgical R0 or R1 resection can be achieved. This is the case with intrathyroidal ATC or extrathyroidal infiltration limited to surrounding soft and fatty tissue, recurrent laryngeal nerve and superficial trachea. In contrast, ATC with cervical multivisceral infiltration (vessels, nerves, aerodigestive tract, substernal space) is usually irresectable [1195], [258], [1196], [1197].

Due to the rapid progression of the disease, if there is sufficient clinical suspicion, imaging can be planned and performed before histological confirmation is available in order to avoid delaying treatment; this applies in particular to impending local

complications. If there are indications of airway involvement, CT cross-sectional imaging is the modality of choice. The most suitable imaging modality for detecting whole-body tumor status is positron emission tomography/computed tomography (PET/CT) with [^{18}F]FDG. PET/CT is clearly superior to CT in the detection of metastasis-suspected lesions (detection rates 99% vs. 62%); PET/CT allows the initially planned treatment regimen to be adjusted in up to 25% to 50% of cases [1198], [1199], [1200]. Using [^{18}F]FDG-PET/CT, ATC metastases can be better differentiated from (coincidental) DTC metastases , which impacts the treatment regimen [1201], [1202]. ATC expresses Glut-1 more strongly, which results in a higher accumulation of the radiopharmaceutical tracer in lesions suspicious for metastases [1203]. If a CT scan is performed, there is no reason to hold off contrast, as neither diagnosis nor treatment with radioiodine is possible (with regard to the prognostically relevant anaplastic tumor components). For the detection of brain metastases, MRI appears to be superior to other imaging modalities, in particular CT [1204], [1205]. For the detection of bone metastases [^{18}F]FDG PET/CT is the modality of choice [1206], [1200].

9.1.5 Esophagoscopy

9.4	Consensus-based Recommendation	2025
EK	An esophagoscopy (i.e. endoscopy), possibly with additional endosonography, shall be performed if the clinical presentation and/or imaging is suspicious for infiltration of the esophagus.	
	Strong Consensus	

An esophagoscopy (i.e. endoscopy) and, if necessary, endosonography allows for an exact assessment of suspected esophageal infiltration. In addition, a biopsy can be performed if the findings are conspicuous. In the case of advanced infiltration of the digestive tract, the tumor would be irresectable. Depending on the findings, the indication for pre-therapeutic stent implantation can be evaluated with regard to palliative radiotherapy [1207].

9.1.6 Tracheobronchoscopy

9.5	Consensus-based Recommendation	2025
EK	A tracheobronchoscopy shall be performed if the clinical presentation and/or imaging is suspicious for infiltration of the trachea.	
	Strong Consensus	

A tracheobronchoscopy allows for an exact assessment of suspected tracheal infiltration based on clinical or imaging findings. In addition, a biopsy can be performed if the findings are not decisive. The findings are also relevant with regard to the assessment of resectability. In the case of advanced airway infiltration, the tumor would not be resectable. Depending on the findings, the indication for pre-therapeutic stent implantation can be evaluated with regard to palliative radiotherapy [1208], [1209].

9.1.7 Further diagnostics

9.6	Consensus-based Recommendation	2025
EK	As soon as the diagnosis is made by core or, if necessary, incisional biopsy, rapid genetic testing of the tumor and immunohistochemical determination of PD-L1 expression shall be performed for treatment planning.	
	Consensus	

For ATC, targeted therapies requiring proof of a specific genetic alteration have been approved by the EMA or FDA (e.g. RET fusion, BRAF V600E mutation). Further biomarker analyses for targeted therapies, approved for advanced tumors regardless of tumor entity (tumor-agnostic), can also be considered as treatment options (e.g. NTRK fusion [1035], microsatellite instability). Large series of genomic analyses of ATCs have revealed genetic alterations in different signaling pathways or DNA repair genes amenable to targeted therapies that are approved for other solid tumors or available in clinical trials. In an analysis of 196 ATC tumors, TP53 (65%) and TERT mutations (65%) were most frequently found to be prognostically relevant. 41% had BRAF mutations and 27% RAS mutations [1210]. Currently, the BRAF mutation, which is detected in 11-45% of ATCs in different series [1188], can be targeted by combined BRAF and MEK inhibition, which is approved by the FDA. Other genetic alterations have been targeted effectively in case reports (e.g. ALK translocation [1211], ROS1 fusions [1212], or nonsense TSC2 mutation [1213]).

In the context of evolving personalized oncology care, initial genetic testing (panel sequencing of the important signaling pathways including fusions, TMB, HRR) of formalin-fixed and paraffinized (FFPE) tumor assessed by the pathologist is recommended. This applies in particular in the context of rapid disease progression considering the time genetic testing takes.

The routine use of whole exome (WES) or whole genome (WGS) sequencing cannot be recommended at this time due to the quantity and quality requirements of DNA/RNA and the longer time for results to come in, if performed outside studies.

Assessment of PD-L1 expression can be used to leverage off-label immune checkpoint inhibitor therapy, shown effective in studies or case reports (e.g. in combination therapy with tyrosine kinase inhibitors (TKIs), see below). For this purpose, the common scores for immunohistologic PD-L1 analysis (IC, CPS, TPS) shall be reported by the pathologist.

9.2 Therapy of resectable ATC

9.2.1 Surgery

9.7	Consensus-based Recommendation	2025
EK	For local tumor control and to improve outcome, radical surgery should be attempted in cases of local resectability (R0 to possibly R1 resection). Depending on the findings, this includes lobectomy or total thyroidectomy, possibly with diagnostic and/or therapeutic central lymph node dissection.	
	Strong Consensus	

Local resection may also be indicated in metastatic disease due to local symptoms or the threat of secondary complications in the context of local tumor progression. Tumor debulking should be avoided if possible and may only be indicated in rare exceptions [1195], [258], [1214], [1215].

If ATC is locally resectable, surgery shall be attempted for local tumor control and to improve the chances of survival. Local radical (R0) resection is the goal. If there is localized extrathyroidal tumor growth, surgery shall be attempted to achieve local tumor control and improve the chances of survival. Alternatively, a neoadjuvant concept with systemic therapy can be attempted with the aim of secondary surgery.

The extent of resection depends on the local findings and the presence of metastatic disease. Unilateral intrathyroidal ATC can be resected by lobectomy if possible, depending on the findings; in most cases a thyroidectomy is required for complete tumor removal. The significance of locoregional lymph node dissection of the central compartment from a diagnostic and therapeutic point of view is assessed inconsistently. Lateral lymph node dissection should only be considered in cases of clinical involvement. For all types of resection, adjuvant early postoperative locoregional external radiotherapy should is essential to ensure surgical outcome.

9.2.2 Radiotherapy

9.2.2.1 Indication for primary or postoperative radiotherapy

9.8	Consensus-based Recommendation	2025
EK	After R0 or R1 resection, patients with ATC with good performance status and no evidence of metastatic disease shall be offered normofractionated intensity-modulated radiotherapy (IMRT) with simultaneous systemic therapy.	
	Strong Consensus	

Despite the poor prognosis of ATC, percutaneous radiotherapy is an essential local treatment option with a predominantly palliative character. Locoregional tumor control is achieved in 60-80% of percutaneously irradiated patients [1216], [1217], [514], [1218], so that death by asphyxiation can usually be prevented. In a large retrospective series, the combination of surgery and percutaneous radiotherapy was an independent prognostic factor for tumor-specific survival [1219]. The benefit of aggressive local therapy was found in patients with locoregionally advanced or distant metastatic disease, but not with only intrathyroidal tumor extension. Even in the presence of distant metastasis, local tumor control appears to prolong survival [1220]. Primary or postoperative radiotherapy is therefore generally indicated for ATC.

In patients without distant metastases in whom complete tumor resection is possible, combined radio-chemotherapy (in the sense of trimodal therapy) with three-year survival rates of at least 50% [1221], [1222], [1223] may even represent a curative treatment approach. Preoperative and postoperative radiochemotherapy yielded comparable results [1221], [1217], [1223], meaning that both sequences are justifiable in principle. Both pre- and postoperative radiotherapy ("split course") is not recommended [1217]. In a larger case series (104 patients, period 1984-2017), a 1-year survival of 45% was described after surgery and combined radio-chemotherapy (doxorubicin in 74%, paclitaxel with or without pazopanib in 24%) [1224].

A recent meta-analysis (17 non-randomized observational studies, 1,147 patients) looked at the value of postoperative radiotherapy after ATC resection (R status not specified) [1225]. Postoperative radiotherapy reduced the risk of death compared to surgery alone with an HR of 0.556 (95% CI, 0.419-0.737; p<0.001). The benefit was most pronounced in patients with stage IVA (HR 0.364; p=0.012) and IVB disease (HR 0.460; p=0.059). In a further meta-analysis (10 studies, 1,163 patients), a reduction in the risk of death with HR 0.51 (95% CI: 0.36-0.73, p=0.0002) was reported after surgery + radiotherapy compared to surgery alone [1226].

9.2.2.2 Implementation of radiotherapy

9.9	Consensus-based Recommendation	2025
EK	Radiotherapy shall be planned and started as soon as the patient has recovered sufficiently from the neck surgery, usually within two to three weeks after the surgery.	
	Strong Consensus	

9.10	Consensus-based Recommendation	2025
EK	Patients receiving radiotherapy for ATC (irresectable or postoperative) shall be treated with intensity-modulated radiotherapy (IMRT).	
	Strong Consensus	

9.11	Consensus-based Recommendation	2025
EK	In patients treated with radiotherapy (at least 50 Gy), simultaneous chemotherapy with a combination of taxane (paclitaxel, docetaxel) and/or anthracycline (doxorubicin) and/or platinum (cisplatin, carboplatin) should be used.	
	Strong Consensus	

9.12	Consensus-based Recommendation	2025
EK	Patients with ATC in poor performance status shall preferably be offered palliative dosed locoregional radiotherapy.	
	Strong Consensus	

The effectiveness of percutaneous radiotherapy for ATC is dose-dependent. The total dose is usually 40-70 Gy; when choosing the fractionation, a short total treatment duration (acceleration, e.g. through hypofractionation) shall be aimed for in view of the usually short survival times. Hyperfractionated radiation (e.g. two fractions per day) can be used as part of intensified radio-chemotherapy protocols.

In retrospective analyses, survival time and local control were significantly improved when total doses above 30 Gy or 40 Gy (cut-off value for comparison in the respective study) were used [1220], [1218].
In smaller series, accelerated, in some cases hyperfractionated, radiation protocols were investigated, which only achieved median survival times of around 3 months without simultaneous chemotherapy, despite total doses of around 60 Gy [1216].

A recent meta-analysis of the National Cancer Data Base with 1,228 patients shows a clear correlation between total dose of radiotherapy and overall survival (compared to no radiotherapy: radiotherapy with <45 Gy: HR 0.834; with 45-59.9 Gy: HR 0.596; with 60-75 Gy: HR 0.419 [1227]. The effect was confirmed in a propensity score-matched analysis. The 1-year survival after radiotherapy with 60-75 Gy was 31% and with 45-59.9 Gy 16% (p=0.008).

Percutaneous radiotherapy of ATC should be performed as intensity-modulated radiotherapy (IMRT) to minimize toxicity, although the urgency of starting treatment or a highly palliative situation may also justify simpler radiotherapy techniques.

In a retrospective analysis of 41 patients with ATC, multivariate analysis showed an advantage in overall survival for patients treated with IMRT vs. patients treated with 3D-conformal radiotherapy (HR 0.33, 95% CI 0.15-0.72, p=0.005) [1228]. IMRT patients received a higher total dose compared to the 3D technique (66 Gy vs. 60 Gy), but did not show increased toxicities.

9.2.3 Systemic therapy

9.13	Consensus-based Recommendation	2025
EK	Adjuvant chemotherapy can be carried out after R0/R1 resection and radiochemotherapy in patients without evidence of residual tumor disease and/or metastasis.	
	Strong Consensus	

Survival of patients with anaplastic thyroid carcinoma is stage-dependent [1202], [1229]. Patients in the non-metastatic stages IVA and IVB have a significantly better survival than patients with metastatic stage IVC disease. In retrospective studies, multivariate analyses showed an advantage for patients with IVA and IVB disease after tumor resection followed by adjuvant radiotherapy and chemotherapy [1190], [1230].

In a large Japanese retrospective multicenter study with 547 ATC cases, patients with stage IVB disease who received multimodal therapy consisting of surgery, radiotherapy and adjuvant chemotherapy had significantly better survival, compared to patients with stage IVA disease [1202]. The median overall survival of stage IVA patients was 389 days with resection and adjuvant radiotherapy versus 314 days with surgery, radiotherapy and chemotherapy. In stage IVB patients, on the other hand, the median survival was 194 versus 420 days with the same treatment sequence. In a retrospective series of 104 ATC patients treated between 1984 and 2017, the median 1-year survival after surgery, radiotherapy and adjuvant chemotherapy was 54.7% compared to 12.8% for patients who received only two or one of the three treatment modalities [1224]. Derbel et al. [1231] studied 44 ATC patients. The majority (35/44) received multimodality therapy and 14 patients achieved complete remission after therapy completion. These 14 patients had an initially stage IVA or IVB disease. The substances administered were doxorubicin in combination with cisplatin, or carboplatin, or paclitaxel monotherapy.

The efficacy of chemotherapy regimens for the adjuvant treatment of stage IVA and IVB anaplastic thyroid carcinoma patients has not been investigated in prospective studies. Several retrospective case series have analyzed the efficacy [1188]. Seto et al. investigated the efficacy of docetaxel (75mg/m²) and cisplatin (75mg/m²) every 4 weeks for 6 cycles [1232]. Included were 8 patients, including 2 patients in stage IVB for postoperative adjuvant therapy. Both patients received adjuvant radiotherapy after R0 and R1 resection, respectively. One patient died of local recurrence 3 years after receiving 5 cycles of chemotherapy and the second patient remained free of recurrence after receiving 6 cycles at the time of publication (>5 years after diagnosis). In a French study, 30 patients were treated with multimodal therapy [1223]. An R0 or R1 situation after surgery was achieved in 12 patients. The 12 patients received adjuvant radiotherapy postoperatively and were treated with 2-9 cycles of doxorubin (60mg/m²) and cisplatin (120mg/m²). Overall survival varied widely between 4 and 78 months (median 24.5 months).

Long-term systemic therapy of resectable ATC without evidence of residual disease in imaging after completion of multimodal therapy is not recommended [1188].

9.3 Treatment of non-resectable or incompletely resected and/or metastasized ATC

9.3.1 Neoadjuvant therapy

9.14	Consensus-based Recommendation	2025
EK	In the non-resectable situation, patients with a BRAF V600E mutation should undergo neoadjuvant therapy.	
	Strong Consensus	

In a case series of 57 ATC patients with a BRAF V600E mutation at the MD Anderson Cancer Center, Texas, from 2017 to 2021, primary tumors became resectable in approximately 70% of patients after at least one month of combination therapy with dabrafenib and trametinib (DT) [1233]. If DT treatment was only given after surgery (n=12), the outcome was slightly worse than in patients (n=32) who received DT treatment in the neoadjuvant setting.

In a further study including 13 patients, surgery could not be performed due to insufficient response (n=9) after DT, insufficient AZ (n=2). Two patients refused surgery. In the DT + surgery group, the median OS [CI 39.2 months - NA) was not reached, the 1- and 2-year OS was 93.6% and 80.3% respectively. In the group without surgery + DT, the 1- and 2-year OS was 38.5% and 15.4%, respectively. In patients with preoperative DT treatment, the 1-year and 2-year OS was 74.1% and 74.1%.

A British study [1234] included 17 patients with unresectable disease and BRAF V600E tumor positivity, who were treated with DT between August 2018 and October 2021. 12 patients underwent surgery after DT, 4 had an R0 resection, 7 had an R1 resection and one had an R2 resection. The median OS was 12 months (range 3 to 43). Although the real-world outcome data is worse than of the ROAR basket study, it is still improved better compared to other retrospective data. In addition to stricter inclusion criteria in studies, delayed access to DT is also mentioned as a possible explanation.

Studies with other drug combinations have been initiated:

DT plus pemprolizumab (30 patients, phase II study; NCT04675710),

MD Anderson Cancer Center immune checkpoint inhibitor atezolizumab combined with the BRAF inhibitor vemurafenib and the MEK inhibitor cobimetinib (VCA) (n=17).

9.15	Consensus-based Recommendation	2025
EK	If effective neoadjuvant therapy results in resectability of the primary tumor with an expected benefit for the patient, surgical therapy should be following.	
	Strong Consensus	

A primary tumor that was considered irresectable can become resectable after radiation, chemotherapy combined radio-chemotherapy or targeted therapy [1221], [1235], [1236]. In the re-evaluation of resectability with the aim of avoiding local recurrence and preventing locoregional complications, the overall prognosis, the increased surgical difficulty, especially after local radiotherapy with the associated increased risk of complications and the individually expected benefit of resection should be taken into account, as data on disease-free and overall survival are lacking.

9.3.2 Surgical treatment of extrathyroidal ATC without multivisceral infiltration

9.16	Consensus-based Recommendation	2025
EK	For local tumor control and to improve the chances and quality of survival in patients with extrathyroidal ATC without multivisceral infiltration, complete tumor removal shall be attempted in cases of local resectability (R0 to possibly R1 resection). Depending on the findings, this includes lobectomy or total thyroidectomy, possibly with diagnostic and/or therapeutic lymph node dissection.	
	Strong Consensus	

In ATC with extrathyroidal spread but without cervicovisceral infiltration, extended resection is indicated if it can achieve local tumor control and improve survival and/or quality of life [1195], [258], [1197]. Selected patients have experienced prolonged recurrence-free survival and/or overall survival after surgery for locoregional disease [1220], [1195], [1237].

9.3.3 Surgical treatment of extrathyroidal ATC with multivisceral infiltration

9.17	Consensus-based Recommendation	2025
EK	In the case of multivisceral ATC infiltration, surgery should generally not be performed, but can be performed in individual cases to debulk the tumor and prevent local complications (e.g. tracheal compression).	
	Strong Consensus	

If multivisceral infiltration is present in ATC with extrathyroidal spread and only tumor debulking (R2 resection) can be performed, surgery is not recommended. If non-surgical palliative measures do not provide sufficient symptomatic improvement, tumor debulking surgery may be indicated on an individual basis, e.g. to avoid secondary complications, e.g. to secure the airway or enable a tracheostoma to be placed. A prophylactic tracheostomy shall be avoided [1088], [1195], [258].

9.3.4 Recurrence surgery

9.18	Consensus-based Recommendation	2025
EK	Completion surgery for adequate or complete primary tumor resection of an ATC should be attempted if R0/R1 resection can be achieved. Re-surgery for ATC recurrence should be evaluated if the benefits of local tumor control or prevention of secondary complications are considered advantageous in the case of resectability, taking into account the overall situation.	
	Strong Consensus	

If ATC is only diagnosed postoperatively and no form of tumor-adequate resection or radical primary tumor resection has been performed (subtotal resection, lobectomy with R1/R2 resection), the possibility of completion surgery of both the ATC component and possible tumor components of other entities should be examined as a completion surgery, as R0 resection improves the overall prognosis [1219], [1238]. Whole-body imaging and the locoregional tumor extent should be assessed to demonstrate resectability and establish an advantage for the patient.

ATC recurrence within primary tumor bed should be evaluated in the context of resectability as in the primary situation. The risk factors for recurrence as well as the overall disease and prognosis must be taken into account.

The considerations for local progression control and prevention of secondary locoregional complications due to tumor growth apply in principle to completion surgery and recurrence surgery for ATC in the same way as for primary surgery, but the increased degree of difficulty and risk of complications must also be taken into account as limiting factors.

9.3.5 Radiotherapy

9.19	Consensus-based Recommendation	2025
EK	After R2 resection or in the case of resectable non-metastatic ATC, patients with good performance status who prefer a radical approach shall be offered normofractionated radiotherapy in the form of intensity-modulated radiotherapy (IMRT) with simultaneous systemic therapy. For patients with BRAF mutations, treatment with BRAF/MEK inhibitors can be considered as an alternative.	
	Strong Consensus	

9.3.6 Systemic therapy

9.20	Consensus-based Recommendation	2025
EK	Multimodal therapy should be offered to patients with metastatic/non-resectable ATC (chemotherapy in addition to and, if necessary, following radiotherapy) if no targetable mutations are present.	
	Strong Consensus	

To date, only one ATC phase III trial has been published, which was terminated prematurely due to recruitment difficulties [1239]. However, several retrospective cohort studies have shown significantly longer overall survival in patients who received multimodal treatment. In all retrospective studies, a clear systematic bias in the allocation of chemotherapy can be assumed [1240], [1229], [1230]. Patients with good performance status, should be treated with cytotoxic chemotherapy [1195]. Reliable data on the most suitable regimen is not yet available. However, with a view to early and sufficiently high-dose radiotherapy, it is advisable to choose a chemotherapy that can be started as a radiosensitizer before or during radiotherapy and continued after it. A typical regimen that is used internationally and also in Germany is carboplatin (AUC2) and paclitaxel (50 mg/m²) as weekly chemotherapy in parallel with radiotherapy, which is adjusted in dose and treatment interval after completion of radiotherapy: paclitaxel 135-175 mg/m² at three to four-week intervals, carboplatin AUC 5-6) [1241]. This regimen can also be used if radiotherapy is omitted. Due to the low rate of objective response and toxicity, doxorubicin is not recommended despite existing approval.

9.21	Consensus-based Recommendation	2025
EK	Inclusion in a suitable treatment study should be offered when a non-resectable/metastatic ATC is diagnosed and during the course of treatment, if available.	
	Strong Consensus	

Due to the rarity of ATC and the lack of evidence-based recommendations as well as the development of new, currently mainly molecularly-targeted and immunotherapy approaches, as many patients as possible should be included in studies. In addition to the gain in knowledge, treatment within a trial offers the advantage for patients that they are closely monitored during the trial and potentially benefit from a new therapy. For this reason, early contact with a center experienced in this entity is recommended.

9.22	Consensus-based Recommendation	2025
EK	BRAF-mutated ATC should be treated with a combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib.	
	Strong Consensus	

9.23	Consensus-based Recommendation	2025
EK	If an ATC with a RET fusion is detected, treatment with the RET inhibitor selpercatinib can be administered.	
	Strong Consensus	

9.24	Consensus-based Recommendation	2025
EK	If an ATC with an NTRK fusion is detected, treatment with an NTRK inhibitor (larotrectinib or entrectinib) can be given.	
	Strong Consensus	

Based on a phase 2 trial in BRAF-mutated ATC, the combination of dabrafenib 150 mg twice daily in combination with trametinib 2 mg daily was approved in the USA for ATC patients with this molecular alteration. In the study, an objective tumor response (partial remission) was observed in 10 of 16 patients; after a median follow-up of 12 months, 8 of the 10 patients continued to have a response [1242]. In an update only available as a congress report, 28 patients were included, the median progression-free survival was 60 weeks, the overall survival 86 weeks. Therefore, patients with BRAF-mutated ATC and good performance status (ECOG performance status ≤2) who are able to take oral medication should urgently consider treatment with this therapy, which is not approved in the EU (as of 07/2021), as part of an individualized treatment trial. The combination therapy is currently not approved for this indication in the EU, but has been approved in the USA by the FDA since 2018 and by the English NHS since 2022.

The selective RET inhibitor selpercatinib was investigated in a total of 162 thyroid cancer patients with an RET mutation or fusion in a phase 1-2 study [1032]. Two ATC patients were included. One ATC patient had stable disease and the other ATC patient had a partial response. The results of this study were the basis for approval for the treatment of advanced medullary thyroid carcinoma with RET mutation. However, in non-medullary thyroid cancer with RET fusions, selpercatinib is only approved as second-line therapy after lenvatinib and/or sorafenib therapy. Further data on selpercatinib in the treatment of ATC are available in the form of a case report [1243].

The NTRK inhibitors larotrectinib and entrectinib have been approved by the EMA for the treatment of patients with tumors with NTRK fusion [1244]. Data for the treatment of ATC patients with an NTRK fusion with an NTRK inhibitor is scarce. Larotrectinib was investigated in a study with 55 patients, including 5 thyroid cancer patients. All 5 patients responded to the therapy with a complete or partial remission. The histology of these patients was not reported. A report from the annual meeting of the European Society of Medical Oncology (ESMO) summarizes the results of a study of the efficacy of larotrectinib in 28 thyroid cancer patients, including 7 ATC patients [1245]. The primary endpoint was best overall response. Two of the seven ATC patients had a partial response, 1/7 had stable disease and 3 of 7 patients had progressive disease.

Efficacy has been shown for other targeted therapies, for example, there are promising case reports on the ALK inhibitor crizotinib [1211] and the mTOR inhibitor everolimus [1213]. These therapeutic options can be utilized in an indvidual treatment approach and ideally by inclusion in corresponding studies.

The tyrosine kinase inhibitors lenvatinib and sorafenib are approved for the systemic treatment of radioiodine-refractory differentiated thyroid carcinoma. Similar to other tyrosine kinase inhibitors, these have also been used in smaller studies in ATC [1241], [1246]. Lenvatinib showed an objective tumor response rate of 24% with a progression-free survival of 7.4 months and a median overall survival of 10.6 months in a phase 2 trial in Japan with 17 patients [1247]. This led to the approval of lenvatinib for the treatment of ATC in Japan, but not yet in Europe or the USA. In an international phase 2 trial of the International Thyroid Oncology Group with 33 patients, which is not yet available as a full publication, a confirmed partial remission with lenvatinib was observed in only one case (NCT02657369). A recent multicenter open-label phase II study investigated the efficacy of lenvatinib monotherapy in 34 patients. The best overall response showed a partial response in 1/34 patients, stable disease in 17/34 patients and progressive disease in 9/34 patients [1248].

The role of immunotherapy in ATC has not been conclusively investigated. Various combination therapies, for example of tyrosine kinase inhibitors with immune checkpoint inhibitors, are currently being investigated [1249], [1250]. In a German retrospective study, a total of 8 patients with metastatic disease, 6 with ATC and 2 with PDTC, were treated with a combination of lenvatinib and the PD-L1 inhibitor pembrolizumab [1052]. All patients had prior treatments including surgery, radiotherapy, chemotherapy or radioiodine therapy. In the first imaging follow-up 3-4 months after initiation of therapy, 4 of the 6 included ATC patients showed complete remission, 1 patient had stable disease and 1 patient had progressive disease. Overall survival in the 4 ATC patients with an initial complete remission was 11, 19, 26 and 40 months.

9.3.7 Management of individual issues

9.25	Consensus-based Recommendation	2025
EK	The indication for surgical and/or local ablative therapy in metastatic stage IVC versus the initiation of systemic therapy should be determined individually and by interdisciplinary consensus, taking into account the mostly palliative situation.	
	Strong Consensus	

ATC in the metastatic stage is associated with an unfavorable prognosis. In autopsy studies and retrospective cohort studies, distant metastasis is reported in around 75% of patients and more than one organ system is affected in around 80% [1202], [1251], [1252], [1253]. The 1-year survival in stage IVC is around 8% [1201]. In the rare case of oligometastatic disease, the effects of local ablative and/or surgical therapy have not been investigated.

9.3.7.1 Lung metastases

9.26	Consensus-based Recommendation	2025
EK	Disseminated lung metastases shall be treated systemically.	
	Strong Consensus	

The lung is the most frequently affected organ system in metastatic ATC patients, with a frequency of 70-80% [1252], [1253]. The majority of patients have multiple lung metastases and at least one other affected organ system [1251], so systemic therapy shall be preferred over local ablative therapy. For systemic therapy of lung metastases, please refer to Chapter 9.3.6.

9.3.7.2 Bone metastases

9.27	Consensus-based Recommendation	2025
EK	In the case of symptomatic bone metastasis, local ablative and/or surgical therapy should be offered.	
	Strong Consensus	

9.28	Consensus-based Recommendation	2025
EK	A stable vertebral body metastasis without myelon compression can be treated conservatively.	
	Strong Consensus	

9.29	Consensus-based Recommendation	2025
EK	In the presence of bone metastases, antiresorptive therapy with bisphosphonates or RANK ligand antibodies should be carried out.	
	Strong Consensus	

Bone metastases occur in 5% of ATC patients, usually in combination with at least one other affected organ system [1252]. The treatment of bone metastases in ATC patients has only been investigated in small case series. In a series of 14 thyroid cancer patients with myelon compression, 4 had histologically confirmed ATC [1254]. The patients were irradiated without primary surgical intervention. There was a response rate of 79% for all thyroid cancer patients. In a retrospective study, a total of 79 thyroid cancer patients with bone metastases were examined, including 10 patients with histologically confirmed ATC [1255]. Six of the 10 patients died in the first year after bone metatases diagnosis.

The aim of the specific treatment of bone metastases is to prevent skeletal complications such as pathological fractures, spinal compression syndrome, bone pain and hypercalcemia. The treatment options are pharmacological pain management, local radiation, surgical intervention and systemic tumor therapy.

Bisphosphonate therapy or therapy with RANKL inhibitors for osteoprotection has not been investigated in ATC patients. In individual cases, osteoprotective therapy with bisphosphonates can be discussed in analogy to other aggressive tumor diseases. Please refer to the interdisciplinary cross-sectional guideline "Supportive therapy in oncology patients".

9.3.7.3 Brain metastases

9.30	Consensus-based Recommendation	2025
EK	The treatment of brain metastases should be determined individually by interdisciplinary consensus in view of the poor prognosis.	
	Strong Consensus	

Brain metastases are rare in ATC patients with a frequency of 1-5%, but are associated with a particularly unfavorable prognosis [1204]. Data on therapy are only available in the form of retrospective cohort studies with small numbers of cases. Salvati et al. [1205] retrospectively examined 12 thyroid cancer patients, including 5 with an ATC, with a single brain metastasis. In 4 of the 5 patients, more than one organ system was affected. The time between diagnosis of the primary disease and brain metastasis was between 7 and 13 months. In all patients, treatment consisted of resection of the metastasis followed by whole-brain radiotherapy. Overall survival was 8.8 months from ATC diagnosis.

Another study included a total of 47 thyroid cancer patients with brain metastases, including 11 ATC patients [1204]. The lesions were multifocal in 80% of the ATC patients and more than one organ system was affected in 80% of the patients. Survival after diagnosis of brain metastases was 1.3 months in ATC patients, which was significantly shorter than that of patients with differentiated thyroid carcinoma at 12.4 months.

No valid conclusions can be drawn from the available data due to the retrospective study design and the small number of patients. The prognosis after diagnosis of brain metastatic disease is dismal, i.e. the indication should be made as part of an

interdisciplinary consensus. Treatment options include resection, radiotherapy and/or systemic therapy.

9.3.7.4 Surgery for metastatic disease

9.31	Consensus-based Recommendation	2025
EK	Depending on the localization, metastasectomy can be offered symptomatically or as a preventive measure against complications, if necessary, in addition to other therapeutic approaches.	
	Strong Consensus	

Disseminated distant metastatic disease to one or more organ systems requires a systemic therapeutic approach. A role for surgery arises in individual cases depending on the localization and existing or impending symptoms or complications that cannot be controlled by therapeutic means or are complementary to them. This is most likely to be the case with bone metastases, cervical, mediastinal, skin and visceral metastases.

9.3.7.5 Further metastasis

In autopsy studies, metastases were found in a variety of organs in patients with anaplastic thyroid carcinoma [1251], [1253]. In addition to metastases in the lungs, bones and brain, lesions were also found in the liver in 20-30%, in the adrenal gland in 21-24%, in the cardiovascular system in 18%, in the stomach in 7% and in the pancreas in 6.7% of ATC patients. More than one organ system was affected in 80% of patients. It is not clear which metastases were already known before death and to what extent they were relevant for the clinical course. However, the studies show that metastases can occur in almost all organ systems.

Folllowed by lungs, the liver is the second most affected organ. However, metastases usually occur multifocally, so that surgical or local ablative therapy is not possible. In this case, systemic therapy should be considered as an option, as described in Chapter 9.3.6.

9.4 Follow-up care for anaplastic thyroid carcinoma

9.4.1 Requirements for evaluation of therapy response

9.32	Consensus-based Recommendation	2025
EK	Patients with anaplastic thyroid carcinoma should receive cross-sectional imaging of the skull, neck, thorax, abdomen and pelvis after initial staging and treatment and without evidence of structural tumor disease if further treatment is desired. The recommended intervals are 1 - 3 months within the first year, then every 3 - 4 months within the following year and then every 6 months for a further 2 - 3 years. In addition to [^{18}F]FDG PET/CT, which is particularly suitable for whole-body staging, CT with contrast and MRI are suitable modalities.	
	Strong Consensus	

9.33	Consensus-based Recommendation	2025
EK	In patients with anaplastic thyroid carcinoma, imaging with [^{18}F]FDG-PET/CT should be performed as part of follow-up care. It is used to detect small metastases that may alter treatment. In addition, [^{18}F]FDG-PET/CT can enable a response assessment to decide on change in treatment in the case of persistent structural disease.	
	Strong Consensus	

9.34	Consensus-based Recommendation	2025
EK	Patients with anaplastic thyroid carcinoma should receive cross-sectional imaging of the skull, neck, thorax, abdomen and pelvis or other affected organs/regions after initial staging and treatment and with evidence of persistent structural tumor disease if further treatment is desired. The choice of modality (CT with CA, MRI, [^{18}F]FDG-PET/CT) depends on the individual findings and the need for therapy monitoring or therapy planning. The intervals should be 1 - 3 months.	
	Strong Consensus	

Despite all therapeutic efforts, the majority of patients with ATC eventually develop tumor progression usually within a short period of time, and succumb to the disease. Approximately one third of patients already have distant metastases at the time of initial diagnosis and a further third develop distant metastases during the course of the disease. Supportive therapy is therefore important (see Chapter 12). Approximately one third of patients die with locoregional disease, one quarter with distant metastases and more than 40% with both. Distant metastasis mainly affects the lungs

(80% - 85%), the bones (5% - 10%) and the brain (5% - 10%). Lack of locoregional tumor control is found early on within 3 months in 20% to 40% of patients [1256], [1257], [1258], [1259], [1260], [1261], [1220], [1262], [1263], [1264], [511], [1265], [1266], [1223], [1218], [1267]. In this overall situation, cross-sectional imaging is a suitable procedure for the follow-up of both locoregional and distant tumor control. The start and intervals of diagnostic imaging depend on the initial tumor stage, the response to therapy and the time since diagnosis.

After initial successful therapy with no evidence of residual tumor, sectional imaging using CT or MRI of the brain, neck (plus sonography if necessary), thorax, abdomen and pelvis should be performed at intervals of 1 - 3 months for the first 6 to 12 months. Thereafter at intervals of 4 - 6 months for the following year. Additional examinations may be necessary in individual contexts. If the patient refuses further therapeutic measures, imaging procedures can be used in close consultation with the patient in a symptom-oriented manner [1195].

If there is no tumor after 2 years, the intervals can be extended to 6 months for another 2 to 3 years. In the event of tumor persistence or recurrence, sectional imaging should be performed in accordance with the clinical situation.

CT, MRI and, if necessary, sonography for the neck are suitable for anatomical response assessment using sectional imaging. The same procedures shall be used for follow-up exams according to the organ-specific requirements and availability. Reference can be made to the explanations in Chapter 9.1.4 on morphological cross-sectional imaging. The RECIST response assessment requires a complete CT, which can also be acquired as part of a PET/CT examination. Study protocols may also require other/additional modalities for response assessment (e.g. PET-based criteria, see below).

^{18}F]FDG-PET/CT is an additional well-suited procedure for tumor follow-up. In the case of persistent tumor burden, (whole-body) [^{18}F]FDG-PET/CT offers the highest diagnostic accuracy [1195]. In particular, with discordant imaging, the metabolic activity measured in [^{18}F]FDG-PET can be more informative than the sole assessment of tumor size in CT [1199], [1200], [1268], [1269]. It is also possible to assess the response to systemic therapy and radiotherapy [1199], [1268], [1269].

9.4.2 Terminology of therapy response

9.35	Consensus-based Recommendation	2025
EK	The evaluation of treatment response in patients with anaplastic thyroid carcinoma should be based on the RECIST 1.1 criteria for the treatment of solid tumors.	
	Strong Consensus	

There are no studies evaluating treatment response criteria specifically for anaplastic thyroid carcinoma. Current studies on systemic therapy for anaplastic thyroid carcinoma use the RECIST criteria [544], [1270], [1249].

There are no tumor markers for response evaluation in anaplastic thyroid carcinoma.

A negative [^{18}F]FDG-PET with a new lesion confirmed by CT during the course is assessed as progression if the new lesion is detected at a new site.

PET-based criteria (PERCIST) [1271] for assessing treatment response have been validated for many solid tumors and are characterized by higher sensitivity and diagnostic accuracy compared to RECIST. Individual observations suggest that this also applies to anaplastic thyroid carcinoma, even if there are no systematic studies on this entity [1272]. Newly detected lesions without [^{18}F]FDG uptake are assessed according to the RECIST 1.1 criteria.

9.4.3 TSH target

9.36	Consensus-based Recommendation	2025
EK	The thyroid metabolism in ATC patients should be euthyroid with a target TSH in the reference range.	
	Strong Consensus	

Anaplastic thyroid carcinoma is an undifferentiated carcinoma that is characterized, among other things, by the loss of expression of the sodium iodide symporter on the basolateral membrane [1273]. A growth stimulus through the pituitary TSH has not been proven and would be implausible, so that no growth-inhibiting effect through exogenous TSH suppression is to be expected.

10 Other tumor entities

10.1 Lymphomas

Primary thyroid lymphomas are rare and account for about 2-5% of all thyroid malignancies and about 2% of all extranodal lymphomas [1274], [1275]. According to data from a Southern Danish tumor registry, the incidence in the 1980/90s was 2 per 1 million inhabitants [1276].

The vast majority (70 %) are high-grade B-cell lymphomas (DLBCL dominates), followed by MALT lymphomas and much rarer follicular lymphomas [1274]. The majority of patients have a localized tumor stage 1-2 [1274], [1277]. Women are overrepresented (3:1) [1274], [1276]. Hashimoto's thyroiditis represents a predisposition in that 2/3 of the patients had pre-existing Hashimoto's thyroiditis and in half of the cases the transformation from Hashimoto's thyroiditis via a low grade lymphoma to a high grade lymphoma could be traced [1276].

Clinically, intrathyroid lymphoma presents as a rapidly growing neck tumor often with tracheal or laryngeal compression [1278], [1279]. Cervical lymph nodes are common, B-symptoms rare [1280]. The sonographic image usually shows a homogeneous, markedly hypoechoic lesion with dorsal sound enhancement, but without calcification or necrosis [1279], [1281], [1282]. A thyroid scintigraphy is unnecessary in most cases [1283]. The diagnosis can be confirmed in around three quarters of patients by fine needle aspiration [1279]. In the case of unclear findings, sonographically assisted punch biopsy has further reduced the role of open surgical tissue removal. However, this may be necessary to determine the lymphoma subtype [1280]

Recommendations for diagnostics, particularly for punch biopsy, can be found under Recommendation 4.11.

10.1	**Consensus-based Recommendation**	**2025**
EK	The treatment of intrathyroid lymphoma shall be determined in the interdisciplinary tumor board and is usually multimodal.	
	Strong Consensus	

A multimodal approach consisting of antibody therapy, chemotherapy and radiotherapy is used therapeutically, particularly for high-grade lymphomas [1280]. In mixed patient collectives, 5-year survival after radiochemotherapy was 74% [1284] and 85% [1285].

Surgical treatment of primary thyroid lymphoma alone is controversial, but in selected cases with stage IE disease it can bring the disease under local control (295). Surgical treatment may be indicated on an emergency basis in the event of airway obstruction [1280].

10.2 Thyroid metastases of extrathyroidal primary tumors

10.2	Consensus-based Recommendation	2025
EK	In patients with a history of tumor disease, suspicious nodules in the thyroid gland should also be investigated with regard to intrathyroid metastasis.	
	Strong Consensus	

Metastases of extrathyroidal primary tumors in the thyroid gland are very rare and often only occur in patients with advanced tumor disease. For this reason, management and prognosis are not well established [1286]

In routine clinical practice, metastases account for only 0.2 % of all thyroid malignancies [1287] and are a rarity in view of the fact that thyroid malignancies are rare per se. In a review by Chung et al., metastases of an extrathyroidal tumor were found in 1.4-3% of cases in patients who underwent surgery for thyroid malignancy [1288]. In a retrospective analysis by Wang et al., 21/1,754 patients who underwent FNAC of a thyroid nodule were diagnosed with metastasis of an extrathyroidal tumor. This corresponds to a rate of 1.2 % [1286].

In autopsies, however, metastases are somewhat more common. In a study over a 16-year period, the rate was 0.9% of all autopsies and 13% of patients with known tumor disease. Lung metastases were the most common (33%), followed by breast carcinoma (8%) and renal cell carcinoma (8%) [1289].

In contrast to the autopsy studies, renal cell carcinoma is the leading tumor type in the clinical series [1288], [1290], [1291], [1292]. In the meta-analysis by Chung et al. it was the most common primary tumor at 48%, followed by colorectal, lung and breast carcinomas [1288]. The reason for the observation that renal cell carcinoma leads in clinical diagnosis is primarily its slow progression. The time interval between initial diagnosis and the appearance of thyroid metastases has a long latency. In a small study, it was 84 months [1293] and is given as 68 months by Chung et al. Patients with thyroid metastases from other tumor entities (lung, colorectum, etc.) are usually diagnosed at an advanced tumor stage, and the primary tumor type rather than the thyroid metastasis is then significant for survival [1292], [1294].

In the majority of cases, the clinical symptoms (appearance of cervical swelling, visible and palpable thyroid nodules, hoarseness, difficulty swallowing, shortness of breath, etc.) are indicative and suggest metastasis to the thyroid gland.

The smaller part is discovered by chance during staging examinations such as PET, CT or sonography of the soft tissues of the neck [1288].

In this situation, FNAC (see Chapter 4.2) also provides the correct diagnosis for the majority of patients [1294], [1295].

10.3	Consensus-based Recommendation	2025
EK	The recommendation for lobectomy or thyroidectomy for local control and to avoid complications should be made in the interdisciplinary tumor board, taking into account the overall clinical situation.	
	Consensus	

In the case of indifferent FNAC or isolated metastasis to the thyroid gland, thyroidectomy can be considered in terms of local control and avoidance of complications (tracheotomy, recurrent nerve palsy, e.g.) [1296], [1297], [1298]. In terms of overall survival, however, surgery is controversially discussed. While Papi et al. found that surgery had no effect on overall survival, Hegerova et al. reported improved (albeit not statistically significant) overall survival after thyroidectomy [1291], [1299].

11 Palliative care

Palliative care is defined as an approach to improving the quality of life of patients and their families who are faced with problems associated with a life-threatening illness. This is done by preventing and alleviating suffering through early detection, careful assessment and treatment of pain and other physical, psychosocial and spiritual problems. Regarding palliative care aspects, regardless of the underlying diagnosis, please refer to the S3 guideline on palliative care of the German Guideline Program in Oncology.

12 Rehabilitation

12.1	Consensus-based Recommendation	2025
EK	All patients with thyroid cancer shall be informed and advised about rehabilitation, particularly in the form of follow-up treatment, and supported in applying for it. When selecting the facility, the patient's right to choose is to be taken into account.	
	Strong Consensus	

12.2	Consensus-based Recommendation	2025
EK	The oncological rehabilitation of thyroid cancer patients shall take place in facilities that have a concept geared to the specific needs of the indication.	
	Strong Consensus	

In Germany, patients are legally entitled to follow-up treatment after every surgery, radioiodine therapy or radiotherapy for thyroid cancer.

The statutory pension insurances are the most frequently responsible service providers. According to German social legislation, people with disabilities or at risk of disability receive rehabilitation services to promote their self-determination and equal participation in society, to avoid disadvantages or to counteract them. The services are provided by the responsible rehabilitation provider in accordance with the Ninth Book of the German Social Code (SGB) and the benefit laws applicable to the respective rehabilitation provider (e.g. SGB V in the case of the statutory health insurance or SGB VI in the case of the German Pension Insurance, *Deutsche Rentenversicherung*, DRV) [1300], [1301], [1302].

In addition to follow-up treatment, it is possible to apply to the cost bearers for treatment at any time during the illness. The prerequisites for approval are a justified "need for rehabilitation" and a positive "rehabilitation prognosis".

The aim of oncological rehabilitation is to regain physical, mental and social well-being and to return to everyday family, social and professional normality. Other goals include maintaining the ability to work and avoiding the need for long-term care.

Some of the consequences of thyroid cancer and thyroid cancer therapy occur immediately after treatment, for example local secondary disorders due to the surgery or radioiodine therapy, discomfort caused by the cervical scar, difficulty swallowing, restricted throat mobility or dry mouth, difficulty swallowing, hoarseness or functional disorders due to recurrent paresis, dyspnea, lymphedema or disorders of calcium metabolism as a result of postoperative hypoparathyroidism [1303].

Other secondary disorders are often only noticed at a later stage, such as chronic tumor-associated fatigue syndrome, problems with thyroid hormone regulation, anxiety and depression.

If patients are eligible for follow-up treatment, they shall be informed and advised by the treating centers about the eligibility, content and benefits of a follow-up treatment measure with reference to their right to choose an appropriate facility.

Oncological rehabilitation for thyroid cancer patients shall take place in suitable facilities. The prerequisite is the existence of an indication-specific concept aimed at the specific needs and a corresponding approval from the German Pension Insurance (indication group 11l, oncological diseases/thyroid). Multimodal rehabilitation treatments are carried out in these facilities, which include various basic elements: Exercise, nutrition, psyche, information on illness and health, social counseling and sociomedical assessment (occupational).

Specific counseling contents are: Biology, diagnostics and therapies of the various thyroid cancers, new therapy options for advanced thyroid cancer, important laboratory values in thyroid cancers, function of the thyroid and parathyroid glands, signs of hypothyroidism and hyperthyroidism, training on thyroid hormone substitution (timing of thyroid hormone intake, TSH target ranges, possible errors or factors influencing the results of laboratory tests, in particular the Tg value), dealing with hypoparathyroidism and calcium substitution, tumor aftercare, safe sources of information, thyroid self-help and self-help organizations.

Often underestimated reasons for oncological rehabilitation are fatigue, anxiety and depression:

Cancer-related fatigue is a common burden of thyroid cancer patients. Yukari Maki et al. showed a prevalence of 41.8% in long-term survivors with no evidence of persistent or recurrent disease. The diagnostics for this are described in the S3 guideline on fatigue [1304]. In thyroid cancer patients, particular attention is paid to the laboratory parameters for thyroid hormone replacement and the calcium-phosphate balance. The forms of therapy with positive connotations in the guideline (exercise training, cognitive behavioral therapy and psychological intervention) are part of the therapeutic offer of oncological rehabilitation (5).

Thyroid cancer patients have poorer scores for depression and anxiety compared to patients with other cancers (non-Hodgkin's lymphoma, breast cancer, prostate cancer, colorectal cancer, uterine cancer, prostate cancer) [1305]. There is evidence of a correlation with the intensity of TSH-suppressive thyroid hormone substitution [1306], [1307]. Various therapeutic elements of oncological rehabilitation are suitable for achieving positive effects in patients with anxiety and depression.

Many therapies provided within oncological rehabilitation are evidence-based. For methodological reasons, most studies are available for breast cancer, prostate cancer and colorectal cancer. The transferability of the results to thyroid cancer patients appears plausible.

13 Psychosocial aspects

13.1	Consensus-based Recommendation	2025
EK	Patients shall be adequately informed about the diagnosis and general prognosis. They shall be advised on the therapeutic options based on the individual findings, the prognosis, taking into account psychosocial aspects and quality of life. They shall have the opportunity to involve other people in the informative discussion.	
	Strong Consensus	

As a cancer diagnosis is accompanied by a great deal of uncertainty and treatment can have far-reaching consequences, it is necessary to inform patients about all relevant points and give them the opportunity to ask questions. Patients shall have the feeling that they are involved in their medical decisions. If patients feel involved in the decision (shared decision making), this can have a positive effect on treatment-relevant outcomes [1308], [1309], [1310], [1311].

Studies [1312], [1313], [1314] have shown that thyroid cancer patients want more information in the areas of diagnosis, treatment and aftercare. These needs should be addressed and adequately addressed in educational discussions.

As the topic of thyroid cancer is stressful and patients have a multitude of thoughts and questions after diagnosis [1312], [1313], [1315], [1316], [1317], the participation of another person in the educational talks can help here.

13.2	Consensus-based Recommendation	2025
EK	The individual preferences, needs, concerns and fears of the patient shall be elicited and taken into account during the medical consultation. If a patient requires several consultations, the offer shall consist of further consultations.	
	Strong Consensus	

With the diagnosis of thyroid cancer and during the course of treatment, patients experience fears and worries [1318], [1315], [1316], [1317]. The diagnosis of thyroid cancer also has an impact on patients' everyday lives and future plans [1313], [1314], [1319].

These must be taken into account during the medical consultation. If worries and fears are not adequately addressed, this can lead to poorer outcomes. This has been shown in studies of other cancer entities [1320], [1321], [1322].

Studies [1312], [1313], [1314] have shown that thyroid cancer patients report a high need for information in various areas (diagnosis, treatment, aftercare, psychological support, etc.). These individual needs and preferences should be taken into account in the medical consultation.

13.3	**Consensus-based Recommendation**	**2025**
EK	All patients with thyroid cancer shall be offered screening for psychosocial stress using a validated and standardized instrument.	
	Consensus	

13.4	**Consensus-based Recommendation**	**2025**
EK	Psycho-oncological screening should be carried out as early as possible at appropriate intervals if clinically indicated or repeatedly during the course of the disease if a patient's disease status changes (e.g. recurrence or progression of the disease). (Guideline adaptation S3 guideline psycho-oncology, version 2022)	
	Strong Consensus	

Screening for psychosocial stress and clarification of support needs shall be carried out on a voluntary basis.

Depending on local circumstances, screening for psychosocial distress can be carried out by any member of the treatment team responsible for the care of cancer patients after appropriate training.

The best national and international evidence for cancer patients is available for the Distress Thermometer (DT), the Hospital Anxiety and Depression Scale (HADS-D), the depression module of the Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety Disorder (GAD-7) module. In German-speaking countries, the questionnaire on stress in cancer patients (FBK-23 and FBK-10) is also well validated (Evidence-based Guideline Psycho-oncological Diagnostics, Counseling and Treatment of Adult Cancer Patients).

Only diagnostic procedures that fulfill the psychometric quality criteria (objectivity, reliability and validity) shall be used in psycho-oncological screening. Practicability, even for patients with severe cancer, and cost-effectiveness are further important requirements. In addition to the aforementioned quality criteria, empirically determined cut-off values should be available for screening procedures that also demonstrate satisfactory sensitivity and specificity. As part of the aforementioned S3 guideline on psycho-oncology, a detailed evaluation of the psychometric quality criteria was carried out on the basis of a systematic literature search of publications relating to German patients.

A study by Loth et al. [1323] showed that systematic psycho-oncological screening leads to increased identification of patients with psycho-oncological needs.

All of the above-mentioned questionnaires have already been used in a large number of studies with patients with thyroid cancer [1318], [1324].

Thyroid cancer patients can experience psychosocial limitations and a reduction in quality of life at any point during the course of the disease and treatment [941], [1325], [1326], [1318], [1327], [1328], [1324]. Despite the relatively good prognosis of thyroid cancer, patients have quality of life impairments that are comparable to those of patients with other cancers with a poorer prognosis [1329].

Furthermore, thyroid cancer patients would like to receive more information on psychosocial counseling, and patients see a major lack of information in this area [1312], [1313]. Dionisi-Vici et al. [1330] were able to show that half of long-term survivors of thyroid cancer complain of unmet psychological needs.

13.5	**Consensus-based Recommendation**	**2025**
EK	If the screening is positive and/or there is a subjective need for support, a diagnostic interview shall be offered to clarify psychosocial stress, psychological comorbidities and the need for support and treatment. (Guideline adaptation S3 guideline psycho-oncology, version 2022)	
	Strong Consensus	

13.6	**Consensus-based Recommendation**	**2025**
EK	Patients with diagnosed mental disorders shall be treated in accordance with the existing disorder-specific guidelines. (Guideline adaptation S3 guideline psycho-oncology, version 2022)	
	Strong Consensus	

A large number of studies in thyroid cancer patients show positive screening results using the above-mentioned instruments. Positive screening results can be seen over the entire course of the disease up to long-term survivors [1331], [1332], [1318], [1314]. In a study of 640 German thyroid cancer survivors, Noto et al. [1333] reported that 37.6% exceeded the cut-off value for anxiety disorders and 15.7% for depression, measured using the HADS.

If a mental disorder worthy of treatment is diagnosed during the diagnostic interview, the corresponding German-language S3 guidelines are applied. An overview of these guidelines can be found in Table 9 of the guideline on 'Psycho-oncology'.

Furthermore, special interventions tailored to thyroid cancer patients have shown success [1334], [1335], [1336],[1337]. Interventions should also be adapted to the individual needs of the patient. For example, Husson et al. [1338] were able to show that age can have an influence on psychological stress and the perception of illness in thyroid cancer patients.

14 Quality indicators

Quality indicators are measures that are used to assess the quality of the underlying structures, processes and results. Quality indicators are an important instrument of quality management. The aim of their use is the continuous improvement of care by presenting, critically reflecting on and, if necessary, improving the results of care. This selection of quality indicators was created in accordance with the methodology of the German Guideline Program in Oncology [1339]. A "Quality Indicators Working Group" (Working group QI) was formed for the derivation process. This group created the final set of quality indicators on the basis of the strong recommendations ("shall") of the newly developed guideline on thyroid cancer, as well as the results of the search for existing international quality indicators. The exact procedure and composition of the QI working group are described in the guideline report.

After two online meetings of this working group, the final set of 7 quality indicators (QI) was defined and adopted.

Quality indicators 1, 2, 4 and 5 are to be documented with the oncological basic data set of the cancer registries (as of 10/2023).

Table 24: Quality Indicators

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
QI 1: Ratio of tumor-infected to examined lymph nodes		
Numerator Patients of the denominator with indication of the ratio "lymph nodes affected by tumor to total lymph nodes examined" **Denominator** All patients with a first diagnosis of thyroid carcinoma with resection and with histopathologically examined lymph nodes	Recommendation 4.4 The histopathological findings shall report the number of tumor-infected lymph nodes in relation to the total number of lymph nodes examined.	Consensus-based recommendation strong consensus **Quality objective:** As often as possible, information on the ratio of "lymph nodes affected by tumors to total lymph nodes examined"
QI 2: No histological confirmation of anaplastic thyroid carcinoma (ATC) or intrathyroid lymphoma by fine needle biopsy		
Numerator Patients of the denominator with fine needle biopsy **Denominator** All patients with a first diagnosis of anaplastic thyroid carcinoma or intrathyroid lymphoma	Recommendation 4.11 If anaplastic thyroid carcinoma or lymphoma is suspected, a histological confirmation shall be carried out instead of a fine needle biopsy - e.g. by means of a punch biopsy.	Consensus-based recommendation strong consensus **Quality objective:** If possible, no histological confirmation of anaplastic thyroid carcinoma or lymphoma by fine-needle biopsy
QI 3: Indication of TNM classification, histological type and extranodal tumor growth in the histopathological report		
Numerator Patients of the denominator with all details in the histopathology report: - Staging according to the current TNM classification of the UICC - Classification of the histological types of thyroid carcinoma according to the current WHO classification, if applicable histological subtypes - as far as they are described in the	Recommendation 4.24 The following information shall be provided in the pathological findings of surgical specimens: • Staging according to the current TNM classification of the UICC. • Classification of the histological types of thyroid carcinoma according to the	Consensus-based recommendation Strong consensus **Quality objective:** Complete reports with TNM classification, histological subtype and capsule-exceeding growth of lymph node metastases as frequently as possible.

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
current WHO classification. - Capsular growth of lymph node metastases. **Denominator** All patients with a first diagnosis of thyroid cancer and resection	current WHO classification, if applicable histological subtypes - insofar as they are described in the current WHO classification. • Capsular growth of lymph node metastases.	
QI 4: Intraoperative neuromonitoring		
Numerator Patients of the denominator with intraoperative neuromonitoring (IONM) **Denominator** All patients with thyroid cancer and bilateral thyroid surgery	Recommendation 5.30 Intraoperative neuromonitoring (IONM) shall be used for bilateral thyroid surgery, preferably in the form of continuous neuromonitoring (CIONM) in the case of special risk constellations.	Evidence-based recommendation GRADE ⊕⊕⊖⊖⊖ **Quality objective:** Intraoperative neuromonitoring as frequently as possible in bilateral thyroid surgery
QI 5: Interdisciplinary recommendation for radioiodine therapy in the tumor board		
Numerator Patients of the denominator with pre-therapeutic presentation in the interdisciplinary tumor conference **Denominator** All patients with thyroid cancer and radioiodine therapy	Recommendation 5.31 The recommendation for radioiodine therapy shall be made on the basis of the clinical and histopathological findings in an interdisciplinary tumor board.	Consensus-based recommendation Strong consensus **Quality objective:** Recommendation for radioiodine therapy based on the clinical and histopathological findings as frequently as possible in the interdisciplinary tumor board
QI 6: Postoperative calcitonin/CEA level and molecular genetic analysis of RET protooncogene in medullary thyroid carcinoma		
Numerator Patients of the denominator with pTNM and postoperative calcitonin and CEA levels (6-8 weeks after surgery)	Recommendation 8.15 The following findings shall be available for planning risk-adapted postoperative follow-up care of a histologically and	Consensus-based recommendation Strong consensus **As frequently as possible**

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
Denominator Patients of the denominator with molecular genetic germline analysis RET protooncogene	immunohistologically confirmed MTC: • pTNM classification = staging • postoperative basal Ctn and CEA levels (6-8 weeks after surgery) • molecular genetic analysis for pathogenic germline variant in the RET protooncogene	1. Determination of pTNM, calcitonin and CEA 2. Molecular genetic germline analysis RET protooncogene
QI 7: Molecular pathological examination of the RET gene in sporadic medullary thyroid carcinoma		
Numerator Patients of the denominator with molecular pathological examination of the tumor for somatic variant in the RET gene before system therapy **Denominator** All patients with metastatic sporadic medullary thyroid carcinoma (MTC), N1 and/or M1 and systemic therapy	Recommendation 8.33 In patients with metastatic sporadic MTC, a molecular genetic analysis of the tumor for the presence of a somatic variant in the RET gene shall be performed before starting systemic therapy with regard to the use of selective RET inhibitors and vandetanib.	**Quality objective:** Molecular pathological analysis for the presence of a somatic variant in the RET gene as frequently as possible before starting systemic therapy

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17 Literature

1. Meisinger, C, Ittermann, T, Wallaschofski, H, Heier, M, Below, H, Kramer, A, et.al. Geographic variations in the frequency of thyroid disorders and thyroid peroxidase antibodies in persons without former thyroid disease within Germany., Eur J Endocrinol, 2012. 167 (3)(3): p. 363-71., https://pubmed.ncbi.nlm.nih.gov/22700599/
2. Reiners, C, Wegscheider, K, Schicha, H, Theissen, P, Vaupel, R, Wrbitzky, R, et.al. Prevalence of thyroid disorders in the working population of Germany: ultrasonography screening in 96,278 unselected employees., Thyroid, 2004. 14 (11)(11): p. 926-32., https://pubmed.ncbi.nlm.nih.gov/15671771/
3. Khattak, RM, Ittermann, T, Nauck, M, Below, H, Völzke, H, Monitoring the prevalence of thyroid disorders in the adult population of Northeast Germany., Popul Health Metr, 2016. 14 (): p. 39., https://pubmed.ncbi.nlm.nih.gov/27833458/
4. Krebs in Deutschland, in Schilddrüse, 2021. p. 126 - 129., https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2021/kid_2021_c73_schilddruese.pdf?__blob=publicationFile
5. Brenner, DR, Ruan, Y, Shaw, E, O'Sullivan, D, Poirier, AE, Heer, E, et.al. Age-standardized cancer-incidence trends in Canada, 1971-2015., CMAJ, 2019. 191 (46)(46): p. E1262-E1273., https://pubmed.ncbi.nlm.nih.gov/31740536/
6. Dal Maso, L, Panato, C, Franceschi, S, Serraino, D, Buzzoni, C, Busco, S, et.al. The impact of overdiagnosis on thyroid cancer epidemic in Italy,1998-2012., Eur J Cancer, 2018. 94 (): p. 6-15., https://pubmed.ncbi.nlm.nih.gov/29502036/
7. Seib, CD, Sosa, JA, Evolving Understanding of the Epidemiology of Thyroid Cancer., Endocrinol Metab Clin North Am, 2019. 48 (1)(1): p. 23-35., https://pubmed.ncbi.nlm.nih.gov/30717905/
8. Powers, AE, Marcadis, AR, Lee, M, Morris, LGT, Marti, JL, Changes in Trends in Thyroid Cancer Incidence in the United States, 1992 to 2016., JAMA, 2019. 322 (24)(24): p. 2440-2441., https://pubmed.ncbi.nlm.nih.gov/31860035/
9. Wiltshire, JJ, Drake, TM, Uttley, L, Balasubramanian, SP, Systematic Review of Trends in the Incidence Rates of Thyroid Cancer., Thyroid, 2016. 26 (11)(11): p. 1541-1552., https://pubmed.ncbi.nlm.nih.gov/27571228/
10. Farahati, J, Mäder, U, Gilman, E, Görges, R, Maric, I, Binse, I, et.al. Changing trends of incidence and prognosis of thyroid carcinoma., Nuklearmedizin, 2019. 58 (2)(2): p. 86-92., https://pubmed.ncbi.nlm.nih.gov/30917397/
11. Krebs in Deutschland, in Schilddrüse, 2019. p. 118 - 121., https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2019/kid_2019_c73_schilddruese.pdf?__blob=publicationFile
12. Mirian, C, Grønhøj, C, Jensen, DH, Jakobsen, KK, Karnov, K, Jensen, JS, et.al. Trends in thyroid cancer: Retrospective analysis of incidence and survival in Denmark 1980-2014., Cancer Epidemiol, 2018. 55 (): p. 81-87., https://pubmed.ncbi.nlm.nih.gov/29852396/
13. Cancer Research UK, Thyroid cancer statistics, 2025., https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer#thyroid_stats0
14. Lim, H, Devesa, SS, Sosa, JA, Check, D, Kitahara, CM, Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013., JAMA, 2017. 317 (13)(13): p. 1338-1348., https://pubmed.ncbi.nlm.nih.gov/28362912/

15. Ren, YJ, Liu, QM, Ge, MH, Li, HZ, Liu, B, Zhang, Y, et.al. [Incidence and mortality of thyroid cancer in cancer registries of Zhejiang Province, 2010-2014]., Zhonghua Yu Fang Yi Xue Za Zhi, 2019. 53 (10)(10): p. 1062-1065., https://pubmed.ncbi.nlm.nih.gov/31607057/

16. Lin, B, Ma, H, Ma, M, Zhang, Z, Sun, Z, Hsieh, IY, et.al. The incidence and survival analysis for anaplastic thyroid cancer: a SEER database analysis., Am J Transl Res, 2019. 11 (9)(9): p. 5888-5896., https://pubmed.ncbi.nlm.nih.gov/31632557/

17. Borges, AKDM, Miranda-Filho, A, Koifman, S, Koifman, RJ, Thyroid Cancer Incidences From Selected South America Population-Based Cancer Registries: An Age-Period-Cohort Study., J Glob Oncol, 2018. 4 (): p. 1-11., https://pubmed.ncbi.nlm.nih.gov/30241178/

18. Safavi, A, Azizi, F, Jafari, R, Chaibakhsh, S, Safavi, AA, Thyroid Cancer Epidemiology in Iran: a Time Trend Study., Asian Pac J Cancer Prev, 2016. 17 (1)(1): p. 407-12., https://pubmed.ncbi.nlm.nih.gov/26838247/

19. Ahn, HS, Kim, HJ, Kim, KH, Lee, YS, Han, SJ, Kim, Y, et.al. Thyroid Cancer Screening in South Korea Increases Detection of Papillary Cancers with No Impact on Other Subtypes or Thyroid Cancer Mortality., Thyroid, 2016. 26 (11)(11): p. 1535-1540., https://pubmed.ncbi.nlm.nih.gov/27627550/

20. Miranda-Filho, A, Lortet-Tieulent, J, Bray, F, Cao, B, Franceschi, S, Vaccarella, S, et.al. Thyroid cancer incidence trends by histology in 25 countries: a population-based study., Lancet Diabetes Endocrinol, 2021. 9 (4)(4): p. 225-234., https://pubmed.ncbi.nlm.nih.gov/33662333/

21. Eng, C, Mulligan, LM, Healey, CS, Houghton, C, Frilling, A, Raue, F, et.al. Heterogeneous mutation of the RET proto-oncogene in subpopulations of medullary thyroid carcinoma., Cancer Res, 1996. 56 (9)(9): p. 2167-70., https://pubmed.ncbi.nlm.nih.gov/8616867/

22. Marsh, DJ, Andrew, SD, Eng, C, Learoyd, DL, Capes, AG, Pojer, R, et.al. Germline and somatic mutations in an oncogene: RET mutations in inherited medullary thyroid carcinoma., Cancer Res, 1996. 56 (6)(6): p. 1241-3., https://pubmed.ncbi.nlm.nih.gov/8640806/

23. Eng, C, Clayton, D, Schuffenecker, I, Lenoir, G, Cote, G, Gagel, RF, et.al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET mutation consortium analysis., JAMA, 1996. 276 (19)(19): p. 1575-9., https://pubmed.ncbi.nlm.nih.gov/8918855/

24. Haugen, BR, Alexander, EK, Bible, KC, Doherty, GM, Mandel, SJ, Nikiforov, YE, et.al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer., Thyroid, 2016. 26 (1)(1): p. 1-133., https://pubmed.ncbi.nlm.nih.gov/26462967/

25. Cirello, V, Familial non-medullary thyroid carcinoma: clinico-pathological features, current knowledge and novelty regarding genetic risk factors., Minerva Endocrinol (Torino), 2021. 46 (1)(1): p. 5-20., https://pubmed.ncbi.nlm.nih.gov/33045820/

26. Cetta, F, FAP Associated Papillary Thyroid Carcinoma: A Peculiar Subtype of Familial Nonmedullary Thyroid Cancer., Patholog Res Int, 2015. 2015 (): p. 309348., https://pubmed.ncbi.nlm.nih.gov/26697262/

27. Tan, MH, Mester, JL, Ngeow, J, Rybicki, LA, Orloff, MS, Eng, C, Lifetime cancer risks in individuals with germline PTEN mutations., Clin Cancer Res, 2012. 18 (2)(2): p. 400-7., https://pubmed.ncbi.nlm.nih.gov/22252256/

28. Kamilaris, CDC, Faucz, FR, Voutetakis, A, Stratakis, CA, Carney Complex., Exp Clin Endocrinol Diabetes, 2019. 127 (2-03)(2-03): p. 156-164., https://pubmed.ncbi.nlm.nih.gov/30428497/

29. Lauper, JM, Krause, A, Vaughan, TL, Monnat, RJ, Spectrum and risk of neoplasia in Werner syndrome: a systematic review., PLoS One, 2013. 8 (4)(4): p. e59709., https://pubmed.ncbi.nlm.nih.gov/23573208/

30. Hińcza, K, Kowalik, A, Kowalska, A, Current Knowledge of Germline Genetic Risk Factors for the Development of Non-Medullary Thyroid Cancer., Genes (Basel), 2019. 10 (7)(7):, https://pubmed.ncbi.nlm.nih.gov/31247975/

31. Nosé, V, Familial follicular cell tumors: classification and morphological characteristics., Endocr Pathol, 2010. 21 (4)(4): p. 219-26., https://pubmed.ncbi.nlm.nih.gov/20878367/

32. Sturgeon, C, Clark, OH, Familial nonmedullary thyroid cancer., Thyroid, 2005. 15 (6)(6): p. 588-93., https://pubmed.ncbi.nlm.nih.gov/16029126/

33. Malchoff, CD, Sarfarazi, M, Tendler, B, Forouhar, F, Whalen, G, Joshi, V, et.al. Papillary thyroid carcinoma associated with papillary renal neoplasia: genetic linkage analysis of a distinct heritable tumor syndrome., J Clin Endocrinol Metab, 2000. 85 (5)(5): p. 1758-64., https://pubmed.ncbi.nlm.nih.gov/10843148/

34. Liao, Shunyao, Song, Wenzhong, Liu, Yunqiang, Deng, Shaoping, Liang, Yaming, Tang, Zhenlin, et.al. Familial multinodular goiter syndrome with papillary thyroid carcinomas: mutational analysis of the associated genes in 5 cases from 1 Chinese family, 2013. 13(1): p. 48., https://doi.org/10.1186/1472-6823-13-48

35. Malchoff, CD, Sarfarazi, M, Tendler, B, Forouhar, F, Whalen, G, Malchoff, DM, Familial papillary thyroid carcinoma is genetically distinct from familial adenomatous polyposis coli., Thyroid, 1999. 9 (3)(3): p. 247-52., https://pubmed.ncbi.nlm.nih.gov/10211600/

36. Guilmette, J, Nosé, V, Hereditary and familial thyroid tumours., Histopathology, 2018. 72 (1)(1): p. 70-81., https://pubmed.ncbi.nlm.nih.gov/29239041/

37. Iglesias, ML, Schmidt, A, Ghuzlan, AA, Lacroix, L, Vathaire, F, Chevillard, S, et.al. Radiation exposure and thyroid cancer: a review., Arch Endocrinol Metab, 2017. 61 (2)(2): p. 180-187., https://pubmed.ncbi.nlm.nih.gov/28225863/

38. Kitahara, CM, Berrington de Gonzalez, A, Bouville, A, Brill, AB, Doody, MM, Melo, DR, et.al. Association of Radioactive Iodine Treatment With Cancer Mortality in Patients With Hyperthyroidism., JAMA Intern Med, 2019. 179 (8)(8): p. 1034-1042., https://pubmed.ncbi.nlm.nih.gov/31260066/

39. Listewnik, MH, Birkenfeld, B, Chosia, M, Elbl, B, Niedziałkowska, K, Sawrymowicz, M, The occurrence of malignant thyroid lesions in patients after radioiodine treatment due to benign thyroid diseases., Endokrynol Pol, 2010. 61 (5)(5): p. 454-7., https://pubmed.ncbi.nlm.nih.gov/21049457/

40. Hu, MJ, Zhang, C, Liang, L, Wang, SY, Zheng, XC, Zhang, Q, et.al. Fasting serum glucose, thyroid-stimulating hormone, and thyroid hormones and risk of papillary thyroid cancer: A case-control study., Head Neck, 2019. 41 (7)(7): p. 2277-2284., https://pubmed.ncbi.nlm.nih.gov/30759328/

41. Cao, Y, Wang, Z, Gu, J, Hu, F, Qi, Y, Yin, Q, et.al. Reproductive Factors but Not Hormonal Factors Associated with Thyroid Cancer Risk: A Systematic Review and Meta-Analysis., Biomed Res Int, 2015. 2015 (): p. 103515., https://pubmed.ncbi.nlm.nih.gov/26339585/

42. Braganza, MZ, Berrington de González, A, Schonfeld, SJ, Wentzensen, N, Brenner, AV, Kitahara, CM, Benign breast and gynecologic conditions, reproductive and hormonal factors, and risk of thyroid cancer., Cancer Prev Res (Phila), 2014. 7 (4)(4): p. 418-25., https://pubmed.ncbi.nlm.nih.gov/24449056/

43. Paparodis, R, Imam, S, Todorova-Koteva, K, Staii, A, Jaume, JC, Hashimoto's thyroiditis pathology and risk for thyroid cancer., Thyroid, 2014. 24 (7)(7): p. 1107-14., https://pubmed.ncbi.nlm.nih.gov/24708347/

44. Silva de Morais, N, Stuart, J, Guan, H, Wang, Z, Cibas, ES, Frates, MC, et.al. The Impact of Hashimoto Thyroiditis on Thyroid Nodule Cytology and Risk of Thyroid Cancer., J Endocr Soc, 2019. 3 (4)(4): p. 791-800., https://pubmed.ncbi.nlm.nih.gov/30963137/

45. Kitahara, CM, Yanik, EL, Ladenson, PW, Hernandez, BY, Lynch, CF, Pawlish, KS, et.al. Risk of Thyroid Cancer Among Solid Organ Transplant Recipients., Am J Transplant, 2017. 17 (11)(11): p. 2911-2921., https://pubmed.ncbi.nlm.nih.gov/28397388/

46. Lengwiler, E, Stampf, S, Zippelius, A, Salati, E, Zaman, K, Schäfer, N, et.al. Solid cancer development in solid organ transplant recipients within the Swiss Transplant Cohort Study., Swiss Med Wkly, 2019. 149 (): p. w20078., https://pubmed.ncbi.nlm.nih.gov/31104307/

47. Lee, JH, Hwang, Y, Song, RY, Yi, JW, Yu, HW, Kim, SJ, et.al. Relationship between iodine levels and papillary thyroid carcinoma: A systematic review and meta-analysis., Head Neck, 2017. 39 (8)(8): p. 1711-1718., https://pubmed.ncbi.nlm.nih.gov/, 28513893/

48. Vaccarella, S, Franceschi, S, Bray, F, Wild, CP, Plummer, M, Dal Maso, L, Worldwide Thyroid-Cancer Epidemic? The Increasing Impact of Overdiagnosis., N Engl J Med, 2016. 375 (7)(7): p. 614-7., https://pubmed.ncbi.nlm.nih.gov/27532827/

49. Remonti, LR, Kramer, CK, Leitão, CB, Pinto, LC, Gross, JL, Thyroid ultrasound features and risk of carcinoma: a systematic review and meta-analysis of observational studies., Thyroid, 2015. 25 (5)(5): p. 538-50., https://pubmed.ncbi.nlm.nih.gov/25747526/

50. Brito, JP, Gionfriddo, MR, Al Nofal, A, Boehmer, KR, Leppin, AL, Reading, C, et.al. The accuracy of thyroid nodule ultrasound to predict thyroid cancer: systematic review and meta-analysis., J Clin Endocrinol Metab, 2014. 99 (4)(4): p. 1253-63., https://pubmed.ncbi.nlm.nih.gov/24276450/

51. Woliński, K, Szkudlarek, M, Szczepanek-Parulska, E, Ruchała, M, Usefulness of different ultrasound features of malignancy in predicting the type of thyroid lesions: a meta-analysis of prospective studies., Pol Arch Med Wewn, 2014. 124 (3)(3): p. 97-104., https://pubmed.ncbi.nlm.nih.gov/24473342/

52. Al Nofal, A, Gionfriddo, MR, Javed, A, Haydour, Q, Brito, JP, Prokop, LJ, et.al. Accuracy of thyroid nodule sonography for the detection of thyroid cancer in children: systematic review and meta-analysis., Clin Endocrinol (Oxf), 2016. 84 (3)(3): p. 423-30., https://pubmed.ncbi.nlm.nih.gov/25845503/

53. Wei, X, Li, Y, Zhang, S, Gao, M, Meta-analysis of thyroid imaging reporting and data system in the ultrasonographic diagnosis of 10,437 thyroid nodules., Head Neck, 2016. 38 (2)(2): p. 309-15., https://pubmed.ncbi.nlm.nih.gov/25244250/

54. Wei, X, Li, Y, Zhang, S, Gao, M, Thyroid imaging reporting and data system (TI-RADS) in the diagnostic value of thyroid nodules: a systematic review., Tumour Biol, 2014. 35 (7)(7): p. 6769-76., https://pubmed.ncbi.nlm.nih.gov/24722822/

55. Migda, B, Migda, M, Migda, MS, A systematic review and meta-analysis of the Kwak TIRADS for the diagnostic assessment of indeterminate thyroid nodules., Clin Radiol, 2019. 74 (2)(2): p. 123-130., https://pubmed.ncbi.nlm.nih.gov/30482561/

56. Kwak, JY, Han, KH, Yoon, JH, Moon, HJ, Son, EJ, Park, SH, et.al. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk., Radiology, 2011. 260 (3)(3): p. 892-9., https://pubmed.ncbi.nlm.nih.gov/21771959/

57. Horvath, E, Silva, CF, Majlis, S, Rodriguez, I, Skoknic, V, Castro, A, et.al. Prospective validation of the ultrasound based TIRADS (Thyroid Imaging Reporting And Data System) classification: results in surgically resected thyroid nodules., Eur Radiol, 2017. 27 (6)(6): p. 2619-2628., https://pubmed.ncbi.nlm.nih.gov/27718080/

58. Tessler, FN, Middleton, WD, Grant, EG, Hoang, JK, Berland, LL, Teefey, SA, et.al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee., J Am Coll Radiol, 2017. 14 (5)(5): p. 587-595., https://pubmed.ncbi.nlm.nih.gov/28372962/

59. Russ, G, Bonnema, SJ, Erdogan, MF, Durante, C, Ngu, R, Leenhardt, L, European Thyroid Association Guidelines for Ultrasound Malignancy Risk Stratification of Thyroid Nodules in Adults: The EU-TIRADS., Eur Thyroid J, 2017. 6 (5)(5): p. 225-237., https://pubmed.ncbi.nlm.nih.gov/29167761/

60. Perros, P, Boelaert, K, Colley, S, Evans, C, Evans, RM, Gerrard Ba, G, et.al. Guidelines for the management of thyroid cancer., Clin Endocrinol (Oxf), 2014. 81 Suppl 1 (): p. 1-122., https://pubmed.ncbi.nlm.nih.gov/24989897/

61. Shin, JH, Baek, JH, Chung, J, Ha, EJ, Kim, JH, Lee, YH, et.al. Ultrasonography Diagnosis and Imaging-Based Management of Thyroid Nodules: Revised Korean Society of Thyroid Radiology Consensus Statement and Recommendations., Korean J Radiol, 2016. 17 (3)(3): p. 370-95., https://pubmed.ncbi.nlm.nih.gov/27134526/

62. Wu, XL, Du, JR, Wang, H, Jin, CX, Sui, GQ, Yang, DY, et.al. Comparison and preliminary discussion of the reasons for the differences in diagnostic performance and unnecessary FNA biopsies between the ACR TIRADS and 2015 ATA guidelines., Endocrine, 2019. 65 (1)(1): p. 121-131., https://pubmed.ncbi.nlm.nih.gov/30830584/

63. Middleton, WD, Teefey, SA, Reading, CC, Langer, JE, Beland, MD, Szabunio, MM, et.al. Comparison of Performance Characteristics of American College of Radiology TI-RADS, Korean Society of Thyroid Radiology TIRADS, and American Thyroid Association Guidelines., AJR Am J Roentgenol, 2018. 210 (5)(5): p. 1148-1154., https://pubmed.ncbi.nlm.nih.gov/29629797/

64. Xu, T, Wu, Y, Wu, RX, Zhang, YZ, Gu, JY, Ye, XH, et.al. Validation and comparison of three newly-released Thyroid Imaging Reporting and Data Systems for cancer risk determination., Endocrine, 2019. 64 (2)(2): p. 299-307., https://pubmed.ncbi.nlm.nih.gov/30474824/

65. Ha, EJ, Na, DG, Moon, WJ, Lee, YH, Choi, N, Diagnostic Performance of Ultrasound-Based Risk-Stratification Systems for Thyroid Nodules: Comparison of the 2015 American Thyroid Association Guidelines with the 2016 Korean Thyroid Association/Korean Society of Thyroid Radiology and 2017 American College of Radiology Guidelines., Thyroid, 2018. 28 (11)(11): p. 1532-1537., https://pubmed.ncbi.nlm.nih.gov/30311862/

66. Seifert, P, Schenke, S, Zimny, M, Stahl, A, Grunert, M, Klemenz, B, et.al. Diagnostic Performance of Kwak, EU, ACR, and Korean TIRADS as Well as ATA Guidelines for the Ultrasound Risk Stratification of Non-Autonomously Functioning Thyroid Nodules in a Region with Long History of Iodine Deficiency: A German Multicenter Trial., Cancers (Basel), 2021. 13 (17)(17):, https://pubmed.ncbi.nlm.nih.gov/34503277/

67. Yoon, JH, Lee, HS, Kim, EK, Moon, HJ, Kwak, JY, Malignancy Risk Stratification of Thyroid Nodules: Comparison between the Thyroid Imaging Reporting and Data System and the 2014 American Thyroid Association Management Guidelines., Radiology, 2016. 278 (3)(3): p. 917-24., https://pubmed.ncbi.nlm.nih.gov/26348102/

68. Tessler, FN, Middleton, WD, Grant, EG, Thyroid Imaging Reporting and Data System (TI-RADS): A User's Guide., Radiology, 2018. 287 (1)(1): p. 29-36., https://pubmed.ncbi.nlm.nih.gov/29558300/

69. Nattabi, HA, Sharif, NM, Yahya, N, Ahmad, R, Mohamad, M, Zaki, FM, et.al. Is Diagnostic Performance of Quantitative 2D-Shear Wave Elastography Optimal for Clinical Classification of Benign and Malignant Thyroid Nodules?: A Systematic Review and Meta-analysis., Acad Radiol, 2022. 29 Suppl 3 (): p. S114-S121., https://pubmed.ncbi.nlm.nih.gov/29054676/

70. Nell, S, Kist, JW, Debray, TP, de Keizer, B, van Oostenbrugge, TJ, Borel Rinkes, IH, et.al. Qualitative elastography can replace thyroid nodule fine-needle aspiration in patients with soft thyroid nodules. A systematic review and meta-analysis., Eur J Radiol, 2015. 84 (4)(4): p. 652-61., https://pubmed.ncbi.nlm.nih.gov/25638577/

71. Zhao, CK, Xu, HX, Ultrasound elastography of the thyroid: principles and current status., Ultrasonography, 2019. 38 (2)(2): p. 106-124., https://pubmed.ncbi.nlm.nih.gov/30690960/

72. Bamber, J, Cosgrove, D, Dietrich, CF, Fromageau, J, Bojunga, J, Calliada, F, et.al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology., Ultraschall Med, 2013. 34 (2)(2): p. 169-84., https://pubmed.ncbi.nlm.nih.gov/23558397/

73. Chammas, MC, Moon, HJ, Kim, EK, Why do we have so many controversies in thyroid nodule Doppler US?, Radiology, 2011. 259 (1)(1): p. 304., https://pubmed.ncbi.nlm.nih.gov/21436101/

74. Razavi, SA, Hadduck, TA, Sadigh, G, Dwamena, BA, Comparative effectiveness of elastographic and B-mode ultrasound criteria for diagnostic discrimination of thyroid nodules: a meta-analysis., AJR Am J Roentgenol, 2013. 200 (6)(6): p. 1317-26., https://pubmed.ncbi.nlm.nih.gov/23701071/

75. Moon, HJ, Kwak, JY, Kim, MJ, Son, EJ, Kim, EK, Can vascularity at power Doppler US help predict thyroid malignancy?, Radiology, 2010. 255 (1)(1): p. 260-9., https://pubmed.ncbi.nlm.nih.gov/20308462/

76. Mohebbi, M, Dehaki, MG, Mozaffari, M, Comparison between ultrasonographic findings and fine needle aspiration cytology in differentiating malignant and benign thyroid nodules., Eur J Transl Myol, 2019. 29 (3)(3): p. 8354., https://pubmed.ncbi.nlm.nih.gov/31579481/

77. Debnam, JM, Vu, T, Sun, J, Wei, W, Krishnamurthy, S, Zafereo, ME, et.al. Vascular flow on doppler sonography may not be a valid characteristic to distinguish colloid nodules from papillary thyroid carcinoma even when accounting for nodular size., Gland Surg, 2019. 8 (5)(5): p. 461-468., https://pubmed.ncbi.nlm.nih.gov/31741876/

78. Lacout, A, Chevenet, C, Salas, J, Marcy, PY, Thyroid Doppler US: Tips and tricks., J Med Imaging Radiat Oncol, 2016. 60 (2)(2): p. 210-5., https://pubmed.ncbi.nlm.nih.gov/26663777/

79. Yang, GCH, Fried, KO, Most Thyroid Cancers Detected by Sonography Lack Intranodular Vascularity on Color Doppler Imaging: Review of the Literature and Sonographic-Pathologic Correlations for 698 Thyroid Neoplasms., J Ultrasound Med, 2017. 36 (1)(1): p. 89-94., https://pubmed.ncbi.nlm.nih.gov/27943373/

80. Chammas, MC, Gerhard, R, de Oliveira, IR, Widman, A, de Barros, N, Durazzo, M, et.al. Thyroid nodules: evaluation with power Doppler and duplex Doppler ultrasound., Otolaryngol Head Neck Surg, 2005. 132 (6)(6): p. 874-82., https://pubmed.ncbi.nlm.nih.gov/15944558/

81. Liu, Q, Cheng, J, Li, J, Gao, X, Li, H, The diagnostic accuracy of contrast-enhanced ultrasound for the differentiation of benign and malignant thyroid nodules: A PRISMA compliant meta-analysis., Medicine (Baltimore), 2018. 97 (49)(49): p. e13325., https://pubmed.ncbi.nlm.nih.gov/30544392/

82. Ma, X, Zhang, B, Ling, W, Liu, R, Jia, H, Zhu, F, et.al. Contrast-enhanced sonography for the identification of benign and malignant thyroid nodules: Systematic review and meta-analysis., J Clin Ultrasound, 2016. 44 (4)(4): p. 199-209., https://pubmed.ncbi.nlm.nih.gov/26402325/

83. Ahuja, AT, Ying, M, Sonographic evaluation of cervical lymph nodes., AJR Am J Roentgenol, 2005. 184 (5)(5): p. 1691-9., https://pubmed.ncbi.nlm.nih.gov/15855141/

84. Leboulleux, S, Girard, E, Rose, M, Travagli, JP, Sabbah, N, Caillou, B, et.al. Ultrasound criteria of malignancy for cervical lymph nodes in patients followed up for differentiated thyroid cancer., J Clin Endocrinol Metab, 2007. 92 (9)(9): p. 3590-4., https://pubmed.ncbi.nlm.nih.gov/17609301/

85. Khokhar, MT, Day, KM, Sangal, RB, Ahmedli, NN, Pisharodi, LR, Beland, MD, et.al. Preoperative High-Resolution Ultrasound for the Assessment of Malignant Central Compartment Lymph Nodes in Papillary Thyroid Cancer., Thyroid, 2015. 25 (12)(12): p. 1351-4., https://pubmed.ncbi.nlm.nih.gov/26431908/

86. U S, V, Shivalli, S, Rai, S, Haris, A, Madhurkar, R, Hemraj, S, Diagnostic accuracy of high resolution ultrasound to differentiate neoplastic and non neoplastic causes of cervical lymphadenopathy., J Clin Diagn Res, 2014. 8 (9)(9): p. RC05-7., https://pubmed.ncbi.nlm.nih.gov/25386501/

87. Sohn, YM, Kwak, JY, Kim, EK, Moon, HJ, Kim, SJ, Kim, MJ, Diagnostic approach for evaluation of lymph node metastasis from thyroid cancer using ultrasound and fine-needle aspiration biopsy., AJR Am J Roentgenol, 2010. 194 (1)(1): p. 38-43., https://pubmed.ncbi.nlm.nih.gov/20028903/

88. do Rosário, PW, Fagundes, TA, Maia, FF, Franco, AC, Figueiredo, MB, Purisch, S, Sonography in the diagnosis of cervical recurrence in patients with differentiated thyroid carcinoma., J Ultrasound Med, 2004. 23 (7)(7): p. 915-20; quiz 921-2., https://pubmed.ncbi.nlm.nih.gov/15292559/

89. Steinkamp, HJ, Cornehl, M, Hosten, N, Pegios, W, Vogl, T, Felix, R, Cervical lymphadenopathy: ratio of long- to short-axis diameter as a predictor of malignancy., Br J Radiol, 1995. 68 (807)(807): p. 266-70., https://pubmed.ncbi.nlm.nih.gov/7735765/

90. Hwang, HS, Orloff, LA, Efficacy of preoperative neck ultrasound in the detection of cervical lymph node metastasis from thyroid cancer., Laryngoscope, 2011. 121 (3)(3): p. 487-91., https://pubmed.ncbi.nlm.nih.gov/21344423/

91. O'Connell, K, Yen, TW, Quiroz, F, Evans, DB, Wang, TS, The utility of routine preoperative cervical ultrasonography in patients undergoing thyroidectomy for differentiated thyroid cancer., Surgery, 2013. 154 (4)(4): p. 697-701; discussion 701-3., https://pubmed.ncbi.nlm.nih.gov/24011674/

92. Yeh, MW, Bauer, AJ, Bernet, VA, Ferris, RL, Loevner, LA, Mandel, SJ, et.al. American Thyroid Association statement on preoperative imaging for thyroid cancer surgery., Thyroid, 2015. 25 (1)(1): p. 3-14., https://pubmed.ncbi.nlm.nih.gov/25188202/

93. Kim, E, Park, JS, Son, KR, Kim, JH, Jeon, SJ, Na, DG, Preoperative diagnosis of cervical metastatic lymph nodes in papillary thyroid carcinoma: comparison of ultrasound, computed tomography, and combined ultrasound with computed tomography., Thyroid, 2008. 18 (4)(4): p. 411-8., https://pubmed.ncbi.nlm.nih.gov/18358074/

94. Kuna, SK, Bracic, I, Tesic, V, Kuna, K, Herceg, GH, Dodig, D, Ultrasonographic differentiation of benign from malignant neck lymphadenopathy in thyroid cancer., J Ultrasound Med, 2006. 25 (12)(12): p. 1531-7; quiz 1538-40., https://pubmed.ncbi.nlm.nih.gov/17121947/

95. Tomoda, C, Sugino, K, Matsuzu, K, Uruno, T, Ohkuwa, K, Kitagawa, W, et.al. Cervical Lymph Node Metastases After Thyroidectomy for Papillary Thyroid Carcinoma Usually Remain Stable for Years., Thyroid, 2016. 26 (12)(12): p. 1706-1711., https://pubmed.ncbi.nlm.nih.gov/27616725/

96. Kupferman, ME, Patterson, M, Mandel, SJ, LiVolsi, V, Weber, RS, Patterns of lateral neck metastasis in papillary thyroid carcinoma., Arch Otolaryngol Head Neck Surg, 2004. 130 (7)(7): p. 857-60., https://pubmed.ncbi.nlm.nih.gov/15262763/

97. Onoda, N, Ishikawa, T, Kawajiri, H, Takashima, T, Hirakawa, K, Pattern of initial metastasis in the cervical lymph node from papillary thyroid carcinoma., Surg Today, 2013. 43 (2)(2): p. 178-84., https://pubmed.ncbi.nlm.nih.gov/22732927/

98. Zhao, H, Li, H, Meta-analysis of ultrasound for cervical lymph nodes in papillary thyroid cancer: Diagnosis of central and lateral compartment nodal metastases., Eur J Radiol, 2019. 112 (): p. 14-21., https://pubmed.ncbi.nlm.nih.gov/30777203/

99. Wu, LM, Gu, HY, Qu, XH, Zheng, J, Zhang, W, Yin, Y, et.al. The accuracy of ultrasonography in the preoperative diagnosis of cervical lymph node metastasis in patients with papillary thyroid carcinoma: A meta-analysis., Eur J Radiol, 2012. 81 (8)(8): p. 1798-805., https://pubmed.ncbi.nlm.nih.gov/21536396/

100. Xing, Z, Qiu, Y, Yang, Q, Yu, Y, Liu, J, Fei, Y, et.al. Thyroid cancer neck lymph nodes metastasis: Meta-analysis of US and CT diagnosis., Eur J Radiol, 2020. 129 (): p. 109103., https://pubmed.ncbi.nlm.nih.gov/32574937/

101. Moreno, MA, Edeiken-Monroe, BS, Siegel, ER, Sherman, SI, Clayman, GL, In papillary thyroid cancer, preoperative central neck ultrasound detects only macroscopic surgical disease, but negative findings predict excellent long-term regional control and survival., Thyroid, 2012. 22 (4)(4): p. 347-55., https://pubmed.ncbi.nlm.nih.gov/22280230/

102. Desmots, F, Fakhry, N, Mancini, J, Reyre, A, Vidal, V, Jacquier, A, et.al. Shear Wave Elastography in Head and Neck Lymph Node Assessment: Image Quality and Diagnostic Impact Compared with B-Mode and Doppler Ultrasonography., Ultrasound Med Biol, 2016. 42 (2)(2): p. 387-98., https://pubmed.ncbi.nlm.nih.gov/26617244/

103. Xu, JM, Xu, XH, Xu, HX, Zhang, YF, Guo, LH, Liu, LN, et.al. Prediction of cervical lymph node metastasis in patients with papillary thyroid cancer using combined conventional ultrasound, strain elastography, and acoustic radiation force impulse (ARFI) elastography., Eur Radiol, 2016. 26 (8)(8): p. 2611-22., https://pubmed.ncbi.nlm.nih.gov/26560715/

104. Azizi, G, Keller, JM, Mayo, ML, Piper, K, Puett, D, Earp, KM, et.al. Shear Wave Elastography and Cervical Lymph Nodes: Predicting Malignancy., Ultrasound Med Biol, 2016. 42 (6)(6): p. 1273-81., https://pubmed.ncbi.nlm.nih.gov/26976785/

105. Leenhardt, L, Erdogan, MF, Hegedus, L, Mandel, SJ, Paschke, R, Rago, T, et.al. 2013 European thyroid association guidelines for cervical ultrasound scan and ultrasound-guided techniques in the postoperative management of patients with thyroid cancer., Eur Thyroid J, 2013. 2 (3)(3): p. 147-59., https://pubmed.ncbi.nlm.nih.gov/24847448/

106. Görges, R, Eising, EG, Fotescu, D, Renzing-Köhler, K, Frilling, A, Schmid, KW, et.al. Diagnostic value of high-resolution B-mode and power-mode sonography in the follow-up of thyroid cancer., Eur J Ultrasound, 2003. 16 (3)(3): p. 191-206., https://pubmed.ncbi.nlm.nih.gov/12573788/

107. Schenke, S, Seifert, P, Zimny, M, Winkens, T, Binse, I, Görges, R, Risk Stratification of Thyroid Nodules Using the Thyroid Imaging Reporting and Data System (TIRADS): The Omission of Thyroid Scintigraphy Increases the Rate of Falsely Suspected Lesions., J Nucl Med, 2019. 60 (3)(3): p. 342-347., https://pubmed.ncbi.nlm.nih.gov/30097501/

108. Ruhlmann, M, Stebner, V, Görges, R, Farahati, J, Simon, D, Bockisch, A, et.al. Diagnosis of hyperfunctional thyroid nodules: impact of US-elastography., Nuklearmedizin, 2014. 53 (5)(5): p. 173-7., https://pubmed.ncbi.nlm.nih.gov/24898434/

109. Trimboli, P, Paone, G, Zatelli, MC, Ceriani, L, Giovanella, L, Real-time elastography in autonomously functioning thyroid nodules: relationship with TSH levels, scintigraphy, and ultrasound patterns., Endocrine, 2017. 58 (3)(3): p. 488-494., https://pubmed.ncbi.nlm.nih.gov/28285385/

110. Görges, R, Kandror, T, Kuschnerus, S, Zimny, M, Pink, R, Palmedo, H, et.al. [Scintigraphically "hot" thyroid nodules mainly go hand in hand with a normal TSH]., Nuklearmedizin, 2011. 50 (5)(5): p. 179-88., https://pubmed.ncbi.nlm.nih.gov/21789340/

111. Graf, D, Helmich-Kapp, B, Graf, S, Veit, F, Lehmann, N, Mann, K, [Functional activity of autonomous adenoma in Germany]., Dtsch Med Wochenschr, 2012. 137 (41)(41): p. 2089-92., https://pubmed.ncbi.nlm.nih.gov/23033166/

112. COLE, WH, MAJARAKIS, JD, SLAUGHTER, DP, Incidence of carcinoma of the thyroid in nodular goiter., J Clin Endocrinol Metab, 1949. 9 (10)(10): p. 1007-11., https://pubmed.ncbi.nlm.nih.gov/18142433/

113. DOBYNS, BM, SKANSE, B, MALOOF, F, A method for the preoperative estimation of function in thyroid tumors; its significance in diagnosis and treatment., J Clin Endocrinol Metab, 1949. 9 (11)(11): p. 1171-84, illust., https://pubmed.ncbi.nlm.nih.gov/15395981/

114. Schröder, S, Marthaler, B, [Autonomy and malignancy of thyroid glad tumors. A critical analysis of the literature on the existence of hyperfunctioning follicular and papillary thyroid gland carcinomas]., Pathologe, 1996. 17 (5)(5): p. 349-57., https://pubmed.ncbi.nlm.nih.gov/8992477/

115. Schicha, H, Hellmich, M, Lehmacher, W, Eschner, W, Schmidt, M, Kobe, C, et.al. [Should all patients with thyroid nodules > or = 1 cm undergo fine-needle aspiration biopsy?]., Nuklearmedizin, 2009. 48 (3)(3): p. 79-83., https://pubmed.ncbi.nlm.nih.gov/19325991/

116. Belfiore, A, La Rosa, GL, Padova, G, Sava, L, Ippolito, O, Vigneri, R, The frequency of cold thyroid nodules and thyroid malignancies in patients from an iodine-deficient area., Cancer, 1987. 60 (12)(12): p. 3096-102., https://pubmed.ncbi.nlm.nih.gov/3677033/

117. Christensen, SB, Bondeson, L, Ericsson, UB, Lindholm, K, Prediction of malignancy in the solitary thyroid nodule by physical examination, thyroid scan, fine-needle biopsy and serum thyroglobulin. A prospective study of 100 surgically treated patients., Acta Chir Scand, 1984. 150 (6)(6): p. 433-9., https://pubmed.ncbi.nlm.nih.gov/6495973/

118. Ross, DS, Burch, HB, Cooper, DS, Greenlee, MC, Laurberg, P, Maia, AL, et.al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis., Thyroid, 2016. 26 (10)(10): p. 1343-1421., https://pubmed.ncbi.nlm.nih.gov/27521067/

119. Biondi, B, Bartalena, L, Cooper, DS, Hegedüs, L, Laurberg, P, Kahaly, GJ, The 2015 European Thyroid Association Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism., Eur Thyroid J, 2015. 4 (3)(3): p. 149-63., https://pubmed.ncbi.nlm.nih.gov/26558232/

120. Kim, HK, Yoon, JH, Kim, SJ, Cho, JS, Kweon, SS, Kang, HC, Higher TSH level is a risk factor for differentiated thyroid cancer., Clin Endocrinol (Oxf), 2013. 78 (3)(3): p. 472-7., https://pubmed.ncbi.nlm.nih.gov/22924613/

121. Fighera, TM, Perez, CL, Faris, N, Scarabotto, PC, da Silva, TT, Cavalcanti, TC, et.al. TSH levels are associated with increased risk of thyroid carcinoma in patients with nodular disease., Endokrynol Pol, 2015. 66 (6)(6): p. 480-5., https://pubmed.ncbi.nlm.nih.gov/26662646/

122. Batool, S, Afridi, MS, Khoja, A, Islam, N, Pre-operative serum TSH levels: A risk factor for advanced metastatic differentiated thyroid carcinoma., Pak J Med Sci, 2019. 35 (5)(5): p. 1312-1317., https://pubmed.ncbi.nlm.nih.gov/31488998/

123. Boelaert, K, Horacek, J, Holder, RL, Watkinson, JC, Sheppard, MC, Franklyn, JA, Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration., J Clin Endocrinol Metab, 2006. 91 (11)(11): p. 4295-301., https://pubmed.ncbi.nlm.nih.gov/16868053/

124. Khan, MA, Malik, N, Khan, KH, Shahzad, MF, Association of Preoperative Serum Thyroid-stimulating Hormone Levels with Thyroid Cancer in Patients with Nodular Thyroid Disease., World J Nucl Med, 2017. 16 (3)(3): p. 202-205., https://pubmed.ncbi.nlm.nih.gov/28670178/

125. Zafón, C, Obiols, G, Mesa, J, Preoperative TSH level and risk of thyroid cancer in patients with nodular thyroid disease: nodule size contribution., Endocrinol Nutr, 2015. 62 (1)(1): p. 24-8., https://pubmed.ncbi.nlm.nih.gov/25066642/

126. Huang, H, Rusiecki, J, Zhao, N, Chen, Y, Ma, S, Yu, H, et.al. Thyroid-Stimulating Hormone, Thyroid Hormones, and Risk of Papillary Thyroid Cancer: A Nested Case-Control Study., Cancer Epidemiol Biomarkers Prev, 2017. 26 (8)(8): p. 1209-1218., https://pubmed.ncbi.nlm.nih.gov/28377419/

127. Zhu, C, Li, S, Gao, X, Zhu, G, Song, M, Gao, F, Retrospective Analysis of Thyroid Nodules: Thyroid Cancer Risk Factors in Suzhou, China., Clin Lab, 2018. 64 (3)(3): p. 333-338., https://pubmed.ncbi.nlm.nih.gov/29739119/

128. Zhao, H, Li, H, Huang, T, High Urinary Iodine, Thyroid Autoantibodies, and Thyroid-Stimulating Hormone for Papillary Thyroid Cancer Risk., Biol Trace Elem Res, 2018. 184 (2)(2): p. 317-324., https://pubmed.ncbi.nlm.nih.gov/29164514/

129. Haymart, MR, Repplinger, DJ, Leverson, GE, Elson, DF, Sippel, RS, Jaume, JC, et.al. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage., J Clin Endocrinol Metab, 2008. 93 (3)(3): p. 809-14., https://pubmed.ncbi.nlm.nih.gov/18160464/

130. Haymart, MR, Glinberg, SL, Liu, J, Sippel, RS, Jaume, JC, Chen, H, Higher serum TSH in thyroid cancer patients occurs independent of age and correlates with extrathyroidal extension., Clin Endocrinol (Oxf), 2009. 71 (3)(3): p. 434-9., https://pubmed.ncbi.nlm.nih.gov/19067720/

131. Kim, SS, Lee, BJ, Lee, JC, Song, SH, Kim, BH, Son, SM, et.al. Preoperative serum thyroid stimulating hormone levels in well-differentiated thyroid carcinoma is a predictive factor for lateral lymph node metastasis as well as extrathyroidal extension in Korean patients: a single-center experience., Endocrine, 2011. 39 (3)(3): p. 259-65., https://pubmed.ncbi.nlm.nih.gov/21161440/

132. Adhami, M, Michail, P, Rao, A, Bhatt, CR, Grodski, S, Serpell, JW, et.al. Anti-Thyroid Antibodies and TSH as Potential Markers of Thyroid Carcinoma and Aggressive Behavior in Patients with Indeterminate Fine-Needle Aspiration Cytology., World J Surg, 2020. 44 (2)(2): p. 363-370., https://pubmed.ncbi.nlm.nih.gov/31502005/

133. Cappelli, C, Pirola, I, Gandossi, E, Rotondi, M, Lombardi, D, Casella, C, et.al. Could Serum TSH Levels Predict Malignancy in Euthyroid Patients Affected by Thyroid Nodules with Indeterminate Cytology?, Int J Endocrinol, 2020. 2020 (): p. 7543930., https://pubmed.ncbi.nlm.nih.gov/32377187/

134. Fernández-Trujillo, C, Pérez-Zaballos, J, Rodríguez-Pérez, CA, López-Plasencia, Y, Marrero-Arencibia, D, Cabrera-Galván, JJ, et.al. TSH Level and Risk of Malignancy in Patients with Bethesda Category IV Thyroid Nodules., Horm Cancer, 2020. 11 (3-4)(3-4): p. 200-204., https://pubmed.ncbi.nlm.nih.gov/32266672/

135. Ahn, D, Sohn, JH, Kim, JH, Shin, CM, Jeon, JH, Park, JY, Preoperative subclinical hypothyroidism in patients with papillary thyroid carcinoma., Am J Otolaryngol, 2013. 34 (4)(4): p. 312-9., https://pubmed.ncbi.nlm.nih.gov/23357595/

136. Fiore, E, Rago, T, Provenzale, MA, Scutari, M, Ugolini, C, Basolo, F, et.al. Lower levels of TSH are associated with a lower risk of papillary thyroid cancer in patients with thyroid nodular disease: thyroid autonomy may play a protective role., Endocr Relat Cancer, 2009. 16 (4)(4): p. 1251-60., https://pubmed.ncbi.nlm.nih.gov/19528244/

137. Paparodis, RD, Bantouna, D, Karvounis, E, Imam, S, Jaume, JC, Higher TSH Is Not Associated With Thyroid Cancer Risk in the Presence of Thyroid Autoimmunity., J Clin Endocrinol Metab, 2020. 105 (7)(7):, https://pubmed.ncbi.nlm.nih.gov/32391913/

138. Schiffmann, L, Kostev, K, Kalder, M, Association between various thyroid gland diseases, TSH values and thyroid cancer: a case-control study., J Cancer Res Clin Oncol, 2020. 146 (11)(11): p. 2989-2994., https://pubmed.ncbi.nlm.nih.gov/32518973/

139. Su, A, Zhao, W, Wu, W, Wei, T, Ruan, M, Li, Z, et.al. The association of preoperative thyroid-stimulating hormone level and the risk of differentiated thyroid cancer in patients with thyroid nodules: A systematic review and meta-analysis., Am J Surg, 2020. 220 (3)(3): p. 634-641., https://pubmed.ncbi.nlm.nih.gov/31955813/

140. Eilsberger, F, Pfestroff, A, Librizzi, D, Luster, M, [Follow-up of differentiated thyroid cancer]., Dtsch Med Wochenschr, 2020. 145 (17)(17): p. 1236-1244., https://pubmed.ncbi.nlm.nih.gov/32634842/

141. Suh, I, Vriens, MR, Guerrero, MA, Griffin, A, Shen, WT, Duh, QY, et.al. Serum thyroglobulin is a poor diagnostic biomarker of malignancy in follicular and Hurthle-cell neoplasms of the thyroid., Am J Surg, 2010. 200 (1)(1): p. 41-6., https://pubmed.ncbi.nlm.nih.gov/20637335/

142. Trimboli, P, Treglia, G, Giovanella, L, Preoperative measurement of serum thyroglobulin to predict malignancy in thyroid nodules: a systematic review., Horm Metab Res, 2015. 47 (4)(4): p. 247-52., https://pubmed.ncbi.nlm.nih.gov/25384015/

143. Hulikal, N, Re, A, Banoth, M, Chowhan, AK, Yutla, M, Sachan, A, Can preoperative serum thyroglobulin levels predict the risk of malignancy? Results from prospective analysis of biochemical predictors of malignancy in thyroid nodules., Acta Otorhinolaryngol Ital, 2020. 40 (1)(1): p. 33-37., https://pubmed.ncbi.nlm.nih.gov/32275647/

144. Lee, EK, Chung, KW, Min, HS, Kim, TS, Kim, TH, Ryu, JS, et.al. Preoperative serum thyroglobulin as a useful predictive marker to differentiate follicular thyroid cancer from benign nodules in indeterminate nodules., J Korean Med Sci, 2012. 27 (9)(9): p. 1014-8., https://pubmed.ncbi.nlm.nih.gov/22969246/

145. Patel, A, Shostrom, V, Treude, K, Lydiatt, W, Smith, R, Goldner, W, Serum Thyroglobulin: Preoperative Levels and Factors Affecting Postoperative Optimal Timing following Total Thyroidectomy., Int J Endocrinol, 2019. 2019 (): p. 1384651., https://pubmed.ncbi.nlm.nih.gov/30915112/

146. Kang, M, Wang, TS, Yen, TW, Doffek, K, Evans, DB, Dream, S, The Clinical Utility of Preoperative Thyroglobulin for Surgical Decision Making in Thyroid Disease., J Surg Res, 2022. 270 (): p. 230-235., https://pubmed.ncbi.nlm.nih.gov/34710703/

147. Petric, R, Besic, H, Besic, N, Preoperative serum thyroglobulin concentration as a predictive factor of malignancy in small follicular and Hürthle cell neoplasms of the thyroid gland., World J Surg Oncol, 2014. 12 (): p. 282., https://pubmed.ncbi.nlm.nih.gov/25213012/

148. Ma, ZF, Skeaff, SA, Thyroglobulin as a biomarker of iodine deficiency: a review., Thyroid, 2014. 24 (8)(8): p. 1195-209., https://pubmed.ncbi.nlm.nih.gov/24762031/

149. Zimmermann, MB, Aeberli, I, Andersson, M, Assey, V, Yorg, JA, Jooste, P, et.al. Thyroglobulin is a sensitive measure of both deficient and excess iodine intakes in children and indicates no adverse effects on thyroid function in the UIC range of 100-299 µg/L: a UNICEF/ICCIDD study group report., J Clin Endocrinol Metab, 2013. 98 (3)(3): p. 1271-80., https://pubmed.ncbi.nlm.nih.gov/23345097/

150. Cheng, X, Xu, S, Zhu, Y, Wu, J, Bao, J, Yu, H, et.al. Markedly elevated serum preoperative thyroglobulin predicts radioiodine-refractory thyroid cancer., Eur J Clin Invest, 2022. 52 (4)(4): p. e13721., https://pubmed.ncbi.nlm.nih.gov/34855206/

151. Kim, H, Park, SY, Choe, JH, Kim, JS, Hahn, SY, Kim, SW, et.al. Preoperative Serum Thyroglobulin and Its Correlation with the Burden and Extent of Differentiated Thyroid Cancer., Cancers (Basel), 2020. 12 (3)(3):, https://pubmed.ncbi.nlm.nih.gov/32182688/

152. Wang, L, Li, H, Yang, Z, Guo, Z, Zhang, Q, Preoperative Serum Thyrotropin to Thyroglobulin Ratio Is Effective for Thyroid Nodule Evaluation in Euthyroid Patients., Otolaryngol Head Neck Surg, 2015. 153 (1)(1): p. 15-9., https://pubmed.ncbi.nlm.nih.gov/25883100/

153. Karvounis, E, Kappas, I, Angelousi, A, Makris, GM, Siamatras, TD, Kassi, E, The diagnostic and predictive accuracy of thyroglobulin to TSH ratio and TSH to thyroglobulin ratio in detecting differentiated thyroid carcinoma in normothyroid patients with thyroid nodules: A retrospective cohort study and systematic review of the literature., Oncol Rev, 2020. 14 (2)(2): p. 439., https://pubmed.ncbi.nlm.nih.gov/33505608/

154. Noel, JE, Thatipamala, P, Hung, KS, Chen, J, Shi, RZ, Orloff, LA, Pre-Operative Antithyroid Antibodies in Differentiated Thyroid Cancer., Endocr Pract, 2021. 27 (11)(11): p. 1114-1118., https://pubmed.ncbi.nlm.nih.gov/34217894/

155. Li, L, Shan, T, Sun, X, Lv, B, Chen, B, Liu, N, et.al. Positive Thyroid Peroxidase Antibody and Thyroglobulin Antibody are Associated With Better Clinicopathologic Features of Papillary Thyroid Cancer., Endocr Pract, 2021. 27 (4)(4): p. 306-311., https://pubmed.ncbi.nlm.nih.gov/33645517/

156. Jo, K, Kim, MH, Ha, J, Lim, Y, Lee, S, Bae, JS, et.al. Prognostic value of preoperative anti-thyroglobulin antibody in differentiated thyroid cancer., Clin Endocrinol (Oxf), 2017. 87 (3)(3): p. 292-299., https://pubmed.ncbi.nlm.nih.gov/28493284/

157. Kim, ES, Lim, DJ, Baek, KH, Lee, JM, Kim, MK, Kwon, HS, et.al. Thyroglobulin antibody is associated with increased cancer risk in thyroid nodules., Thyroid, 2010. 20 (8)(8): p. 885-91., https://pubmed.ncbi.nlm.nih.gov/20465529/

158. Vasileiadis, I, Boutzios, G, Charitoudis, G, Koukoulioti, E, Karatzas, T, Thyroglobulin antibodies could be a potential predictive marker for papillary thyroid carcinoma., Ann Surg Oncol, 2014. 21 (8)(8): p. 2725-32., https://pubmed.ncbi.nlm.nih.gov/24595799/

159. Hosseini, S, Payne, RJ, Zawawi, F, Mlynarek, A, Hier, MP, Tamilia, M, et.al. Can preoperative thyroglobulin antibody levels be used as a marker for well differentiated thyroid cancer?, J Otolaryngol Head Neck Surg, 2016. 45 (1)(1): p. 31., https://pubmed.ncbi.nlm.nih.gov/27179632/

160. Jia, X, Pang, P, Wang, L, Zhao, L, Jiang, L, Song, Y, et.al. Clinical Analysis of Preoperative Anti-thyroglobulin Antibody in Papillary Thyroid Cancer Between 2011 and 2015 in Beijing, China: A Retrospective Study., Front Endocrinol (Lausanne), 2020. 11 (): p. 452., https://pubmed.ncbi.nlm.nih.gov/32760349/

161. Grani, G, Calvanese, A, Carbotta, G, D'Alessandri, M, Nesca, A, Bianchini, M, et.al. Thyroid autoimmunity and risk of malignancy in thyroid nodules submitted to fine-needle aspiration cytology., Head Neck, 2015. 37 (2)(2): p. 260-4., https://pubmed.ncbi.nlm.nih.gov/24375752/

162. Wong, SL, Grodski, S, Yeung, MJ, Serpell, JW, Anti-thyroid antibodies as a predictor of thyroid cancer., ANZ J Surg, 2015. 85 (11)(11): p. 849-53., https://pubmed.ncbi.nlm.nih.gov/24299506/

163. Karatzas, T, Vasileiadis, I, Zapanti, E, Charitoudis, G, Karakostas, E, Boutzios, G, Thyroglobulin antibodies as a potential predictive marker of papillary thyroid carcinoma in patients with indeterminate cytology., Am J Surg, 2016. 212 (5)(5): p. 946-952., https://pubmed.ncbi.nlm.nih.gov/27324384/

164. Knappe, L, Giovanella, L, Life after thyroid cancer: the role of thyroglobulin and thyroglobulin antibodies for postoperative follow-up., Expert Rev Endocrinol Metab, 2021. 16 (6)(6): p. 273-279., https://pubmed.ncbi.nlm.nih.gov/34693849/

165. Lee, YK, Park, KH, Park, SH, Kim, KJ, Shin, DY, Nam, KH, et.al. Association between diffuse lymphocytic infiltration and papillary thyroid cancer aggressiveness according to the presence of thyroid peroxidase antibody and BRAF, Head Neck, 2018. 40 (10)(10): p. 2271-2279., https://pubmed.ncbi.nlm.nih.gov/29935011/

166. Wu, X, Lun, Y, Jiang, H, Gang, Q, Xin, S, Duan, Z, et.al. Coexistence of thyroglobulin antibodies and thyroid peroxidase antibodies correlates with elevated thyroid-stimulating hormone level and advanced tumor stage of papillary thyroid cancer., Endocrine, 2014. 46 (3)(3): p. 554-60., https://pubmed.ncbi.nlm.nih.gov/24338678/

167. Resende de Paiva, C, Grønhøj, C, Feldt-Rasmussen, U, von Buchwald, C, Association between Hashimoto's Thyroiditis and Thyroid Cancer in 64,628 Patients., Front Oncol, 2017. 7 (): p. 53., https://pubmed.ncbi.nlm.nih.gov/28443243/

168. Boi, F, Pani, F, Calò, PG, Lai, ML, Mariotti, S, High prevalence of papillary thyroid carcinoma in nodular Hashimoto's thyroiditis at the first diagnosis and during the follow-up., J Endocrinol Invest, 2018. 41 (4)(4): p. 395-402., https://pubmed.ncbi.nlm.nih.gov/28875268/

169. Song, E, Oh, HS, Jeon, MJ, Chung, KW, Hong, SJ, Ryu, JS, et.al. The value of preoperative antithyroidperoxidase antibody as a novel predictor of recurrence in papillary thyroid carcinoma., Int J Cancer, 2019. 144 (6)(6): p. 1414-1420., https://pubmed.ncbi.nlm.nih.gov/30357831/

170. Krátký, J, Ježková, J, Kosák, M, Vítková, H, Bartáková, J, Mráz, M, et.al. Positive Antithyroid Antibodies and Nonsuppressed TSH Are Associated with Thyroid Cancer: A Retrospective Cross-Sectional Study., Int J Endocrinol, 2018. 2018 (): p. 9793850., https://pubmed.ncbi.nlm.nih.gov/30258461/

171. Lai, X, Xia, Y, Zhang, B, Li, J, Jiang, Y, A meta-analysis of Hashimoto's thyroiditis and papillary thyroid carcinoma risk., Oncotarget, 2017. 8 (37)(37): p. 62414-62424., https://pubmed.ncbi.nlm.nih.gov/28977955/

172. Lloyd, Ricardo V., Osamura, Robert Y., Klöppel, Günter, Rosai, Juan, World Health Organization, International Agency for Research on Cancer, WHO classification of tumours of endocrine organsInternational Agency for Research on Cancer (IARC), World Health Organization classification of tumours, 2017.

173. Accurso, A, Rocco, N, Palumbo, A, Feleppa, C, Usefulness of ultrasound-guided fine-needle aspiration cytology in the diagnosis of non-palpable small thyroid nodules: our growing experience., J Endocrinol Invest, 2009. 32 (2)(2): p. 156-9., https://pubmed.ncbi.nlm.nih.gov/19411815/

174. Słowińska-Klencka, D, Popowicz, B, Lewiński, A, Sporny, S, Klencki, M, The fine-needle aspiration biopsy efficacy of small thyroid nodules in the area of recently normalized iodine supply., Eur J Endocrinol, 2008. 159 (6)(6): p. 747-54., https://pubmed.ncbi.nlm.nih.gov/18794209/

175. Scheuba, C, Kaserer, K, Kaczirek, K, Asari, R, Niederle, B, Desmoplastic stromal reaction in medullary thyroid cancer-an intraoperative "marker" for lymph node metastases., World J Surg, 2006. 30 (5)(5): p. 853-9., https://pubmed.ncbi.nlm.nih.gov/16680600/

176. Koperek, O, Scheuba, C, Cherenko, M, Neuhold, N, De Micco, C, Schmid, KW, et.al. Desmoplasia in medullary thyroid carcinoma: a reliable indicator of metastatic potential., Histopathology, 2008. 52 (5)(5): p. 623-30., https://pubmed.ncbi.nlm.nih.gov/18370959/

177. Machens, A, Dralle, H, Clinical relevance of desmoplasia in medullary thyroid carcinoma., Histopathology, 2008. 53 (4)(4): p. 481; author reply 482-3., https://pubmed.ncbi.nlm.nih.gov/18764881/

178. Niederle, MB, Riss, P, Selberherr, A, Koperek, O, Kaserer, K, Niederle, B, et.al. Omission of lateral lymph node dissection in medullary thyroid cancer without a desmoplastic stromal reaction., Br J Surg, 2021. 108 (2)(2): p. 174-181., https://pubmed.ncbi.nlm.nih.gov/33704404/

179. Machens, A, Kaatzsch, P, Lorenz, K, Horn, LC, Wickenhauser, C, Schmid, KW, et.al. Abandoning node dissection for desmoplasia-negative encapsulated unifocal sporadic medullary thyroid cancer., Surgery, 2022. 171 (2)(2): p. 360-367., https://pubmed.ncbi.nlm.nih.gov/34602296/

180. Wu, M, A comparative study of 200 head and neck FNAs performed by a cytopathologist with versus without ultrasound guidance: evidence for improved diagnostic value with ultrasound guidance., Diagn Cytopathol, 2011. 39 (10)(10): p. 743-51., https://pubmed.ncbi.nlm.nih.gov/20949470/

181. Conrad, R, Yang, SE, Chang, S, Bhasin, M, Sullivan, PS, Moatamed, NA, et.al. Comparison of Cytopathologist-Performed Ultrasound-Guided Fine-Needle Aspiration With Cytopathologist-Performed Palpation-Guided Fine-Needle Aspiration: A Single Institutional Experience., Arch Pathol Lab Med, 2018. 142 (10)(10): p. 1260-1267., https://pubmed.ncbi.nlm.nih.gov/29697276/

182. Taha, I, Al-Thani, H, El-Menyar, A, Asim, M, Al-Sulaiti, M, Tabeb, A, Diagnostic accuracy of preoperative palpation- versus ultrasound-guided thyroid fine needle aspiration cytology: an observational study., Postgrad Med, 2020. 132 (5)(5): p. 465-472., https://pubmed.ncbi.nlm.nih.gov/32163318/

183. Zhang, L, Liu, Y, Tan, X, Liu, X, Zhang, H, Qian, L, Comparison of Different-Gauge Needles for Fine-Needle Aspiration Biopsy of Thyroid Nodules., J Ultrasound Med, 2018. 37 (7)(7): p. 1713-1716., https://pubmed.ncbi.nlm.nih.gov/29288581/

184. İnci, MF, Özkan, F, Yüksel, M, Şalk, İ, Şahin, M, The effects of sonographic and demographic features and needle size on obtaining adequate cytological material in sonography-guided fine-needle aspiration biopsy of thyroid nodules., Endocrine, 2013. 43 (2)(2): p. 424-9., https://pubmed.ncbi.nlm.nih.gov/22956413/

185. Moss, WJ, Finegersh, A, Pang, J, Califano, JA, Coffey, CS, Orosco, RK, et.al. Needle Biopsy of Routine Thyroid Nodules Should Be Performed Using a Capillary Action Technique with 24- to 27-Gauge Needles: A Systematic Review and Meta-Analysis., Thyroid, 2018. 28 (7)(7): p. 857-863., https://pubmed.ncbi.nlm.nih.gov/29742978/

186. Tanaka, A, Hirokawa, M, Higuchi, M, Kanematsu, R, Suzuki, A, Kuma, S, et.al. Optimal needle size for thyroid fine needle aspiration cytology., Endocr J, 2019. 66 (2)(2): p. 143-147., https://pubmed.ncbi.nlm.nih.gov/30464152/

187. Pothier, DD, Narula, AA, Should we apply suction during fine needle cytology of thyroid lesions? A systematic review and meta-analysis., Ann R Coll Surg Engl, 2006. 88 (7)(7): p. 643-5., https://pubmed.ncbi.nlm.nih.gov/17132312/

188. Song, H, Wei, C, Li, D, Hua, K, Song, J, Maskey, N, et.al. Comparison of Fine Needle Aspiration and Fine Needle Nonaspiration Cytology of Thyroid Nodules: A Meta-Analysis., Biomed Res Int, 2015. 2015 (): p. 796120., https://pubmed.ncbi.nlm.nih.gov/26491689/

189. Wang, D, Fu, HJ, Xu, HX, Guo, LH, Li, XL, He, YP, et.al. Comparison of fine needle aspiration and non-aspiration cytology for diagnosis of thyroid nodules: A prospective, randomized, and controlled trial., Clin Hemorheol Microcirc, 2017. 66 (1)(1): p. 67-81., https://pubmed.ncbi.nlm.nih.gov/28128748/

190. Nagarajah, J, Sheu-Grabellus, SY, Farahati, J, Kamruddin, KA, Bockisch, A, Schmid, KW, et.al. Ultrasound-guided fine-needle aspiration biopsy of clinically suspicious thyroid nodules with an automatic aspirator: a novel technique., Thyroid, 2012. 22 (7)(7): p. 695-8., https://pubmed.ncbi.nlm.nih.gov/22524469/

191. Chong, Y, Ji, SJ, Kang, CS, Lee, EJ, Can liquid-based preparation substitute for conventional smear in thyroid fine-needle aspiration? A systematic review based on meta-analysis., Endocr Connect, 2017. 6 (8)(8): p. 817-829., https://pubmed.ncbi.nlm.nih.gov/29018157/

192. Nagarajan, N, Schneider, EB, Ali, SZ, Zeiger, MA, Olson, MT, How do liquid-based preparations of thyroid fine-needle aspiration compare with conventional smears? An analysis of 5475 specimens., Thyroid, 2015. 25 (3)(3): p. 308-13., https://pubmed.ncbi.nlm.nih.gov/25420135/

193. [Public health requirements in punctures and injections]., Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz, 2011. 54 (9)(9): p. 1135-44., https://pubmed.ncbi.nlm.nih.gov/21887628/

194. Lyle, MA, Dean, DS, Ultrasound-guided fine-needle aspiration biopsy of thyroid nodules in patients taking novel oral anticoagulants., Thyroid, 2015. 25 (4)(4): p. 373-6., https://pubmed.ncbi.nlm.nih.gov/25584817/

195. Khadra, H, Kholmatov, R, Monlezun, D, Kandil, E, Do anticoagulation medications increase the risk of haematoma in ultrasound-guided fine needle aspiration of thyroid lesions?, Cytopathology, 2018. 29 (6)(6): p. 565-568., https://pubmed.ncbi.nlm.nih.gov/29969159/

196. Kim, SY, Lee, HS, Moon, J, Kim, EK, Moon, HJ, Yoon, JH, et.al. Fine-needle aspiration versus core needle biopsy for diagnosis of thyroid malignancy and neoplasm: a matched cohort study., Eur Radiol, 2017. 27 (2)(2): p. 801-811., https://pubmed.ncbi.nlm.nih.gov/27260342/

197. Chen, JV, Morgan, TA, Liu, C, Khanafshar, E, Choi, HH, Cervical Lymph Node Features Predictive of Suboptimal Adequacy During Ultrasound-Guided Fine-Needle Aspiration in Thyroid Cancer Patients., J Ultrasound Med, 2022. 41 (1)(1): p. 135-145., https://pubmed.ncbi.nlm.nih.gov/33665844/

198. Suh, CH, Baek, JH, Lee, JH, Choi, YJ, Kim, KW, Lee, J, et.al. The role of core-needle biopsy in the diagnosis of thyroid malignancy in 4580 patients with 4746 thyroid nodules: a systematic review and meta-analysis., Endocrine, 2016. 54 (2)(2): p. 315-328., https://pubmed.ncbi.nlm.nih.gov/27220941/

199. Du, W, Fang, Q, Dai, L, Fan, J, Fine-needle aspiration biopsy versus frozen section examination in assessing cervical lymph node metastasis in primary clinically positive neck papillary thyroid carcinoma., Diagn Cytopathol, 2022. 50 (5)(5): p. 217-222., https://pubmed.ncbi.nlm.nih.gov/35103414/

200. Zhang, X, Zhang, X, Du, W, Dai, L, Luo, R, Fang, Q, et.al. Fine Needle Biopsy Versus Core Needle Biopsy Combined With/Without Thyroglobulin or BRAF 600E Mutation Assessment for Detecting Cervical Nodal Metastasis of Papillary Thyroid Carcinoma., Front Endocrinol (Lausanne), 2021. 12 (): p. 663720., https://pubmed.ncbi.nlm.nih.gov/33912138/

201. Landry, CS, Grubbs, EG, Busaidy, NL, Monroe, BJ, Staerkel, GA, Perrier, ND, et.al. Cystic lymph nodes in the lateral neck as indicators of metastatic papillary thyroid cancer., Endocr Pract, 2011. 17 (2)(2): p. 240-4., https://pubmed.ncbi.nlm.nih.gov/20713342/

202. Jiang, HJ, Hsiao, PJ, Clinical application of the ultrasound-guided fine needle aspiration for thyroglobulin measurement to diagnose lymph node metastasis from differentiated thyroid carcinoma-literature review., Kaohsiung J Med Sci, 2020. 36 (4)(4): p. 236-243., https://pubmed.ncbi.nlm.nih.gov/31909556/

203. Eun, NL, Son, EJ, Kim, JA, Gweon, HM, Kang, JH, Youk, JH, Comparison of the diagnostic performances of ultrasonography, CT and fine needle aspiration cytology for the prediction of lymph node metastasis in patients with lymph node dissection of papillary thyroid carcinoma: A retrospective cohort study., Int J Surg, 2018. 51 (): p. 145-150., https://pubmed.ncbi.nlm.nih.gov/29337176/

204. Kahramangil, B, Kose, E, Donmez, M, Aydin, H, El-Dabh, D, Krishnamurthy, V, et.al. Efficacy of surgeon-performed, ultrasound-guided lymph node fine needle aspiration in patients with thyroid

pathologic conditions., Surgery, 2018. 164 (4)(4): p. 657-664., https://pubmed.ncbi.nlm.nih.gov/30072253/

205. Ke, Z, Liu, Y, Zhang, Y, Li, J, Kuang, M, Peng, S, et.al. Diagnostic value and lymph node metastasis prediction of a custom-made panel (thyroline) in thyroid cancer., Oncol Rep, 2018. 40 (2)(2): p. 659-668., https://pubmed.ncbi.nlm.nih.gov/29901149/

206. Jun, HH, Kim, SM, Kim, BW, Lee, YS, Chang, HS, Park, CS, Overcoming the limitations of fine needle aspiration biopsy: detection of lateral neck node metastasis in papillary thyroid carcinoma., Yonsei Med J, 2015. 56 (1)(1): p. 182-8., https://pubmed.ncbi.nlm.nih.gov/25510763/

207. Zhu, XH, Zhou, JN, Qian, YY, Yang, K, Wen, QL, Zhang, QH, et.al. Diagnostic values of thyroglobulin in lymph node fine-needle aspiration washout: a systematic review and meta-analysis diagnostic values of FNA-Tg., Endocr J, 2020. 67 (2)(2): p. 113-123., https://pubmed.ncbi.nlm.nih.gov/31723088/

208. Snozek, CL, Chambers, EP, Reading, CC, Sebo, TJ, Sistrunk, JW, Singh, RJ, et.al. Serum thyroglobulin, high-resolution ultrasound, and lymph node thyroglobulin in diagnosis of differentiated thyroid carcinoma nodal metastases., J Clin Endocrinol Metab, 2007. 92 (11)(11): p. 4278-81., https://pubmed.ncbi.nlm.nih.gov/17684045/

209. Kim, DW, Jeon, SJ, Kim, CG, Usefulness of thyroglobulin measurement in needle washouts of fine-needle aspiration biopsy for the diagnosis of cervical lymph node metastases from papillary thyroid cancer before thyroidectomy., Endocrine, 2012. 42 (2)(2): p. 399-403., https://pubmed.ncbi.nlm.nih.gov/22350587/

210. Salmaslıoğlu, A, Erbil, Y, Cıtlak, G, Ersöz, F, Sarı, S, Olmez, A, et.al. Diagnostic value of thyroglobulin measurement in fine-needle aspiration biopsy for detecting metastatic lymph nodes in patients with papillary thyroid carcinoma., Langenbecks Arch Surg, 2011. 396 (1)(1): p. 77-81., https://pubmed.ncbi.nlm.nih.gov/21052711/

211. Uruno, T, Miyauchi, A, Shimizu, K, Tomoda, C, Takamura, Y, Ito, Y, et.al. Usefulness of thyroglobulin measurement in fine-needle aspiration biopsy specimens for diagnosing cervical lymph node metastasis in patients with papillary thyroid cancer., World J Surg, 2005. 29 (4)(4): p. 483-5., https://pubmed.ncbi.nlm.nih.gov/15776292/

212. Xu, Y, Wu, D, Wu, W, Jiang, J, Xi, C, Ye, N, et.al. Diagnostic value of cytology, thyroglobulin, and combination of them in fine-needle aspiration of metastatic lymph nodes in patients with differentiated thyroid cancer: A systematic review and network meta-analysis., Medicine (Baltimore), 2019. 98 (45)(45): p. e17859., https://pubmed.ncbi.nlm.nih.gov/31702649/

213. Yi, KS, Kim, JH, Na, DG, Seo, H, Min, HS, Won, JK, et.al. Usefulness of core needle biopsy for thyroid nodules with macrocalcifications: comparison with fine-needle aspiration., Thyroid, 2015. 25 (6)(6): p. 657-64., https://pubmed.ncbi.nlm.nih.gov/25851539/

214. Na, DG, Kim, DS, Kim, SJ, Ryoo, JW, Jung, SL, Thyroid nodules with isolated macrocalcification: malignancy risk and diagnostic efficacy of fine-needle aspiration and core needle biopsy., Ultrasonography, 2016. 35 (3)(3): p. 212-9., https://pubmed.ncbi.nlm.nih.gov/26810196/

215. Park, KW, Shin, JH, Hahn, SY, Oh, YL, Kim, SW, Kim, TH, et.al. Ultrasound-guided fine-needle aspiration or core needle biopsy for diagnosing follicular thyroid carcinoma?, Clin Endocrinol (Oxf), 2020. 92 (5)(5): p. 468-474., https://pubmed.ncbi.nlm.nih.gov/32012326/

216. Ha, EJ, Baek, JH, Lee, JH, Kim, JK, Song, DE, Kim, WB, et.al. Core needle biopsy could reduce diagnostic surgery in patients with anaplastic thyroid cancer or thyroid lymphoma., Eur Radiol, 2016. 26 (4)(4): p. 1031-6., https://pubmed.ncbi.nlm.nih.gov/26201291/

217. Kim, SJ, Lee, SW, Jeong, SY, Pak, K, Kim, K, Diagnostic Performance of Technetium-99m Methoxy-Isobutyl-Isonitrile for Differentiation of Malignant Thyroid Nodules: A Systematic Review and Meta-

Analysis., Thyroid, 2018. 28 (10)(10): p. 1339-1348., https://pubmed.ncbi.nlm.nih.gov/30129898/

218. Treglia, G, Caldarella, C, Saggiorato, E, Ceriani, L, Orlandi, F, Salvatori, M, et.al. Diagnostic performance of (99m)Tc-MIBI scan in predicting the malignancy of thyroid nodules: a meta-analysis., Endocrine, 2013. 44 (1)(1): p. 70-8., https://pubmed.ncbi.nlm.nih.gov/23529672/

219. Wale, A, Miles, KA, Young, B, Zammit, C, Williams, A, Quin, J, et.al. Combined (99m)Tc-methoxyisobutylisonitrile scintigraphy and fine-needle aspiration cytology offers an accurate and potentially cost-effective investigative strategy for the assessment of solitary or dominant thyroid nodules., Eur J Nucl Med Mol Imaging, 2014. 41 (1)(1): p. 105-15., https://pubmed.ncbi.nlm.nih.gov/24030667/

220. Schenke, SA, Klett, R, Wagner, PR, Mott, S, Zimny, M, Feek, U, et.al. Characteristics of different histological subtypes of thyroid nodules classified with 99mTc-methoxy-isobutyl-isonitrile imaging and Thyroid Imaging Reporting And Data System., Nucl Med Commun, 2021. 42 (1)(1): p. 73-80., https://pubmed.ncbi.nlm.nih.gov/33122502/

221. Chen, W, Parsons, M, Torigian, DA, Zhuang, H, Alavi, A, Evaluation of thyroid FDG uptake incidentally identified on FDG-PET/CT imaging., Nucl Med Commun, 2009. 30 (3)(3): p. 240-4., https://pubmed.ncbi.nlm.nih.gov/19262287/

222. Nishimori, H, Tabah, R, Hickeson, M, How, J, Incidental thyroid "PETomas": clinical significance and novel description of the self-resolving variant of focal FDG-PET thyroid uptake., Can J Surg, 2011. 54 (2)(2): p. 83-8., https://pubmed.ncbi.nlm.nih.gov/21251421/

223. Marcus, C, Whitworth, PW, Surasi, DS, Pai, SI, Subramaniam, RM, PET/CT in the management of thyroid cancers., AJR Am J Roentgenol, 2014. 202 (6)(6): p. 1316-29., https://pubmed.ncbi.nlm.nih.gov/24848831/

224. Soelberg, KK, Bonnema, SJ, Brix, TH, Hegedüs, L, Risk of malignancy in thyroid incidentalomas detected by 18F-fluorodeoxyglucose positron emission tomography: a systematic review., Thyroid, 2012. 22 (9)(9): p. 918-25., https://pubmed.ncbi.nlm.nih.gov/22827552/

225. Pattison, DA, Bozin, M, Gorelik, A, Hofman, MS, Hicks, RJ, Skandarajah, A, None, J Nucl Med, 2018. 59 (5)(5): p. 749-755., https://pubmed.ncbi.nlm.nih.gov/29025986/

226. Vriens, D, de Wilt, JH, van der Wilt, GJ, Netea-Maier, RT, Oyen, WJ, de Geus-Oei, LF, The role of [18F]-2-fluoro-2-deoxy-d-glucose-positron emission tomography in thyroid nodules with indeterminate fine-needle aspiration biopsy: systematic review and meta-analysis of the literature., Cancer, 2011. 117 (20)(20): p. 4582-94., https://pubmed.ncbi.nlm.nih.gov/21432844/

227. Wang, N, Zhai, H, Lu, Y, Is fluorine-18 fluorodeoxyglucose positron emission tomography useful for the thyroid nodules with indeterminate fine needle aspiration biopsy? A meta-analysis of the literature., J Otolaryngol Head Neck Surg, 2013. 42 (1)(1): p. 38., https://pubmed.ncbi.nlm.nih.gov/24228840/

228. Castellana, M, Trimboli, P, Piccardo, A, Giovanella, L, Treglia, G, Performance of , J Clin Med, 2019. 8 (9)(9):, https://pubmed.ncbi.nlm.nih.gov/31466411/

229. Vriens, D, Adang, EM, Netea-Maier, RT, Smit, JW, de Wilt, JH, Oyen, WJ, et.al. Cost-effectiveness of FDG-PET/CT for cytologically indeterminate thyroid nodules: a decision analytic approach., J Clin Endocrinol Metab, 2014. 99 (9)(9): p. 3263-74., https://pubmed.ncbi.nlm.nih.gov/24873995/

230. Deandreis, D, Al Ghuzlan, A, Auperin, A, Vielh, P, Caillou, B, Chami, L, et.al. Is (18)F-fluorodeoxyglucose-PET/CT useful for the presurgical characterization of thyroid nodules with indeterminate fine needle aspiration cytology?, Thyroid, 2012. 22 (2)(2): p. 165-72., https://pubmed.ncbi.nlm.nih.gov/22257371/

231. Piccardo, A, Puntoni, M, Treglia, G, Foppiani, L, Bertagna, F, Paparo, F, et.al. Thyroid nodules with indeterminate cytology: prospective comparison between 18F-FDG-PET/CT, multiparametric neck ultrasonography, 99mTc-MIBI scintigraphy and histology., Eur J Endocrinol, 2016. 174 (5)(5): p. 693-703., https://pubmed.ncbi.nlm.nih.gov/26966173/

232. Rosario, PW, Rocha, TG, Calsolari, MR, Fluorine-18-fluorodeoxyglucose positron emission tomography in thyroid nodules with indeterminate cytology: a prospective study., Nucl Med Commun, 2019. 40 (2)(2): p. 185-187., https://pubmed.ncbi.nlm.nih.gov/30444748/

233. Urhan, M, Velioglu, M, Rosenbaum, J, Basu, S, Alavi, A, Imaging for the diagnosis of thyroid cancer., Expert Opin Med Diagn, 2009. 3 (3)(3): p. 237-49., https://pubmed.ncbi.nlm.nih.gov/23488460/

234. Choi, WH, Chung, YA, Han, EJ, Sohn, HS, Lee, SH, Clinical value of integrated [18F]fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography in the preoperative assessment of papillary thyroid carcinoma: comparison with sonography., J Ultrasound Med, 2011. 30 (9)(9): p. 1267-73., https://pubmed.ncbi.nlm.nih.gov/21876098/

235. Morita, S, Mizoguchi, K, Suzuki, M, Iizuka, K, The accuracy of (18)[F]-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography, ultrasonography, and enhanced computed tomography alone in the preoperative diagnosis of cervical lymph node metastasis in patients with papillary thyroid carcinoma., World J Surg, 2010. 34 (11)(11): p. 2564-9., https://pubmed.ncbi.nlm.nih.gov/20645089/

236. Kim, BS, Kim, SJ, Kim, IJ, Pak, K, Kim, K, Factors associated with positive F-18 flurodeoxyglucose positron emission tomography before thyroidectomy in patients with papillary thyroid carcinoma., Thyroid, 2012. 22 (7)(7): p. 725-9., https://pubmed.ncbi.nlm.nih.gov/22524470/

237. Chung, JK, So, Y, Lee, JS, Choi, CW, Lim, SM, Lee, DS, et.al. Value of FDG PET in papillary thyroid carcinoma with negative 131I whole-body scan., J Nucl Med, 1999. 40 (6)(6): p. 986-92., https://pubmed.ncbi.nlm.nih.gov/10452315/

238. Rosenbaum-Krumme, SJ, Görges, R, Bockisch, A, Binse, I, ^{18}F-FDG PET/CT changes therapy management in high-risk DTC after first radioiodine therapy., Eur J Nucl Med Mol Imaging, 2012. 39 (9)(9): p. 1373-80., https://pubmed.ncbi.nlm.nih.gov/22718304/

239. Nascimento, C, Borget, I, Al Ghuzlan, A, Deandreis, D, Hartl, D, Lumbroso, J, et.al. Postoperative fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography: an important imaging modality in patients with aggressive histology of differentiated thyroid cancer., Thyroid, 2015. 25 (4)(4): p. 437-44., https://pubmed.ncbi.nlm.nih.gov/25633259/

240. Pryma, DA, Schöder, H, Gönen, M, Robbins, RJ, Larson, SM, Yeung, HW, Diagnostic accuracy and prognostic value of 18F-FDG PET in Hürthle cell thyroid cancer patients., J Nucl Med, 2006. 47 (8)(8): p. 1260-6., https://pubmed.ncbi.nlm.nih.gov/16883003/

241. Lowe, VJ, Mullan, BP, Hay, ID, McIver, B, Kasperbauer, JL, 18F-FDG PET of patients with Hürthle cell carcinoma., J Nucl Med, 2003. 44 (9)(9): p. 1402-6., https://pubmed.ncbi.nlm.nih.gov/12960183/

242. Schoenberger, J, Fuchs, E, Fertig, V, Szikszai, A, Maenner, P, Eilles, C, Clinical value of planar and tomographic dual-isotope scintigraphy using 99mTc-methylene diphosphonate and 131I in patients with thyroid cancer., Nucl Med Commun, 2006. 27 (11)(11): p. 865-71., https://pubmed.ncbi.nlm.nih.gov/17021426/

243. Qiu, ZL, Xue, YL, Song, HJ, Luo, QY, Comparison of the diagnostic and prognostic values of 99mTc-MDP-planar bone scintigraphy, 131I-SPECT/CT and 18F-FDG-PET/CT for the detection of bone metastases from differentiated thyroid cancer., Nucl Med Commun, 2012. 33 (12)(12): p. 1232-42., https://pubmed.ncbi.nlm.nih.gov/23111353/

244. Ota, N, Kato, K, Iwano, S, Ito, S, Abe, S, Fujita, N, et.al. Comparison of ^{18}F-fluoride PET/CT, ^{18}F-FDG PET/CT and bone scintigraphy (planar and SPECT) in detection of bone metastases of differentiated thyroid cancer: a pilot study., Br J Radiol, 2014. 87 (1034)(1034): p. 20130444., https://pubmed.ncbi.nlm.nih.gov/24297809/

245. Ito, S, Kato, K, Ikeda, M, Iwano, S, Makino, N, Tadokoro, M, et.al. Comparison of 18F-FDG PET and bone scintigraphy in detection of bone metastases of thyroid cancer., J Nucl Med, 2007. 48 (6)(6): p. 889-95., https://pubmed.ncbi.nlm.nih.gov/17504877/

246. Huellner, MW, Strobel, K, Clinical applications of SPECT/CT in imaging the extremities., Eur J Nucl Med Mol Imaging, 2014. 41 Suppl 1 (): p. S50-8., https://pubmed.ncbi.nlm.nih.gov/23963296/

247. Mikhael, A, Patell, R, Tabet, M, Bena, J, Berber, E, Nasr, C, Chest X-ray Prior to Thyroidectomy: Is It Really Needed?, World J Surg, 2018. 42 (5)(5): p. 1403-1407., https://pubmed.ncbi.nlm.nih.gov/29147894/

248. Bongers, PJ, Verzijl, R, Dzingala, M, Vriens, MR, Yu, E, Pasternak, JD, et.al. Preoperative Computed Tomography Changes Surgical Management for Clinically Low-Risk Well-Differentiated Thyroid Cancer., Ann Surg Oncol, 2019. 26 (13)(13): p. 4439-4444., https://pubmed.ncbi.nlm.nih.gov/31583547/

249. Ahn, JE, Lee, JH, Yi, JS, Shong, YK, Hong, SJ, Lee, DH, et.al. Diagnostic accuracy of CT and ultrasonography for evaluating metastatic cervical lymph nodes in patients with thyroid cancer., World J Surg, 2008. 32 (7)(7): p. 1552-8., https://pubmed.ncbi.nlm.nih.gov/18408961/

250. Lesnik, D, Cunnane, ME, Zurakowski, D, Acar, GO, Ecevit, C, Mace, A, et.al. Papillary thyroid carcinoma nodal surgery directed by a preoperative radiographic map utilizing CT scan and ultrasound in all primary and reoperative patients., Head Neck, 2014. 36 (2)(2): p. 191-202., https://pubmed.ncbi.nlm.nih.gov/23554058/

251. Kim, H, Kim, JA, Son, EJ, Youk, JH, Chung, TS, Park, CS, et.al. Preoperative prediction of the extrathyroidal extension of papillary thyroid carcinoma with ultrasonography versus MRI: a retrospective cohort study., Int J Surg, 2014. 12 (5)(5): p. 544-8., https://pubmed.ncbi.nlm.nih.gov/24631554/

252. Lloyd, R. V.; Osamura, R.Y.; Klöppel, G.; Rosai, J., WHO classification of tumours of enndocrine organs, World Health Organization Classification of Tumours, International Agency for Research on Cancer (IARC), 2017.

253. Baloch, ZW, Asa, SL, Barletta, JA, Ghossein, RA, Juhlin, CC, Jung, CK, et.al. Overview of the 2022 WHO Classification of Thyroid Neoplasms., Endocr Pathol, 2022. 33 (1)(1): p. 27-63., https://pubmed.ncbi.nlm.nih.gov/35288841/

254. Theurer, S, Dralle, H, Führer-Sakel, D, Herrmann, K, Schmid, KW, [Morphologic diagnostic criteria of noninvasive follicular neoplasia with papillary-like nuclear features (NIFTP) : A diagnostic challenge for the patient's benefit], 2019. 40(3): p. 220 - 226., http://europepmc.org/abstract/MED/31049677, https://doi.org/10.1007/s00292-019-0597-0

255. Schmid, KW, Farid, NR, How to define follicular thyroid carcinoma?, Virchows Arch, 2006. 448 (4)(4): p. 385-93., https://pubmed.ncbi.nlm.nih.gov/16506015/

256. Cooper, DS, Doherty, GM, Haugen, BR, Kloos, RT, Lee, SL, Mandel, SJ, et.al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer., Thyroid, 2009. 19 (11)(11): p. 1167-214., https://pubmed.ncbi.nlm.nih.gov/19860577/

257. Hermann, M, Tonninger, K, Kober, F, Furtlehner, EM, Schultheis, A, Neuhold, N, [Minimally invasive follicular thyroid carcinoma : Not always total thyroidectomy]., Chirurg, 2010. 81 (7)(7): p. 627-30, 632-5., https://pubmed.ncbi.nlm.nih.gov/20544166/

258. Dralle, H, Musholt, TJ, Schabram, J, Steinmüller, T, Frilling, A, Simon, D, et.al. German Association of Endocrine Surgeons practice guideline for the surgical management of malignant thyroid tumors., Langenbecks Arch Surg, 2013. 398 (3)(3): p. 347-75., https://pubmed.ncbi.nlm.nih.gov/23456424/

259. Goffredo, P., Cheung, K., Roman, S. A., Sosa, J. A., Can minimally invasive follicular thyroid cancer be approached as a benign lesion?: a population-level analysis of survival among 1,200 patients, Ann Surg Oncol, 2013. 20(3): p. 767-72., https://pubmed.ncbi.nlm.nih.gov/23111705/

260. Jung, CK, Bychkov, A, Kakudo, K, Update from the 2022 World Health Organization Classification of Thyroid Tumors: A Standardized Diagnostic Approach., Endocrinol Metab (Seoul), 2022. 37 (5)(5): p. 703-718., https://pubmed.ncbi.nlm.nih.gov/36193717/

261. Volante, M, Collini, P, Nikiforov, YE, Sakamoto, A, Kakudo, K, Katoh, R, et.al. Poorly differentiated thyroid carcinoma: the Turin proposal for the use of uniform diagnostic criteria and an algorithmic diagnostic approach., Am J Surg Pathol, 2007. 31 (8)(8): p. 1256-64., https://pubmed.ncbi.nlm.nih.gov/17667551/

262. Abe, I, Lam, AK, Anaplastic thyroid carcinoma: Updates on WHO classification, clinicopathological features and staging., Histol Histopathol, 2021. 36 (3)(3): p. 239-248., https://pubmed.ncbi.nlm.nih.gov/33170501/

263. Abiri, A, Pang, J, Prasad, KR, Goshtasbi, K, Kuan, EC, Armstrong, WB, et.al. Prognostic Utility of Tumor Stage versus American Thyroid Association Risk Class in Thyroid Cancer., Laryngoscope, 2023. 133 (1)(1): p. 205-211., https://pubmed.ncbi.nlm.nih.gov/35716358/

264. Morosán Allo, YJ, Bosio, L, Morejón, A, Parisi, C, Faingold, MC, Ilera, V, et.al. Comparison of the prognostic value of AJCC cancer staging system 7th and 8th editions for differentiated thyroid cancer., BMC Endocr Disord, 2022. 22 (1)(1): p. 146., https://pubmed.ncbi.nlm.nih.gov/35650574/

265. Bai, Y, Kakudo, K, Jung, CK, Updates in the Pathologic Classification of Thyroid Neoplasms: A Review of the World Health Organization Classification., Endocrinol Metab (Seoul), 2020. 35 (4)(4): p. 696-715., https://pubmed.ncbi.nlm.nih.gov/33261309/

266. Borda, A, Zahan, AE, Piciu, D, Barbuş, E, Berger, N, Nechifor-Boilă, A, A 15 year institutional experience of well-differentiated follicular cell-derived thyroid carcinomas; impact of the new 2017 TNM and WHO Classifications of Tumors of Endocrine Organs on the epidemiological trends and pathological characteristics., Endocrine, 2020. 67 (3)(3): p. 630-642., https://pubmed.ncbi.nlm.nih.gov/31838728/

267. Ito, Y, Miyauchi, A, Hirokawa, M, Yamamoto, M, Oda, H, Masuoka, H, et.al. Prognostic value of the 8, Endocr J, 2018. 65 (6)(6): p. 621-627., https://pubmed.ncbi.nlm.nih.gov/29618671/

268. Jeon, YW, Gwak, HG, Lim, ST, Schneider, J, Suh, YJ, Long-Term Prognosis of Unilateral and Multifocal Papillary Thyroid Microcarcinoma After Unilateral Lobectomy Versus Total Thyroidectomy., Ann Surg Oncol, 2019. 26 (9)(9): p. 2952-2958., https://pubmed.ncbi.nlm.nih.gov/31264119/

269. Scheffel, RS, de Cristo, AP, Romitti, M, Vargas, CVF, Ceolin, L, Zanella, AB, et.al. The BRAF, Arch Endocrinol Metab, 2021. 64 (6)(6): p. 751-757., https://pubmed.ncbi.nlm.nih.gov/34033285/

270. Harries, V, Wang, LY, McGill, M, Xu, B, Tuttle, RM, Wong, RJ, et.al. Should multifocality be an indication for completion thyroidectomy in papillary thyroid carcinoma?, Surgery, 2020. 167 (1)(1): p. 10-17., https://pubmed.ncbi.nlm.nih.gov/31515125/

271. Haugen, BR, Sawka, AM, Alexander, EK, Bible, KC, Caturegli, P, Doherty, GM, et.al. American Thyroid Association Guidelines on the Management of Thyroid Nodules and Differentiated Thyroid Cancer Task Force Review and Recommendation on the Proposed Renaming of Encapsulated Follicular Variant Papillary Thyroid Carcinoma Without Invasion to Noninvasive Follicular Thyroid

Neoplasm with Papillary-Like Nuclear Features., Thyroid, 2017. 27 (4)(4): p. 481-483., https://pubmed.ncbi.nlm.nih.gov/28114862/

272. Christofer Juhlin, C, Mete, O, Baloch, ZW, The 2022 WHO classification of thyroid tumors: novel concepts in nomenclature and grading., Endocr Relat Cancer, 2023. 30 (2)(2):, https://pubmed.ncbi.nlm.nih.gov/36445235/

273. van Velsen, EFS, Peeters, RP, Stegenga, MT, Mäder, U, Reiners, C, van Kemenade, FJ, et.al. Evaluating the use of a two-step age-based cutoff for the UICC/AJCC TNM staging system in patients with papillary or follicular thyroid cancer., Eur J Endocrinol, 2022. 186 (3)(3): p. 389-397., https://pubmed.ncbi.nlm.nih.gov/35038308/

274. Tuttle, RM, Haugen, B, Perrier, ND, Updated American Joint Committee on Cancer/Tumor-Node-Metastasis Staging System for Differentiated and Anaplastic Thyroid Cancer (Eighth Edition): What Changed and Why?, Thyroid, 2017. 27 (6)(6): p. 751-756., https://pubmed.ncbi.nlm.nih.gov/28463585/

275. Schmid, KW, Synoracki, S, Dralle, H, Wittekind, C, [Proposal for an extended pTNM classification of thyroid carcinoma : Commentary on deficits of the 8th edition of the TNM classification (German version)]., Pathologe, 2018. 39 (1)(1): p. 49-56., https://pubmed.ncbi.nlm.nih.gov/29372307/

276. Su, HK, Wenig, BM, Haser, GC, Rowe, ME, Asa, SL, Baloch, Z, et.al. Inter-Observer Variation in the Pathologic Identification of Minimal Extrathyroidal Extension in Papillary Thyroid Carcinoma., Thyroid, 2016. 26 (4)(4): p. 512-7., https://pubmed.ncbi.nlm.nih.gov/26953223/

277. Clain, JB, Scherl, S, Dos Reis, L, Turk, A, Wenig, BM, Mehra, S, et.al. Extrathyroidal extension predicts extranodal extension in patients with positive lymph nodes: an important association that may affect clinical management., Thyroid, 2014. 24 (6)(6): p. 951-7., https://pubmed.ncbi.nlm.nih.gov/24443878/

278. Machens, A, Dralle, H, Breach of the thyroid capsule and lymph node capsule in node-positive papillary and medullary thyroid cancer: Different biology., Eur J Surg Oncol, 2015. 41 (6)(6): p. 766-72., https://pubmed.ncbi.nlm.nih.gov/25468749/

279. Roh, JL, Park, JW, Jeong, J, Gong, G, Cho, KJ, Choi, SH, et.al. Extranodal extension of lymph node metastasis as a prognostic indicator of recurrence and survival in papillary thyroid carcinoma., J Surg Oncol, 2017. 116 (4)(4): p. 450-458., https://pubmed.ncbi.nlm.nih.gov/28608492/

280. Schmid, KW, Synoracki, S, Dralle, H, Wittekind, C, Proposal for an extended pTNM classification of thyroid carcinoma : Commentary on deficits of the 8th edition of the TNM classification., Pathologe, 2019. 40 (Suppl 1)(Suppl 1): p. 18-24., https://pubmed.ncbi.nlm.nih.gov/29459993/

281. Nagarajan, N, Najafian, A, Schneider, EB, Zeiger, MA, Olson, MT, Conventional smears versus liquid-based preparations for thyroid fine-needle aspirates: a systematic review and meta-analysis., J Am Soc Cytopathol, 2015. 4 (5)(5): p. 253-260., https://pubmed.ncbi.nlm.nih.gov/31051762/

282. Burch, HB, Drug Effects on the Thyroid., N Engl J Med, 2019. 381 (8)(8): p. 749-761., https://pubmed.ncbi.nlm.nih.gov/31433922/

283. Weber, AL, Rahemtullah, A, Ferry, JA, Hodgkin and non-Hodgkin lymphoma of the head and neck: clinical, pathologic, and imaging evaluation., Neuroimaging Clin N Am, 2003. 13 (3)(3): p. 371-92., https://pubmed.ncbi.nlm.nih.gov/14631680/

284. Hart, J, Mandavilli, S, Epithelioid angiosarcoma: a brief diagnostic review and differential diagnosis., Arch Pathol Lab Med, 2011. 135 (2)(2): p. 268-72., https://pubmed.ncbi.nlm.nih.gov/21284449/

285. Sen, R, Gupta, S, Batra, A, Gill, M, Gupta, V, Marwah, N, Acute lymphoblastic leukaemia (ALL) with infiltration of the thyroid: a cytological diagnosis., Endocr Pathol, 2012. 23 (4)(4): p. 268-9., https://pubmed.ncbi.nlm.nih.gov/22562766/

286. Yang, GY, Zhao, D, Zhang, WZ, Meng, J, Li, J, Li, XH, et.al. Role of ultrasound evaluation for the diagnosis and monitoring of thyroid tuberculosis: A case report and review of the literature., Oncol Lett, 2015. 9 (1)(1): p. 227-230., https://pubmed.ncbi.nlm.nih.gov/25435964/

287. Okuma, H, Hashimoto, K, Wang, X, Ohkiba, N, Murooka, N, Akizuki, N, et.al. Systemic Sarcoidosis with Thyroid Involvement., Intern Med, 2017. 56 (16)(16): p. 2181-2186., https://pubmed.ncbi.nlm.nih.gov/28781308/

288. Tjahjono, R, Phung, D, Gurney, H, Gupta, R, Riffat, F, Palme, CE, Thyroid gland metastasis from renal cell carcinoma: a case series and literature review., ANZ J Surg, 2021. 91 (4)(4): p. 708-715., https://pubmed.ncbi.nlm.nih.gov/33319504/

289. Cibas, ES, Ali, SZ, The Bethesda System for Reporting Thyroid Cytopathology., Thyroid, 2009. 19 (11)(11): p. 1159-65., https://pubmed.ncbi.nlm.nih.gov/19888858/

290. Cibas, ES, Ali, SZ, The 2017 Bethesda System for Reporting Thyroid Cytopathology., Thyroid, 2017. 27 (11)(11): p. 1341-1346., https://pubmed.ncbi.nlm.nih.gov/29091573/

291. Cross P, Chandra A, Giles T, et al., Guidance on the Reporting of Thyroid Cytology Specimens, 2016.

292. Nardi, F, Basolo, F, Crescenzi, A, Fadda, G, Frasoldati, A, Orlandi, F, et.al. Italian consensus for the classification and reporting of thyroid cytology., J Endocrinol Invest, 2014. 37 (6)(6): p. 593-9., https://pubmed.ncbi.nlm.nih.gov/24789536/

293. Ting, S, Synoracki, S, Bockisch, A, Führer, D, Schmid, KW, [Clinical importance of thyroid gland cytology]., Pathologe, 2015. 36 (6)(6): p. 543-52., https://pubmed.ncbi.nlm.nih.gov/26462485/

294. Alhashem, MH, Alabidi, A, Aly, MG, The Bethesda System for Reporting Thyroid Cytopathology: A Retrospective Review of its Diagnostic Utility at Johns Hopkins Aramco Healthcare, Saudi Arabia., Am J Otolaryngol, 2021. 42 (6)(6): p. 103088., https://pubmed.ncbi.nlm.nih.gov/34090018/

295. Linhares, SM, Handelsman, R, Picado, O, Farrá, JC, Lew, JI, Fine needle aspiration and the Bethesda system: Correlation with histopathology in 1,228 surgical patients., Surgery, 2021. 170 (5)(5): p. 1364-1368., https://pubmed.ncbi.nlm.nih.gov/34134896/

296. Madgar, O, Avior, G, Shochat, I, Joshua, BZ, Baraf, L, Avidor, Y, et.al. Thyroid malignancy rates according to the Bethesda reporting system in Israel - A multicenter study., Eur J Surg Oncol, 2021. 47 (6)(6): p. 1370-1375., https://pubmed.ncbi.nlm.nih.gov/33745793./

297. Cherella, CE, Angell, TE, Richman, DM, Frates, MC, Benson, CB, Moore, FD, et.al. Differences in Thyroid Nodule Cytology and Malignancy Risk Between Children and Adults., Thyroid, 2019. 29 (8)(8): p. 1097-1104., https://pubmed.ncbi.nlm.nih.gov/31298618/

298. Vivero, M, Renshaw, AA, Krane, JF, Adequacy criteria for thyroid FNA evaluated by ThinPrep slides only., Cancer Cytopathol, 2017. 125 (7)(7): p. 534-543., https://pubmed.ncbi.nlm.nih.gov/28388017/

299. Goldner, WS, Angell, TE, McAdoo, SL, Babiarz, J, Sadow, PM, Nabhan, FA, et.al. Molecular Variants and Their Risks for Malignancy in Cytologically Indeterminate Thyroid Nodules., Thyroid, 2019. 29 (11)(11): p. 1594-1605., https://pubmed.ncbi.nlm.nih.gov/31469053/

300. Musholt, TJ, Clerici, T, Dralle, H, Frilling, A, Goretzki, PE, Hermann, MM, et.al. German Association of Endocrine Surgeons practice guidelines for the surgical treatment of benign thyroid disease., Langenbecks Arch Surg, 2011. 396 (5)(5): p. 639-49., https://pubmed.ncbi.nlm.nih.gov/21424798/

301. Synoracki, S, Ting, S, Siebolts, U, Dralle, H, Koperek, O, Schmid, KW, [Intraoperative frozen sections of the thyroid gland]., Pathologe, 2015. 36 (4)(4): p. 362-71., https://pubmed.ncbi.nlm.nih.gov/26055332/

302. Sheu, S.-Y. , Frilling, A.,, Betzler M., , Peitsch, W. , Schmid K. W., Der intraoperative Gefrierschnitt von SchilddrüsenknotenGeorg Thieme Verlag, Viszeralchirurgie, 2005. 40(3): p. 174-179., https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-2005-836556

303. Schmid, KW, Ladurner, D, Zechmann, W, Feichtinger, H, Clinicopathologic management of tumors of the thyroid gland in an endemic goiter area. Combined use of preoperative fine needle aspiration biopsy and intraoperative frozen section., Acta Cytol, 1989. 33 (1)(1): p. 27-30., https://pubmed.ncbi.nlm.nih.gov/2916368/

304. Rosen, Y, Rosenblatt, P, Saltzman, E, Intraoperative pathologic diagnosis of thyroid neoplasms. Report on experience with 504 specimens., Cancer, 1990. 66 (9)(9): p. 2001-6., https://pubmed.ncbi.nlm.nih.gov/2146011/

305. Shaha, A, Gleich, L, Di Maio, T, Jaffe, BM, Accuracy and pitfalls of frozen section during thyroid surgery., J Surg Oncol, 1990. 44 (2)(2): p. 84-92., https://pubmed.ncbi.nlm.nih.gov/2355746/

306. de Micco, C, [Anatomo-pathology and histological prognosis of follicular thyroid carcinoma]., Ann Endocrinol (Paris), 1997. 58 (3)(3): p. 172-82., https://pubmed.ncbi.nlm.nih.gov/9239238/

307. Schmid, KW, Ladurner, D, [Intraoperative diagnostic frozen section of the thyroid gland]., Pathologe, 1997. 18 (1)(1): p. 98-101., https://pubmed.ncbi.nlm.nih.gov/9157412/

308. Chadwick, DR, Harrison, BJ, The role of fine-needle aspiration cytology and frozen section histology in management of differentiated thyroid cancer: the UK experience., Langenbecks Arch Surg, 1998. 383 (2)(2): p. 164-6., https://pubmed.ncbi.nlm.nih.gov/9641891/

309. DeMay, RM, Frozen section of thyroid? Just say no., Am J Clin Pathol, 1998. 110 (4)(4): p. 423-4., https://pubmed.ncbi.nlm.nih.gov/9763027/

310. McHenry, CR, Thomas, SR, Slusarczyk, SJ, Khiyami, A, Follicular or Hürthle cell neoplasm of the thyroid: can clinical factors be used to predict carcinoma and determine extent of thyroidectomy?, Surgery, 1999. 126 (4)(4): p. 798-802; discussion 802-4., https://pubmed.ncbi.nlm.nih.gov/10520931/

311. Shaha, AR, Controversies in the management of thyroid nodule., Laryngoscope, 2000. 110 (2 Pt 1)(2 Pt 1): p. 183-93., https://pubmed.ncbi.nlm.nih.gov/10680914/

312. Leteurtre, E, Leroy, X, Pattou, F, Wacrenier, A, Carnaille, B, Proye, C, et.al. Why do frozen sections have limited value in encapsulated or minimally invasive follicular carcinoma of the thyroid?, Am J Clin Pathol, 2001. 115 (3)(3): p. 370-4., https://pubmed.ncbi.nlm.nih.gov/11242793/

313. Caraci, P, Aversa, S, Mussa, A, Pancani, G, Ondolo, C, Conticello, S, Role of fine-needle aspiration biopsy and frozen-section evaluation in the surgical management of thyroid nodules., Br J Surg, 2002. 89 (6)(6): p. 797-801., https://pubmed.ncbi.nlm.nih.gov/12027995/

314. Dosen, D, Turić, M, Smalcelj, J, Janusić, R, Grgić, MP, Separović, V, The value of frozen section in intraoperative surgical management of thyroid follicular carcinoma., Head Neck, 2003. 25 (7)(7): p. 521-8., https://pubmed.ncbi.nlm.nih.gov/12808654/

315. Grannan, K, Snyder, J, McDonough, S, Engel, A, Farnum, J, Operative decision-making for follicular thyroid lesions: a community hospital system experience., Am Surg, 2011. 77 (4)(4): p. 443-6., https://pubmed.ncbi.nlm.nih.gov/21679553/

316. Marshall, R, Alexander, D, Fleming, J, Grayson, J, Peters, G, Buczek, E, Utility of intraoperative frozen sections of thyroid tissue in the age of molecular testing., Clin Otolaryngol, 2021. 46 (5)(5): p. 991-997., https://pubmed.ncbi.nlm.nih.gov/33811452/

317. Sanabria, A, Zafereo, M, Thompson, LDR, Hernandez-Prera, JC, Kowalski, LP, Nixon, IJ, et.al. Frozen section in thyroid gland follicular neoplasms: It's high time to abandon it!, Surg Oncol, 2021. 36 (): p. 76-81., https://pubmed.ncbi.nlm.nih.gov/33316682/

318. Staubitz, JI, Elmrich, I, Musholt, PB, Cámara, RJA, Watzka, F, Dralle, H, et.al. Targeted use of intraoperative frozen-section analysis lowers the frequency of completion thyroidectomy., BJS Open, 2021. 5 (2)(2):, https://pubmed.ncbi.nlm.nih.gov/33851986/

319. Goemann, IM, Paixão, F, Migliavacca, A, Guimarães, JR, Scheffel, RS, Maia, AL, Intraoperative frozen section performance for thyroid cancer diagnosis., Arch Endocrinol Metab, 2022. 66 (1)(1): p. 50-57., https://pubmed.ncbi.nlm.nih.gov/35263048/

320. Lee, S, Han, BK, Ko, EY, Oh, YL, Choe, JH, Shin, JH, The ultrasonography features of hyalinizing trabecular tumor of the thyroid are more consistent with its benign behavior than cytology or frozen section readings., Thyroid, 2011. 21 (3)(3): p. 253-9., https://pubmed.ncbi.nlm.nih.gov/21190434/

321. Ting, S, Puttinger, C, Schmid, KW, Sheu-Grabellus, SY, [Hyalinizing trabecular tumor of the thyroid. An overcautious designation of a benign thyroid tumour?]., Pathologe, 2012. 33 (2)(2): p. 135-41., https://pubmed.ncbi.nlm.nih.gov/21842215/

322. Sung, SY, Shen, HY, Hsieh, CB, Duh, QY, Su, TF, Chan, DC, et.al. Hyalinizing trabecular tumor of thyroid: does frozen section prevent unnecessarily aggressive operation? Six new cases and a literature review., J Chin Med Assoc, 2014. 77 (11)(11): p. 573-7., https://pubmed.ncbi.nlm.nih.gov/25278150/

323. Schenke, SA, Kreissl, MC, Grunert, M, Hach, A, Haghghi, S, Kandror, T, et.al. Distribution of Functional Status of Thyroid Nodules and Malignancy Rates of Hyperfunctioning and Hypofunctioning Thyroid Nodules in Germany., Nuklearmedizin, 2022. 61 (5)(5): p. 376-384., https://pubmed.ncbi.nlm.nih.gov/35917825/

324. Li, H, Goh, JPN, Anand, KA, Bundele, MM, Fu, EWZ, Gan, JY, et.al. Routine intraoperative frozen section adds little value to the management of thyroid nodules with Bethesda III cytology., Ann Acad Med Singap, 2021. 50 (11)(11): p. 865-867., https://pubmed.ncbi.nlm.nih.gov/34877593/

325. De Schutter, H, Van Damme, N, Colpaert, C, Galant, C, Lambein, K, Cornelis, A, et.al. Quality of pathology reporting is crucial for cancer care and registration: a baseline assessment for breast cancers diagnosed in Belgium in 2008., Breast, 2015. 24 (2)(2): p. 143-52., https://pubmed.ncbi.nlm.nih.gov/25572136/

326. Ellis, DW, Surgical pathology reporting at the crossroads: beyond synoptic reporting., Pathology, 2011. 43 (5)(5): p. 404-9., https://pubmed.ncbi.nlm.nih.gov/21753714/

327. Ellis, DW, Srigley, J, Does standardised structured reporting contribute to quality in diagnostic pathology? The importance of evidence-based datasets., Virchows Arch, 2016. 468 (1)(1): p. 51-9., https://pubmed.ncbi.nlm.nih.gov/26316184/

328. Aumann, K, Niermann, K, Asberger, J, Wellner, U, Bronsert, P, Erbes, T, et.al. Structured reporting ensures complete content and quick detection of essential data in pathology reports of oncological breast resection specimens., Breast Cancer Res Treat, 2016. 156 (3)(3): p. 495-500., https://pubmed.ncbi.nlm.nih.gov/27059032/

329. Słodkowska, J, Cierniak, S, Patera, J, Kopik, J, Baranowski, W, Markiewicz, T, et.al. Functional Assessment of Synoptic Pathology Reporting for Ovarian Cancer., Pathobiology, 2016. 83 (2-3)(2-3): p. 70-8., https://pubmed.ncbi.nlm.nih.gov/27100104/

330. Sluijter, CE, van Lonkhuijzen, LR, van Slooten, HJ, Nagtegaal, ID, Overbeek, LI, The effects of implementing synoptic pathology reporting in cancer diagnosis: a systematic review., Virchows Arch, 2016. 468 (6)(6): p. 639-49., https://pubmed.ncbi.nlm.nih.gov/27097810/

331. Baranov, NS, Nagtegaal, ID, van Grieken, NCT, Verhoeven, RHA, Voorham, QJM, Rosman, C, et.al. Synoptic reporting increases quality of upper gastrointestinal cancer pathology reports., Virchows Arch, 2019. 475 (2)(2): p. 255-259., https://pubmed.ncbi.nlm.nih.gov/31144018/

332. Tsan, CJ, Serpell, JW, Poh, YY, The impact of synoptic cytology reporting on fine-needle aspiration cytology of thyroid nodules., ANZ J Surg, 2007. 77 (11)(11): p. 991-5., https://pubmed.ncbi.nlm.nih.gov/17931264/

333. Kahn, C, Simonella, L, Sywak, M, Boyages, S, Ung, O, O'Connell, D, Postsurgical pathology reporting of thyroid cancer in New South Wales, Australia., Thyroid, 2012. 22 (6)(6): p. 604-10., https://pubmed.ncbi.nlm.nih.gov/22524497/

334. Lam, E, Vy, N, Bajdik, C, Strugnell, SS, Walker, B, Wiseman, SM, Synoptic pathology reporting for thyroid cancer: a review and institutional experience., Expert Rev Anticancer Ther, 2013. 13 (9)(9): p. 1073-9., https://pubmed.ncbi.nlm.nih.gov/24053206/

335. Wells, SA, Asa, SL, Dralle, H, Elisei, R, Evans, DB, Gagel, RF, et.al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma., Thyroid, 2015. 25 (6)(6): p. 567-610., https://pubmed.ncbi.nlm.nih.gov/25810047/

336. Xu, B, Ghossein, R, Critical Prognostic Parameters in the Anatomic Pathology Reporting of Differentiated Follicular Cell-Derived Thyroid Carcinoma., Cancers (Basel), 2019. 11 (8)(8):, https://pubmed.ncbi.nlm.nih.gov/31382401/

337. Bible, KC, Kebebew, E, Brierley, J, Brito, JP, Cabanillas, ME, Clark, TJ, et.al. 2021 American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer., Thyroid, 2021. 31 (3)(3): p. 337-386., https://pubmed.ncbi.nlm.nih.gov/33728999/

338. Ghossein, R, Barletta, JA, Bullock, M, Johnson, SJ, Kakudo, K, Lam, AK, et.al. Data set for reporting carcinoma of the thyroid: recommendations from the International Collaboration on Cancer Reporting., Hum Pathol, 2021. 110 (): p. 62-72., https://pubmed.ncbi.nlm.nih.gov/32920035/

339. Cibas, ES, Ali, SZ, The 2017 Bethesda System for Reporting Thyroid Cytopathology., J Am Soc Cytopathol, 2017. 6 (6)(6): p. 217-222., https://pubmed.ncbi.nlm.nih.gov/31043290/

340. Musholt, T. J., Bockisch, A., Clerici, T., Dotzenrath, C., Dralle, H., Goretzki, P. E., et.al. Aktualisierung der S2k-Leitlinie, 2018. 89(9): p. 699 - 709., https://doi.org/10.1007/s00104-018-0653-y

341. Robbins, KT, Shaha, AR, Medina, JE, Califano, JA, Wolf, GT, Ferlito, A, et.al. Consensus statement on the classification and terminology of neck dissection., Arch Otolaryngol Head Neck Surg, 2008. 134 (5)(5): p. 536-8., https://pubmed.ncbi.nlm.nih.gov/18490577/

342. Carty, SE, Cooper, DS, Doherty, GM, Duh, QY, Kloos, RT, Mandel, SJ, et.al. Consensus statement on the terminology and classification of central neck dissection for thyroid cancer., Thyroid, 2009. 19 (11)(11): p. 1153-8., https://pubmed.ncbi.nlm.nih.gov/19860578/

343. Dralle, H, Damm, I, Scheumann, GF, Kotzerke, J, Kupsch, E, Geerlings, H, et.al. Compartment-oriented microdissection of regional lymph nodes in medullary thyroid carcinoma., Surg Today, 1994. 24 (2)(2): p. 112-21., https://pubmed.ncbi.nlm.nih.gov/8054788/

344. Dralle, H., Lorenz, K., Machens, A., Chirurgie der Schilddrüsenkarzinome, 2009. 80(11): p. 1069 - 1084., https://doi.org/10.1007/s00104-009-1769-x

345. Dralle, H, Machens, A, Lorenz, K, [Hereditary thyroid cancer]., Chirurg, 2008. 79 (11)(11): p. 1017-28., https://pubmed.ncbi.nlm.nih.gov/18818894/

346. von Lanz, T., Wachsmuth, W., Praktische Anatomie, Hals, 1955. Volume 1 / 2:

347. Földi, Michael;, Kubik, Stefan (Hrsg.), Lehrbuch LymphologieGustav Fischer Verlag, Für Mediziner und Physiotherapeuten, 1989.

348. Shonka, DC, Ho, A, Chintakuntlawar, AV, Geiger, JL, Park, JC, Seetharamu, N, et.al. American Head and Neck Society Endocrine Surgery Section and International Thyroid Oncology Group consensus statement on mutational testing in thyroid cancer: Defining advanced thyroid cancer and its targeted treatment., Head Neck, 2022. 44 (6)(6): p. 1277-1300., https://pubmed.ncbi.nlm.nih.gov/35274388/

349. Kelley, S, Beck, AC, Weigel, RJ, Howe, JR, Sugg, SL, Lal, G, Influence of endocrine multidisciplinary tumor board on patient management and treatment decision making., Am J Surg, 2022. 223 (1)(1): p. 76-80., https://pubmed.ncbi.nlm.nih.gov/34303521/

350. El Saghir, NS, Keating, NL, Carlson, RW, Khoury, KE, Fallowfield, L, Tumor boards: optimizing the structure and improving efficiency of multidisciplinary management of patients with cancer worldwide., Am Soc Clin Oncol Educ Book, 2014. (): p. e461-6., https://pubmed.ncbi.nlm.nih.gov/24857140/

351. Lamb, BW, Green, JS, Benn, J, Brown, KF, Vincent, CA, Sevdalis, N, Improving decision making in multidisciplinary tumor boards: prospective longitudinal evaluation of a multicomponent intervention for 1,421 patients., J Am Coll Surg, 2013. 217 (3)(3): p. 412-20., https://pubmed.ncbi.nlm.nih.gov/23891067/

352. Bibbins-Domingo, K, Grossman, DC, Curry, SJ, Barry, MJ, Davidson, KW, Doubeni, CA, et.al. Screening for Thyroid Cancer: US Preventive Services Task Force Recommendation Statement., JAMA, 2017. 317 (18)(18): p. 1882-1887., https://pubmed.ncbi.nlm.nih.gov/28492905/

353. Robert-Koch-Institut, Krebs in Deutschland für 2017/2018, Zentrum für Krebsregisterdaten, 2018., https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/krebs_in_deutschland_inhalt.html?nn=2378942

354. Christakis, I, Dimas, S, Kafetzis, ID, Roukounakis, N, Risk stratification of 282 differentiated thyroid cancers found incidentally in 1369 total thyroidectomies according to the 2015 ATA guidelines; implications for management and treatment., Ann R Coll Surg Engl, 2018. 100 (5)(5): p. 357-365., https://pubmed.ncbi.nlm.nih.gov/29484944/

355. Miyauchi, A, Ito, Y, Oda, H, Insights into the Management of Papillary Microcarcinoma of the Thyroid., Thyroid, 2018. 28 (1)(1): p. 23-31., https://pubmed.ncbi.nlm.nih.gov/28629253/

356. Ito, Y, Miyauchi, A, Oda, H, Low-risk papillary microcarcinoma of the thyroid: A review of active surveillance trials., Eur J Surg Oncol, 2018. 44 (3)(3): p. 307-315., https://pubmed.ncbi.nlm.nih.gov/28343733/

357. Venkatesh, S, Pasternak, JD, Beninato, T, Drake, FT, Kluijfhout, WP, Liu, C, et.al. Cost-effectiveness of active surveillance versus hemithyroidectomy for micropapillary thyroid cancer., Surgery, 2017. 161 (1)(1): p. 116-126., https://pubmed.ncbi.nlm.nih.gov/27839930/

358. Sugitani, I, Ito, Y, Takeuchi, D, Nakayama, H, Masaki, C, Shindo, H, et.al. Indications and Strategy for Active Surveillance of Adult Low-Risk Papillary Thyroid Microcarcinoma: Consensus Statements from the Japan Association of Endocrine Surgery Task Force on Management for Papillary Thyroid Microcarcinoma., Thyroid, 2021. 31 (2)(2): p. 183-192., https://pubmed.ncbi.nlm.nih.gov/33023426/

359. Miyauchi, A, Kudo, T, Ito, Y, Oda, H, Sasai, H, Higashiyama, T, et.al. Estimation of the lifetime probability of disease progression of papillary microcarcinoma of the thyroid during active surveillance., Surgery, 2018. 163 (1)(1): p. 48-52., https://pubmed.ncbi.nlm.nih.gov/29103582/

360. Oh, HS, Ha, J, Kim, HI, Kim, TH, Kim, WG, Lim, DJ, et.al. Active Surveillance of Low-Risk Papillary Thyroid Microcarcinoma: A Multi-Center Cohort Study in Korea., Thyroid, 2018. 28 (12)(12): p. 1587-1594., https://pubmed.ncbi.nlm.nih.gov/30226447/

361. Sugitani, I, Ito, Y, Miyauchi, A, Imai, T, Suzuki, S, Active Surveillance Versus Immediate Surgery: Questionnaire Survey on the Current Treatment Strategy for Adult Patients with Low-Risk Papillary Thyroid Microcarcinoma in Japan., Thyroid, 2019. 29 (11)(11): p. 1563-1571., https://pubmed.ncbi.nlm.nih.gov/31441377/

362. Jeon, MJ, Kim, WG, Kwon, H, Kim, M, Park, S, Oh, HS, et.al. Clinical outcomes after delayed thyroid surgery in patients with papillary thyroid microcarcinoma., Eur J Endocrinol, 2017. 177 (1)(1): p. 25-31., https://pubmed.ncbi.nlm.nih.gov/28432268/

363. Vuong, HG, Altibi, AMA, Duong, UNP, Hassell, L, Prognostic implication of BRAF and TERT promoter mutation combination in papillary thyroid carcinoma-A meta-analysis., Clin Endocrinol (Oxf), 2017. 87 (5)(5): p. 411-417., https://pubmed.ncbi.nlm.nih.gov/28666074/

364. Ng, SC, Kuo, SF, Chen, ST, Hsueh, C, Huang, BY, Lin, JD, Therapeutic Outcomes of Patients with Multifocal Papillary Thyroid Microcarcinomas and Larger Tumors., Int J Endocrinol, 2017. 2017 (): p. 4208178., https://pubmed.ncbi.nlm.nih.gov/28642790/

365. Chien, MN, Yang, PS, Lee, JJ, Wang, TY, Hsu, YC, Cheng, SP, Recurrence-associated genes in papillary thyroid cancer: An analysis of data from The Cancer Genome Atlas., Surgery, 2017. 161 (6)(6): p. 1642-1650., https://pubmed.ncbi.nlm.nih.gov/28237646/

366. Song, JY, Sun, SR, Dong, F, Huang, T, Wu, B, Zhou, J, Predictive Value of BRAF, Curr Med Sci, 2018. 38 (5)(5): p. 785-797., https://pubmed.ncbi.nlm.nih.gov/30341513/

367. Tong, M, Li, S, Li, Y, Li, Y, Feng, Y, Che, Y, Efficacy and safety of radiofrequency, microwave and laser ablation for treating papillary thyroid microcarcinoma: a systematic review and meta-analysis., Int J Hyperthermia, 2019. 36 (1)(1): p. 1278-1286., https://pubmed.ncbi.nlm.nih.gov/31826684/

368. Chen, J, Cao, J, Qiu, F, Huang, P, The Efficacy and The Safety of Ultrasound-guided Ablation Therapy for Treating Papillary Thyroid Microcarcinoma., J Cancer, 2019. 10 (21)(21): p. 5272-5282., https://pubmed.ncbi.nlm.nih.gov/31602278/

369. Liu, Z, Zhao, Q, Liu, C, Zeng, W, Ming, J, Chen, C, et.al. Is biopsy enough for papillary thyroid microcarcinoma?: An analysis of the SEER database 2004 to 2013 with propensity score matching., Medicine (Baltimore), 2018. 97 (31)(31): p. e11791., https://pubmed.ncbi.nlm.nih.gov/30075609/

370. Chan, S, Karamali, K, Kolodziejczyk, A, Oikonomou, G, Watkinson, J, Paleri, V, et.al. Systematic Review of Recurrence Rate after Hemithyroidectomy for Low-Risk Well-Differentiated Thyroid Cancer., Eur Thyroid J, 2020. 9 (2)(2): p. 73-84., https://pubmed.ncbi.nlm.nih.gov/32257956/

371. Adam, MA, Thomas, S, Hyslop, T, Scheri, RP, Roman, SA, Sosa, JA, Exploring the Relationship Between Patient Age and Cancer-Specific Survival in Papillary Thyroid Cancer: Rethinking Current Staging Systems., J Clin Oncol, 2016. 34 (36)(36): p. 4415-4420., https://pubmed.ncbi.nlm.nih.gov/27998233/

372. Dal Maso, L, Tavilla, A, Pacini, F, Serraino, D, van Dijk, BAC, Chirlaque, MD, et.al. Survival of 86,690 patients with thyroid cancer: A population-based study in 29 European countries from EUROCARE-5., Eur J Cancer, 2017. 77 (): p. 140-152., https://pubmed.ncbi.nlm.nih.gov/28410490/

373. Passler, C, Scheuba, C, Asari, R, Kaczirek, K, Kaserer, K, Niederle, B, Importance of tumour size in papillary and follicular thyroid cancer., Br J Surg, 2005. 92 (2)(2): p. 184-9., https://pubmed.ncbi.nlm.nih.gov/15685703/

374. Noguchi, S, Yamashita, H, Uchino, S, Watanabe, S, Papillary microcarcinoma., World J Surg, 2008. 32 (5)(5): p. 747-53., https://pubmed.ncbi.nlm.nih.gov/18264828/

375. Kim, SK, Park, I, Woo, JW, Lee, JH, Choe, JH, Kim, JH, et.al. Total thyroidectomy versus lobectomy in conventional papillary thyroid microcarcinoma: Analysis of 8,676 patients at a single institution., Surgery, 2017. 161 (2)(2): p. 485-492., https://pubmed.ncbi.nlm.nih.gov/27593085/

376. Kwon, H, Jeon, MJ, Kim, WG, Park, S, Kim, M, Song, DE, et.al. A comparison of lobectomy and total thyroidectomy in patients with papillary thyroid microcarcinoma: a retrospective individual risk factor-matched cohort study., Eur J Endocrinol, 2017. 176 (4)(4): p. 371-378., https://pubmed.ncbi.nlm.nih.gov/28089996/

377. Wu, ZG, Yan, XQ, Su, RS, Ma, ZS, Xie, BJ, Cao, FL, How Many Contralateral Carcinomas in Patients with Unilateral Papillary Thyroid Microcarcinoma are Preoperatively Misdiagnosed as Benign?, World J Surg, 2017. 41 (1)(1): p. 129-135., https://pubmed.ncbi.nlm.nih.gov/27541032/

378. Sullivan, MC, Graham, PH, Alexander, EK, Ruan, DT, Nehs, MA, Gawande, AA, et.al. Prevalence of Contralateral Tumors in Patients with Follicular Variant of Papillary Thyroid Cancer., J Am Coll Surg, 2017. 224 (6)(6): p. 1021-1027., https://pubmed.ncbi.nlm.nih.gov/28017809/

379. Ding, Y, Mao, Z, Ruan, J, Su, X, Li, L, Fahey, TJ, et.al. Nomogram-Based New Recurrence Predicting System in Early-Stage Papillary Thyroid Cancer., Int J Endocrinol, 2019. 2019 (): p. 1029092., https://pubmed.ncbi.nlm.nih.gov/31582973/

380. Wang, F, Yu, X, Shen, X, Zhu, G, Huang, Y, Liu, R, et.al. The Prognostic Value of Tumor Multifocality in Clinical Outcomes of Papillary Thyroid Cancer., J Clin Endocrinol Metab, 2017. 102 (9)(9): p. 3241-3250., https://pubmed.ncbi.nlm.nih.gov/28582521/

381. Dong, S, Xie, XJ, Xia, Q, Wu, YJ, Indicators of multifocality in papillary thyroid carcinoma concurrent with Hashimoto's thyroiditis., Am J Cancer Res, 2019. 9 (8)(8): p. 1786-1795., https://pubmed.ncbi.nlm.nih.gov/31497359/

382. Kim, KJ, Kim, SG, Tan, J, Shen, X, Viola, D, Elisei, R, et.al. BRAF V600E status may facilitate decision-making on active surveillance of low-risk papillary thyroid microcarcinoma., Eur J Cancer, 2020. 124 (): p. 161-169., https://pubmed.ncbi.nlm.nih.gov/31790974/

383. Joseph, KR, Edirimanne, S, Eslick, GD, Multifocality as a prognostic factor in thyroid cancer: A meta-analysis., Int J Surg, 2018. 50 (): p. 121-125., https://pubmed.ncbi.nlm.nih.gov/29337178/

384. Liu, LS, Liang, J, Li, JH, Liu, X, Jiang, L, Long, JX, et.al. The incidence and risk factors for central lymph node metastasis in cN0 papillary thyroid microcarcinoma: a meta-analysis., Eur Arch Otorhinolaryngol, 2017. 274 (3)(3): p. 1327-1338., https://pubmed.ncbi.nlm.nih.gov/27645473/

385. Liu, W, Cheng, R, Su, Y, Diao, C, Qian, J, Zhang, J, et.al. Risk factors of central lymph node metastasis of papillary thyroid carcinoma: A single-center retrospective analysis of 3273 cases., Medicine (Baltimore), 2017. 96 (43)(43): p. e8365., https://pubmed.ncbi.nlm.nih.gov/29069024/

386. Sun, W., Lan, X., Zhang, H., Dong, W., Wang, Z., He, L., et.al. Risk Factors for Central Lymph Node Metastasis in CN0 Papillary Thyroid Carcinoma: A Systematic Review and Meta-Analysis, PLoS One, 2015. 10(10): p. e0139021., https://pubmed.ncbi.nlm.nih.gov/26431346/

387. Wang, Y, Guan, Q, Xiang, J, Nomogram for predicting central lymph node metastasis in papillary thyroid microcarcinoma: A retrospective cohort study of 8668 patients., Int J Surg, 2018. 55 (): p. 98-102., https://pubmed.ncbi.nlm.nih.gov/29803769/

388. Xu, Y, Xu, L, Wang, J, Clinical predictors of lymph node metastasis and survival rate in papillary thyroid microcarcinoma: analysis of 3607 patients at a single institution., J Surg Res, 2018. 221 (): p. 128-134., https://pubmed.ncbi.nlm.nih.gov/29229118/

389. Chen, BD, Zhang, Z, Wang, KK, Shang, MY, Zhao, SS, Ding, WB, et.al. A multivariable model of BRAF, Cancer Manag Res, 2019. 11 (): p. 7211-7217., https://pubmed.ncbi.nlm.nih.gov/31440100/

390. Liu, Z., Wang, L., Yi, P., Wang, C. Y., Huang, T., Risk factors for central lymph node metastasis of patients with papillary thyroid microcarcinoma: a meta-analysis, Int J Clin Exp Pathol, 2014. 7(3): p. 932-7., https://pubmed.ncbi.nlm.nih.gov/24696711/

391. Qu, N, Zhang, L, Ji, QH, Chen, JY, Zhu, YX, Cao, YM, et.al. Risk Factors for Central Compartment Lymph Node Metastasis in Papillary Thyroid Microcarcinoma: A Meta-Analysis., World J Surg, 2015. 39 (10)(10): p. 2459-70., https://pubmed.ncbi.nlm.nih.gov/26099728/

392. Slijepcevic, N, Zivaljevic, V, Diklic, A, Jovanovic, M, Oluic, B, Paunovic, I, Risk factors associated with intrathyroid extension of thyroid microcarcinomas., Langenbecks Arch Surg, 2018. 403 (5)(5): p. 615-622., https://pubmed.ncbi.nlm.nih.gov/29770856/

393. Wei, X, Wang, M, Wang, X, Zheng, X, Li, Y, Pan, Y, et.al. Prediction of cervical lymph node metastases in papillary thyroid microcarcinoma by sonographic features of the primary site., Cancer Biol Med, 2019. 16 (3)(3): p. 587-594., https://pubmed.ncbi.nlm.nih.gov/31565487/

394. Feng, J, Gan, X, Shen, F, Cai, W, Xu, B, The role of two tumor foci for predicting central lymph node metastasis in papillary thyroid carcinoma: A meta-analysis., Int J Surg, 2018. 52 (): p. 166-170., https://pubmed.ncbi.nlm.nih.gov/29481991/

395. Zheng, W, Wang, K, Wu, J, Wang, W, Shang, J, Multifocality is associated with central neck lymph node metastases in papillary thyroid microcarcinoma., Cancer Manag Res, 2018. 10 (): p. 1527-1533., https://pubmed.ncbi.nlm.nih.gov/29942154/

396. Zhao, Q, Ming, J, Liu, C, Shi, L, Xu, X, Nie, X, et.al. Multifocality and total tumor diameter predict central neck lymph node metastases in papillary thyroid microcarcinoma., Ann Surg Oncol, 2013. 20 (3)(3): p. 746-52., https://pubmed.ncbi.nlm.nih.gov/22972508/

397. Hu, JQ, Wen, D, Ma, B, Zhang, TT, Liao, T, Shi, X, et.al. The extent of lymph node yield in central neck dissection can be affected by preoperative and intraoperative assessment and alter the prognosis of papillary thyroid carcinoma., Cancer Med, 2020. 9 (3)(3): p. 1017-1024., https://pubmed.ncbi.nlm.nih.gov/31854077/

398. Ito, Y, Miyauchi, A, Kudo, T, Kihara, M, Fukushima, M, Miya, A, The Effectiveness of Prophylactic Modified Neck Dissection for Reducing the Development of Lymph Node Recurrence of Papillary Thyroid Carcinoma., World J Surg, 2017. 41 (9)(9): p. 2283-2289., https://pubmed.ncbi.nlm.nih.gov/28429089/

399. Qiu, Y, Fei, Y, Liu, J, Liu, C, He, X, Zhu, N, et.al. Prevalence, Risk Factors And Location Of Skip Metastasis In Papillary Thyroid Carcinoma: A Systematic Review And Meta-Analysis., Cancer Manag Res, 2019. 11 (): p. 8721-8730., https://pubmed.ncbi.nlm.nih.gov/31576174/

400. Shan, CX, Zhang, W, Jiang, DZ, Zheng, XM, Liu, S, Qiu, M, Routine central neck dissection in differentiated thyroid carcinoma: a systematic review and meta-analysis., Laryngoscope, 2012. 122 (4)(4): p. 797-804., https://pubmed.ncbi.nlm.nih.gov/22294492/

401. Hughes, DT, Rosen, JE, Evans, DB, Grubbs, E, Wang, TS, Solórzano, CC, Prophylactic Central Compartment Neck Dissection in Papillary Thyroid Cancer and Effect on Locoregional Recurrence., Ann Surg Oncol, 2018. 25 (9)(9): p. 2526-2534., https://pubmed.ncbi.nlm.nih.gov/29786126/

402. Song, E, Han, M, Oh, HS, Kim, WW, Jeon, MJ, Lee, YM, et.al. Lobectomy Is Feasible for 1-4 cm Papillary Thyroid Carcinomas: A 10-Year Propensity Score Matched-Pair Analysis on Recurrence., Thyroid, 2019. 29 (1)(1): p. 64-70., https://pubmed.ncbi.nlm.nih.gov/30375260/

403. Vargas-Pinto, S, Romero Arenas, MA, Lobectomy Compared to Total Thyroidectomy for Low-Risk Papillary Thyroid Cancer: A Systematic Review., J Surg Res, 2019. 242 (): p. 244-251., https://pubmed.ncbi.nlm.nih.gov/31103828/

404. Adam, MA, Pura, J, Goffredo, P, Dinan, MA, Hyslop, T, Reed, SD, et.al. Impact of extent of surgery on survival for papillary thyroid cancer patients younger than 45 years., J Clin Endocrinol Metab, 2015. 100 (1)(1): p. 115-21., https://pubmed.ncbi.nlm.nih.gov/25337927/

405. Kim, MJ, Lee, MC, Lee, GH, Choi, HS, Cho, SW, Kim, SJ, et.al. Extent of surgery did not affect recurrence during 7-years follow-up in papillary thyroid cancer sized 1-4 cm: Preliminary results., Clin Endocrinol (Oxf), 2017. 87 (1)(1): p. 80-86., https://pubmed.ncbi.nlm.nih.gov/28338234/

406. Machens, Andreas, Dralle, Henning, Prediction of Mediastinal Lymph Node Metastasis in Papillary Thyroid Cancer, 2009. 16(1): p. 171 - 176., https://doi.org/10.1245/s10434-008-0201-y

407. Giordano, D, Valcavi, R, Thompson, GB, Pedroni, C, Renna, L, Gradoni, P, et.al. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature., Thyroid, 2012. 22 (9)(9): p. 911-7., https://pubmed.ncbi.nlm.nih.gov/22827494/

408. Moo, TA, Umunna, B, Kato, M, Butriago, D, Kundel, A, Lee, JA, et.al. Ipsilateral versus bilateral central neck lymph node dissection in papillary thyroid carcinoma., Ann Surg, 2009. 250 (3)(3): p. 403-8., https://pubmed.ncbi.nlm.nih.gov/19661784/

409. Sadowski, BM, Snyder, SK, Lairmore, TC, Routine bilateral central lymph node clearance for papillary thyroid cancer., Surgery, 2009. 146 (4)(4): p. 696-703; discussion 703-5., https://pubmed.ncbi.nlm.nih.gov/19789029/

410. Yan, B, Hou, Y, Chen, D, He, J, Jiang, Y, Risk factors for contralateral central lymph node metastasis in unilateral cN0 papillary thyroid carcinoma: A meta-analysis., Int J Surg, 2018. 59 (): p. 90-98., https://pubmed.ncbi.nlm.nih.gov/30342280/

411. Sun, W, Zheng, B, Wang, Z, Dong, W, Qin, Y, Zhang, H, Meta-analysis of risk factors for CCLNM in patients with unilateral cN0 PTC., Endocr Connect, 2020. 9 (5)(5): p. 387-395., https://pubmed.ncbi.nlm.nih.gov/32272445/

412. Sanabria, A, Betancourt-Agüero, C, Sánchez-Delgado, JG, García-Lozano, C, Prophylactic Central Neck Lymph Node Dissection in Low-risk Thyroid Carcinoma Patients Does Not Decrease the Incidence of Locoregional Recurrence: A Meta-analysis of Randomized Trials., Ann Surg, 2022. 276 (1)(1): p. 66-73., https://pubmed.ncbi.nlm.nih.gov/35129470/

413. Ji, YB, Lee, DW, Song, CM, Kim, KR, Park, CW, Tae, K, Accuracy of intraoperative determination of central node metastasis by the surgeon in papillary thyroid carcinoma., Otolaryngol Head Neck Surg, 2014. 150 (4)(4): p. 542-7., https://pubmed.ncbi.nlm.nih.gov/24429357/

414. Machens, A, Hauptmann, S, Dralle, H, Lymph node dissection in the lateral neck for completion in central node-positive papillary thyroid cancer., Surgery, 2009. 145 (2)(2): p. 176-81., https://pubmed.ncbi.nlm.nih.gov/19167972/

415. Chung, YS, Kim, JY, Bae, JS, Song, BJ, Kim, JS, Jeon, HM, et.al. Lateral lymph node metastasis in papillary thyroid carcinoma: results of therapeutic lymph node dissection., Thyroid, 2009. 19 (3)(3): p. 241-6., https://pubmed.ncbi.nlm.nih.gov/19265495/

416. Cooper, DS, Tufano, RP, Prophylactic central neck dissection in differentiated thyroid cancer: a procedure in search of an indication., Thyroid, 2012. 22 (4)(4): p. 341-3., https://pubmed.ncbi.nlm.nih.gov/22458971/

417. Dralle, H, Lorenz, K, Schabram, P, Musholt, TJ, Dotzenrath, C, Goretzki, PE, et.al. [Intraoperative neuromonitoring in thyroid surgery. Recommendations of the Surgical Working Group for Endocrinology]., Chirurg, 2013. 84 (12)(12): p. 1049-56., https://pubmed.ncbi.nlm.nih.gov/24337220/

418. Ito, Y, Tomoda, C, Uruno, T, Takamura, Y, Miya, A, Kobayashi, K, et.al. Ultrasonographically and anatomopathologically detectable node metastases in the lateral compartment as indicators of

worse relapse-free survival in patients with papillary thyroid carcinoma., World J Surg, 2005. 29 (7)(7): p. 917-20., https://pubmed.ncbi.nlm.nih.gov/15951927/

419. Ito, Y, Higashiyama, T, Takamura, Y, Miya, A, Kobayashi, K, Matsuzuka, F, et.al. Risk factors for recurrence to the lymph node in papillary thyroid carcinoma patients without preoperatively detectable lateral node metastasis: validity of prophylactic modified radical neck dissection., World J Surg, 2007. 31 (11)(11): p. 2085-91., https://pubmed.ncbi.nlm.nih.gov/17885787/

420. Caron, NR, Tan, YY, Ogilvie, JB, Triponez, F, Reiff, ES, Kebebew, E, et.al. Selective modified radical neck dissection for papillary thyroid cancer-is level I, II and V dissection always necessary?, World J Surg, 2006. 30 (5)(5): p. 833-40., https://pubmed.ncbi.nlm.nih.gov/16555024/

421. Lim, YC, Choi, EC, Yoon, YH, Koo, BS, Occult lymph node metastases in neck level V in papillary thyroid carcinoma., Surgery, 2010. 147 (2)(2): p. 241-5., https://pubmed.ncbi.nlm.nih.gov/19910012/

422. van Wilgen, CP, Dijkstra, PU, van der Laan, BF, Plukker, JT, Roodenburg, JL, Shoulder complaints after nerve sparing neck dissections., Int J Oral Maxillofac Surg, 2004. 33 (3)(3): p. 253-7., https://pubmed.ncbi.nlm.nih.gov/15287308/

423. Kupferman, ME, Patterson, DM, Mandel, SJ, LiVolsi, V, Weber, RS, Safety of modified radical neck dissection for differentiated thyroid carcinoma., Laryngoscope, 2004. 114 (3)(3): p. 403-6., https://pubmed.ncbi.nlm.nih.gov/15091209/

424. Roh, JL, Kim, DH, Park, CI, Prospective identification of chyle leakage in patients undergoing lateral neck dissection for metastatic thyroid cancer., Ann Surg Oncol, 2008. 15 (2)(2): p. 424-9., https://pubmed.ncbi.nlm.nih.gov/17999116/

425. Lorenz, K, Abuazab, M, Sekulla, C, Nguyen-Thanh, P, Brauckhoff, M, Dralle, H, Management of lymph fistulas in thyroid surgery., Langenbecks Arch Surg, 2010. 395 (7)(7): p. 911-7., https://pubmed.ncbi.nlm.nih.gov/20652586/

426. McGarvey, AC, Chiarelli, PE, Osmotherly, PG, Hoffman, GR, Physiotherapy for accessory nerve shoulder dysfunction following neck dissection surgery: a literature review., Head Neck, 2011. 33 (2)(2): p. 274-80., https://pubmed.ncbi.nlm.nih.gov/20222043/

427. Madenci, AL, Caragacianu, D, Boeckmann, JO, Stack, BC, Shin, JJ, Lateral neck dissection for well-differentiated thyroid carcinoma: a systematic review., Laryngoscope, 2014. 124 (7)(7): p. 1724-34., https://pubmed.ncbi.nlm.nih.gov/24390830/

428. Attard, A, Paladino, NC, Lo Monte, AI, Falco, N, Melfa, G, Rotolo, G, et.al. Skip metastases to lateral cervical lymph nodes in differentiated thyroid cancer: a systematic review., BMC Surg, 2019. 18 (Suppl 1)(Suppl 1): p. 112., https://pubmed.ncbi.nlm.nih.gov/31074393/

429. Wada, N, Masudo, K, Nakayama, H, Suganuma, N, Matsuzu, K, Hirakawa, S, et.al. Clinical outcomes in older or younger patients with papillary thyroid carcinoma: impact of lymphadenopathy and patient age., Eur J Surg Oncol, 2008. 34 (2)(2): p. 202-7., https://pubmed.ncbi.nlm.nih.gov/18023321/

430. Xiao, GZ, Gao, L, Central lymph node metastasis: is it a reliable indicator of lateral node involvement in papillary thyroid carcinoma?, World J Surg, 2010. 34 (2)(2): p. 237-41., https://pubmed.ncbi.nlm.nih.gov/20041247/

431. Park, JH, Lee, YS, Kim, BW, Chang, HS, Park, CS, Skip lateral neck node metastases in papillary thyroid carcinoma., World J Surg, 2012. 36 (4)(4): p. 743-7., https://pubmed.ncbi.nlm.nih.gov/22354485/

432. Xiang, D, Xie, L, Xu, Y, Li, Z, Hong, Y, Wang, P, Papillary thyroid microcarcinomas located at the middle part of the middle third of the thyroid gland correlates with the presence of neck metastasis., Surgery, 2015. 157 (3)(3): p. 526-33., https://pubmed.ncbi.nlm.nih.gov/25433730/

433. Zhao, H, Huang, T, Li, H, Risk factors for skip metastasis and lateral lymph node metastasis of papillary thyroid cancer., Surgery, 2019. 166 (1)(1): p. 55-60., https://pubmed.ncbi.nlm.nih.gov/30876667/

434. Zhang, C, Li, Y, Li, J, Chen, X, Total thyroidectomy versus lobectomy for papillary thyroid cancer: A systematic review and meta-analysis., Medicine (Baltimore), 2020. 99 (6)(6): p. e19073., https://pubmed.ncbi.nlm.nih.gov/32028431/

435. Zhan, X, Xue, S, Yin, Y, Chen, G, [Related factors on skip metastasis of neck lymph node in papillary thyroid carcinoma]., Zhonghua Wai Ke Za Zhi, 2017. 55 (8)(8): p. 599-602., https://pubmed.ncbi.nlm.nih.gov/28789510/

436. Ito, Y, Miyauchi, A, Lateral and mediastinal lymph node dissection in differentiated thyroid carcinoma: indications, benefits, and risks., World J Surg, 2007. 31 (5)(5): p. 905-15., https://pubmed.ncbi.nlm.nih.gov/17219265/

437. Kayser, C., Tittelbach-Helmrich, Dietlind, Meyer, Sebastian, Thomusch, Oliver, Indikation und Ausmaß der zervikalen Lymphadenektomie beim differenzierten Schilddrüsenkarzinom, 2010/08/01. 135:

438. Moritani, S, Impact of superior mediastinal metastasis on the prognosis of papillary thyroid carcinoma., Endocr J, 2016. 63 (4)(4): p. 349-57., https://pubmed.ncbi.nlm.nih.gov/26765269/

439. Gartland, RM, Lubitz, CC, Impact of Extent of Surgery on Tumor Recurrence and Survival for Papillary Thyroid Cancer Patients., Ann Surg Oncol, 2018. 25 (9)(9): p. 2520-2525., https://pubmed.ncbi.nlm.nih.gov/29855833/

440. Bilimoria, KY, Bentrem, DJ, Ko, CY, Stewart, AK, Winchester, DP, Talamonti, MS, et.al. Extent of surgery affects survival for papillary thyroid cancer., Ann Surg, 2007. 246 (3)(3): p. 375-81; discussion 381-4., https://pubmed.ncbi.nlm.nih.gov/17717441/

441. Rajjoub, SR, Yan, H, Calcatera, NA, Kuchta, K, Wang, CE, Lutfi, W, et.al. Thyroid lobectomy is not sufficient for T2 papillary thyroid cancers., Surgery, 2018. 163 (5)(5): p. 1134-1143., https://pubmed.ncbi.nlm.nih.gov/29426618/

442. Macedo, FI, Mittal, VK, Total thyroidectomy versus lobectomy as initial operation for small unilateral papillary thyroid carcinoma: A meta-analysis., Surg Oncol, 2015. 24 (2)(2): p. 117-22., https://pubmed.ncbi.nlm.nih.gov/25956302/

443. Glockzin, G, Hornung, M, Kienle, K, Thelen, K, Boin, M, Schreyer, AG, et.al. Completion thyroidectomy: effect of timing on clinical complications and oncologic outcome in patients with differentiated thyroid cancer., World J Surg, 2012. 36 (5)(5): p. 1168-73., https://pubmed.ncbi.nlm.nih.gov/22366982/

444. Sosa, JA, Bowman, HM, Tielsch, JM, Powe, NR, Gordon, TA, Udelsman, R, The importance of surgeon experience for clinical and economic outcomes from thyroidectomy., Ann Surg, 1998. 228 (3)(3): p. 320-30., https://pubmed.ncbi.nlm.nih.gov/9742915/

445. Sosa, JA, Mehta, PJ, Wang, TS, Boudourakis, L, Roman, SA, A population-based study of outcomes from thyroidectomy in aging Americans: at what cost?, J Am Coll Surg, 2008. 206 (6)(6): p. 1097-105., https://pubmed.ncbi.nlm.nih.gov/18501806/

446. Papaleontiou, M, Gauger, PG, Haymart, MR, REFERRAL OF OLDER THYROID CANCER PATIENTS TO A HIGH-VOLUME SURGEON: RESULTS OF A MULTIDISCIPLINARY PHYSICIAN SURVEY., Endocr Pract, 2017. 23 (7)(7): p. 808-815., https://pubmed.ncbi.nlm.nih.gov/28534681/

447. Youngwirth, LM, Adam, MA, Scheri, RP, Roman, SA, Sosa, JA, Patients Treated at Low-Volume Centers have Higher Rates of Incomplete Resection and Compromised Outcomes: Analysis of 31,129 Patients with Papillary Thyroid Cancer., Ann Surg Oncol, 2016. 23 (2)(2): p. 403-9., https://pubmed.ncbi.nlm.nih.gov/26416710/

448. Kim, MJ, Chung, WY, Yonsei Experience of 5000 Gasless Transaxillary Robotic Thyroidectomies: Reply., World J Surg, 2018. 42 (7)(7): p. 2281-2282., https://pubmed.ncbi.nlm.nih.gov/29362890/

449. Lorenz, K, Raffaeli, M, Barczyński, M, Lorente-Poch, L, Sancho, J, Volume, outcomes, and quality standards in thyroid surgery: an evidence-based analysis-European Society of Endocrine Surgeons (ESES) positional statement., Langenbecks Arch Surg, 2020. 405 (4)(4): p. 401-425., https://pubmed.ncbi.nlm.nih.gov/32524467/

450. Ito, Y, Tomoda, C, Uruno, T, Takamura, Y, Miya, A, Kobayashi, K, et.al. Prognostic significance of extrathyroid extension of papillary thyroid carcinoma: massive but not minimal extension affects the relapse-free survival., World J Surg, 2006. 30 (5)(5): p. 780-6., https://pubmed.ncbi.nlm.nih.gov/16411013/

451. Mercante, G, Frasoldati, A, Pedroni, C, Formisano, D, Renna, L, Piana, S, et.al. Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients., Thyroid, 2009. 19 (7)(7): p. 707-16., https://pubmed.ncbi.nlm.nih.gov/19348581/

452. Rivera, M, Ricarte-Filho, J, Tuttle, RM, Ganly, I, Shaha, A, Knauf, J, et.al. Molecular, morphologic, and outcome analysis of thyroid carcinomas according to degree of extrathyroid extension., Thyroid, 2010. 20 (10)(10): p. 1085-93., https://pubmed.ncbi.nlm.nih.gov/20860430/

453. Fukushima, M, Ito, Y, Hirokawa, M, Miya, A, Shimizu, K, Miyauchi, A, Prognostic impact of extrathyroid extension and clinical lymph node metastasis in papillary thyroid carcinoma depend on carcinoma size., World J Surg, 2010. 34 (12)(12): p. 3007-14., https://pubmed.ncbi.nlm.nih.gov/20824274/

454. Brauckhoff, M, Meinicke, A, Bilkenroth, U, Lorenz, K, Brauckhoff, K, Gimm, O, et.al. Long-term results and functional outcome after cervical evisceration in patients with thyroid cancer., Surgery, 2006. 140 (6)(6): p. 953-9., https://pubmed.ncbi.nlm.nih.gov/17188144/

455. Brauckhoff, M., Dralle, H., Zervikoviszerale Resektionen beim organüberschreitenden Schilddrüsenkarzinom, 2009. 80(2): p. 88 - 98., https://doi.org/10.1007/s00104-008-1610-y

456. Musholt, TJ, Musholt, PB, Behrend, M, Raab, R, Scheumann, GF, Klempnauer, J, Invasive differentiated thyroid carcinoma: tracheal resection and reconstruction procedures in the hands of the endocrine surgeon., Surgery, 1999. 126 (6)(6): p. 1078-87; discussion 1087-8., https://pubmed.ncbi.nlm.nih.gov/10598191/

457. Brauckhoff, M, Machens, A, Thanh, PN, Lorenz, K, Schmeil, A, Stratmann, M, et.al. Impact of extent of resection for thyroid cancer invading the aerodigestive tract on surgical morbidity, local recurrence, and cancer-specific survival., Surgery, 2010. 148 (6)(6): p. 1257-66., https://pubmed.ncbi.nlm.nih.gov/21134559/

458. Piazza, C, Del Bon, F, Barbieri, D, Grazioli, P, Paderno, A, Perotti, P, et.al. Tracheal and Crico-Tracheal Resection and Anastomosis for Malignancies Involving the Thyroid Gland and the Airway., Ann Otol Rhinol Laryngol, 2016. 125 (2)(2): p. 97-104., https://pubmed.ncbi.nlm.nih.gov/26296930/

459. Kim, H, Jung, HJ, Lee, SY, Kwon, TK, Kim, KH, Sung, MW, et.al. Prognostic factors of locally invasive well-differentiated thyroid carcinoma involving the trachea., Eur Arch Otorhinolaryngol, 2016. 273 (7)(7): p. 1919-26., https://pubmed.ncbi.nlm.nih.gov/26198285/

460. Nixon, IJ, Simo, R, Newbold, K, Rinaldo, A, Suarez, C, Kowalski, LP, et.al. Management of Invasive Differentiated Thyroid Cancer., Thyroid, 2016. 26 (9)(9): p. 1156-66., https://pubmed.ncbi.nlm.nih.gov/27480110/

461. Hotomi, M, Sugitani, I, Toda, K, Kawabata, K, Fujimoto, Y, A novel definition of extrathyroidal invasion for patients with papillary thyroid carcinoma for predicting prognosis., World J Surg, 2012. 36 (6)(6): p. 1231-40., https://pubmed.ncbi.nlm.nih.gov/22402972/

462. Francis, GL, Waguespack, SG, Bauer, AJ, Angelos, P, Benvenga, S, Cerutti, JM, et.al. Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer., Thyroid, 2015. 25 (7)(7): p. 716-59., https://pubmed.ncbi.nlm.nih.gov/25900731/

463. Baumgarten, H, Jenks, CM, Isaza, A, Bhatti, T, Mostoufi-Moab, S, Kazahaya, K, et.al. Bilateral papillary thyroid cancer in children: Risk factors and frequency of postoperative diagnosis., J Pediatr Surg, 2020. 55 (6)(6): p. 1117-1122., https://pubmed.ncbi.nlm.nih.gov/32171533/

464. Chen, J, Huang, N, Ji, Q, Wang, Y, Zhu, Y, Li, D, Multifocal papillary thyroid cancer in children and adolescents: 12-year experience in a single center., Gland Surg, 2019. 8 (5)(5): p. 507-515., https://pubmed.ncbi.nlm.nih.gov/31741881/

465. Hay, I. D., Gonzalez-Losada, T., Reinalda, M. S., Honetschlager, J. A., Richards, M. L., Thompson, G. B., Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008, World J Surg, 2010. 34(6): p. 1192-202., https://pubmed.ncbi.nlm.nih.gov/20087589/

466. Balachandar, S, La Quaglia, M, Tuttle, RM, Heller, G, Ghossein, RA, Sklar, CA, Pediatric Differentiated Thyroid Carcinoma of Follicular Cell Origin: Prognostic Significance of Histologic Subtypes., Thyroid, 2016. 26 (2)(2): p. 219-26., https://pubmed.ncbi.nlm.nih.gov/26854950/

467. Onder, S, Ozturk Sari, S, Yegen, G, Sormaz, IC, Yilmaz, I, Poyrazoglu, S, et.al. Classic Architecture with Multicentricity and Local Recurrence, and Absence of TERT Promoter Mutations are Correlates of BRAF (V600E) Harboring Pediatric Papillary Thyroid Carcinomas., Endocr Pathol, 2016. 27 (2)(2): p. 153-61., https://pubmed.ncbi.nlm.nih.gov/26951110/

468. Vassilopoulou-Sellin, R, Goepfert, H, Raney, B, Schultz, PN, Differentiated thyroid cancer in children and adolescents: clinical outcome and mortality after long-term follow-up., Head Neck, 1998. 20 (6)(6): p. 549-55., https://pubmed.ncbi.nlm.nih.gov/9702543/

469. Al-Qurayshi, Z, Hauch, A, Srivastav, S, Aslam, R, Friedlander, P, Kandil, E, A National Perspective of the Risk, Presentation, and Outcomes of Pediatric Thyroid Cancer., JAMA Otolaryngol Head Neck Surg, 2016. 142 (5)(5): p. 472-8., https://pubmed.ncbi.nlm.nih.gov/27031884/

470. Leboulleux, S, Baudin, E, Hartl, DW, Travagli, JP, Schlumberger, M, Follicular cell-derived thyroid cancer in children., Horm Res, 2005. 63 (3)(3): p. 145-51., https://pubmed.ncbi.nlm.nih.gov/15802922/

471. Machens, A, Lorenz, K, Nguyen Thanh, P, Brauckhoff, M, Dralle, H, Papillary thyroid cancer in children and adolescents does not differ in growth pattern and metastatic behavior., J Pediatr, 2010. 157 (4)(4): p. 648-52., https://pubmed.ncbi.nlm.nih.gov/20553841/

472. Machens, A, Elwerr, M, Thanh, PN, Lorenz, K, Schneider, R, Dralle, H, Impact of central node dissection on postoperative morbidity in pediatric patients with suspected or proven thyroid cancer., Surgery, 2016. 160 (2)(2): p. 484-92., https://pubmed.ncbi.nlm.nih.gov/27117577/

473. Farahati, J, Reiners, C, Demidchik, EP, Is the UICC/AJCC classification of primary tumor in childhood thyroid carcinoma valid?, J Nucl Med, 1999. 40 (12)(12): p. 2125., https://pubmed.ncbi.nlm.nih.gov/10616895/

474. Dralle, H, [Thyroid gland surgery: risk factor surgeon]., Chirurg, 2012. 83 (3)(3): p. 280-1., https://pubmed.ncbi.nlm.nih.gov/22349789/

475. Hundahl, SA, Cady, B, Cunningham, MP, Mazzaferri, E, McKee, RF, Rosai, J, et.al. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the united states during 1996. U.S. and German Thyroid Cancer Study Group. An American College of Surgeons Commission on Cancer Patient Care Evaluation study., Cancer, 2000. 89 (1)(1): p. 202-17., https://pubmed.ncbi.nlm.nih.gov/10897019/

476. DeLellis, RA., , Lloyd, RV.,, Heitz, PU.,, Eng, C., WHO Classification of tumors., in Pathology and Genetics of Tumors of Endocrine Organs., 2004, IARC Press: Lyon. p. 49 - 133.

477. Clerici, T, Kolb, W, Beutner, U, Bareck, E, Dotzenrath, C, Kull, C, et.al. Diagnosis and treatment of small follicular thyroid carcinomas., Br J Surg, 2010. 97 (6)(6): p. 839-44., https://pubmed.ncbi.nlm.nih.gov/20473996/

478. Asari, R, Koperek, O, Scheuba, C, Riss, P, Kaserer, K, Hoffmann, M, et.al. Follicular thyroid carcinoma in an iodine-replete endemic goiter region: a prospectively collected, retrospectively analyzed clinical trial., Ann Surg, 2009. 249 (6)(6): p. 1023-31., https://pubmed.ncbi.nlm.nih.gov/19474675/

479. Schmid, KW, Sheu, SY, Görges, R, Ensinger, C, Tötsch, M, [Thyroid tumors]., Pathologe, 2003. 24 (5)(5): p. 357-72., https://pubmed.ncbi.nlm.nih.gov/12961024/

480. LiVolsi, Virginia A, Papillary thyroid carcinoma: an update, 2011. 24(2): p. S1 - S9., https://doi.org/10.1038/modpathol.2010.129

481. Udelsman, R, Westra, WH, Donovan, PI, Sohn, TA, Cameron, JL, Randomized prospective evaluation of frozen-section analysis for follicular neoplasms of the thyroid., Ann Surg, 2001. 233 (5)(5): p. 716-22., https://pubmed.ncbi.nlm.nih.gov/11323510/

482. Miller, MC, Rubin, CJ, Cunnane, M, Bibbo, M, Miller, JL, Keane, WM, et.al. Intraoperative pathologic examination: cost effectiveness and clinical value in patients with cytologic diagnosis of cellular follicular thyroid lesion., Thyroid, 2007. 17 (6)(6): p. 557-65., https://pubmed.ncbi.nlm.nih.gov/17614777/

483. Basolo, F, Torregrossa, L, Giannini, R, Miccoli, M, Lupi, C, Sensi, E, et.al. Correlation between the BRAF V600E mutation and tumor invasiveness in papillary thyroid carcinomas smaller than 20 millimeters: analysis of 1060 cases., J Clin Endocrinol Metab, 2010. 95 (9)(9): p. 4197-205., https://pubmed.ncbi.nlm.nih.gov/20631031/

484. Lin, JD, Chao, TC, Hsueh, C, Clinical characteristics of poorly differentiated thyroid carcinomas compared with those of classical papillary thyroid carcinomas., Clin Endocrinol (Oxf), 2007. 66 (2)(2): p. 224-8., https://pubmed.ncbi.nlm.nih.gov/17223992/

485. Baloch, Z, LiVolsi, VA, Jain, P, Jain, R, Aljada, I, Mandel, S, et.al. Role of repeat fine-needle aspiration biopsy (FNAB) in the management of thyroid nodules., Diagn Cytopathol, 2003. 29 (4)(4): p. 203-6., https://pubmed.ncbi.nlm.nih.gov/14506672/

486. O'Neill, CJ, Bullock, M, Chou, A, Sidhu, SB, Delbridge, LW, Robinson, BG, et.al. BRAF(V600E) mutation is associated with an increased risk of nodal recurrence requiring reoperative surgery in patients with papillary thyroid cancer., Surgery, 2010. 148 (6)(6): p. 1139-45; discussion 1145-6., https://pubmed.ncbi.nlm.nih.gov/21134544/

487. Dionigi, G, Kraimps, JL, Schmid, KW, Hermann, M, Sheu-Grabellus, SY, De Wailly, P, et.al. Minimally invasive follicular thyroid cancer (MIFTC)--a consensus report of the European Society of Endocrine Surgeons (ESES)., Langenbecks Arch Surg, 2014. 399 (2)(2): p. 165-84., https://pubmed.ncbi.nlm.nih.gov/24233345/

488. Huang, CC, Hsueh, C, Liu, FH, Chao, TC, Lin, JD, Diagnostic and therapeutic strategies for minimally and widely invasive follicular thyroid carcinomas., Surg Oncol, 2011. 20 (1)(1): p. 1-6., https://pubmed.ncbi.nlm.nih.gov/19596568/

489. Sugino, K, Ito, K, Nagahama, M, Kitagawa, W, Shibuya, H, Ohkuwa, K, et.al. Prognosis and prognostic factors for distant metastases and tumor mortality in follicular thyroid carcinoma., Thyroid, 2011. 21 (7)(7): p. 751-7., https://pubmed.ncbi.nlm.nih.gov/21615311/

490. British Thyroid Association, Guidelines for the management of thyroid cancer., 2007., http://www.british-thyroid-association.org

491. Pacini, F, Schlumberger, M, Dralle, H, Elisei, R, Smit, JW, Wiersinga, W, European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium., Eur J Endocrinol, 2006. 154 (6)(6): p. 787-803., https://pubmed.ncbi.nlm.nih.gov/16728537/

492. Dutch Association of comprehensive cancer centres thyroid cancer, National evidence-based guideline., 2007. Version 1.0.:, http://www.oncoline.nl

493. Luster, M, Clarke, SE, Dietlein, M, Lassmann, M, Lind, P, Oyen, WJ, et.al. Guidelines for radioiodine therapy of differentiated thyroid cancer., Eur J Nucl Med Mol Imaging, 2008. 35 (10)(10): p. 1941-59., https://pubmed.ncbi.nlm.nih.gov/18670773/

494. Dietlein, M, Dressler, J, Eschner, W, Grünwald, F, Lassmann, M, Leisner, B, et.al. [Procedure guidelines for radioiodine therapy of differentiated thyroid cancer (version 3)]., Nuklearmedizin, 2007. 46 (5)(5): p. 213-9., https://pubmed.ncbi.nlm.nih.gov/17938757/

495. Takami, H, Ito, Y, Okamoto, T, Yoshida, A, Therapeutic strategy for differentiated thyroid carcinoma in Japan based on a newly established guideline managed by Japanese Society of Thyroid Surgeons and Japanese Association of Endocrine Surgeons., World J Surg, 2011. 35 (1)(1): p. 111-21., https://pubmed.ncbi.nlm.nih.gov/21042913/

496. Dralle, H, Lorenz, K, Machens, A, [Surgery of thyroid carcinoma]., Chirurg, 2009. 80 (11)(11): p. 1069-82; quiz 1083., https://pubmed.ncbi.nlm.nih.gov/19902289/

497. Reiners, C, Hänscheid, H, Luster, M, Lassmann, M, Verburg, FA, Radioiodine for remnant ablation and therapy of metastatic disease., Nat Rev Endocrinol, 2011. 7 (10)(10): p. 589-95., https://pubmed.ncbi.nlm.nih.gov/21826102/

498. Machens, A, Holzhausen, HJ, Lautenschläger, C, Thanh, PN, Dralle, H, Enhancement of lymph node metastasis and distant metastasis of thyroid carcinoma., Cancer, 2003. 98 (4)(4): p. 712-9., https://pubmed.ncbi.nlm.nih.gov/12910514/

499. Lopez-Penabad, L, Chiu, AC, Hoff, AO, Schultz, P, Gaztambide, S, Ordoñez, NG, et.al. Prognostic factors in patients with Hürthle cell neoplasms of the thyroid., Cancer, 2003. 97 (5)(5): p. 1186-94., https://pubmed.ncbi.nlm.nih.gov/12599224/

500. Carcangiu, ML, Hürthle cell carcinoma: clinic-pathological and biological aspects., Tumori, 2003. 89 (5)(5): p. 529-32., https://pubmed.ncbi.nlm.nih.gov/14870778/

501. Kushchayeva, Y, Duh, QY, Kebebew, E, Clark, OH, Prognostic indications for Hürthle cell cancer., World J Surg, 2004. 28 (12)(12): p. 1266-70., https://pubmed.ncbi.nlm.nih.gov/15517492/

502. Carling, T, Udelsman, R, Follicular neoplasms of the thyroid: what to recommend., Thyroid, 2005. 15 (6)(6): p. 583-7., https://pubmed.ncbi.nlm.nih.gov/16029125/

503. Besic, N, Hocevar, M, Zgajnar, J, Petric, R, Pilko, G, Aggressiveness of therapy and prognosis of patients with Hürthle cell papillary thyroid carcinoma., Thyroid, 2006. 16 (1)(1): p. 67-72., https://pubmed.ncbi.nlm.nih.gov/16487016/

504. Montone, KT, Baloch, ZW, LiVolsi, VA, The thyroid Hürthle (oncocytic) cell and its associated pathologic conditions: a surgical pathology and cytopathology review., Arch Pathol Lab Med, 2008. 132 (8)(8): p. 1241-50., https://pubmed.ncbi.nlm.nih.gov/18684023/

505. Guerrero, MA, Suh, I, Vriens, MR, Shen, WT, Gosnell, J, Kebebew, E, et.al. Age and tumor size predicts lymph node involvement in Hürthle Cell Carcinoma., J Cancer, 2010. 1 (): p. 23-6., https://pubmed.ncbi.nlm.nih.gov/20842220/

506. Volante, M, Landolfi, S, Chiusa, L, Palestini, N, Motta, M, Codegone, A, et.al. Poorly differentiated carcinomas of the thyroid with trabecular, insular, and solid patterns: a clinicopathologic study of 183 patients., Cancer, 2004. 100 (5)(5): p. 950-7., https://pubmed.ncbi.nlm.nih.gov/14983490/

507. Akaishi, J, Kondo, T, Sugino, K, Ogimi, Y, Masaki, C, Hames, KY, et.al. Prognostic Impact of the Turin Criteria in Poorly Differentiated Thyroid Carcinoma., World J Surg, 2019. 43 (9)(9): p. 2235-2244., https://pubmed.ncbi.nlm.nih.gov/31098668/

508. Volante, M, Papotti, M, Poorly differentiated thyroid carcinoma: 5 years after the 2004 WHO classification of endocrine tumours., Endocr Pathol, 2010. 21 (1)(1): p. 1-6., https://pubmed.ncbi.nlm.nih.gov/19960273/

509. Hiltzik, D., Carlson, D. L., Tuttle, R. M., Chuai, S., Ishill, N., Shaha, A., et.al. Poorly differentiated thyroid carcinomas defined on the basis of mitosis and necrosis: a clinicopathologic study of 58 patients, Cancer, 2006. 106(6): p. 1286-95., https://pubmed.ncbi.nlm.nih.gov/16470605/

510. Wong, KS, Lorch, JH, Alexander, EK, Marqusee, E, Cho, NL, Nehs, MA, et.al. Prognostic Significance of Extent of Invasion in Poorly Differentiated Thyroid Carcinoma., Thyroid, 2019. 29 (9)(9): p. 1255-1261., https://pubmed.ncbi.nlm.nih.gov/31397224/

511. Lam, KY, Lo, CY, Chan, KW, Wan, KY, Insular and anaplastic carcinoma of the thyroid: a 45-year comparative study at a single institution and a review of the significance of p53 and p21., Ann Surg, 2000. 231 (3)(3): p. 329-38., https://pubmed.ncbi.nlm.nih.gov/10714625/

512. Dettmer, M, Schmitt, A, Steinert, H, Haldemann, A, Meili, A, Moch, H, et.al. Poorly differentiated thyroid carcinomas: how much poorly differentiated is needed?, Am J Surg Pathol, 2011. 35 (12)(12): p. 1866-72., https://pubmed.ncbi.nlm.nih.gov/21989341/

513. Chao, T. C., Lin, J. D., Chen, M. F., Insular carcinoma: infrequent subtype of thyroid cancer with aggressive clinical course, World J Surg, 2004. 28(4): p. 393-6., https://pubmed.ncbi.nlm.nih.gov/14994145/

514. Patel, KN, Shaha, AR, Poorly differentiated and anaplastic thyroid cancer., Cancer Control, 2006. 13 (2)(2): p. 119-28., https://pubmed.ncbi.nlm.nih.gov/16735986/

515. Jung, TS, Kim, TY, Kim, KW, Oh, YL, Park, DJ, Cho, BY, et.al. Clinical features and prognostic factors for survival in patients with poorly differentiated thyroid carcinoma and comparison to the patients with the aggressive variants of papillary thyroid carcinoma., Endocr J, 2007. 54 (2)(2): p. 265-74., https://pubmed.ncbi.nlm.nih.gov/17379963/

516. Chambers, AJ., , Pasieka, JL., Poorly differentiated and undifferentiated thyroid cancern, in In: Endocrine Surgery, 2009, Springer: London. p. 121 - 136.

517. Sanders, EM, LiVolsi, VA, Brierley, J, Shin, J, Randolph, GW, An evidence-based review of poorly differentiated thyroid cancer., World J Surg, 2007. 31 (5)(5): p. 934-45., https://pubmed.ncbi.nlm.nih.gov/17431717/

518. Hescot, S, Al Ghuzlan, A, Henry, T, Sheikh-Alard, H, Lamartina, L, Borget, I, et.al. Prognostic of recurrence and survival in poorly differentiated thyroid cancer., Endocr Relat Cancer, 2022. 29 (11)(11): p. 625-634., https://pubmed.ncbi.nlm.nih.gov/36040800/

519. Walczyk, A, Kopczyński, J, Gąsior-Perczak, D, Pałyga, I, Kowalik, A, Chrapek, M, et.al. Poorly differentiated thyroid cancer in the context of the revised 2015 American Thyroid Association Guidelines and the Updated American Joint Committee on Cancer/Tumor-Node-Metastasis Staging System (eighth edition)., Clin Endocrinol (Oxf), 2019. 91 (2)(2): p. 331-339., https://pubmed.ncbi.nlm.nih.gov/30525210/

520. Walczyk, A, Kopczyński, J, Gąsior-Perczak, D, Pałyga, I, Kowalik, A, Chrapek, M, et.al. Histopathology and immunohistochemistry as prognostic factors for poorly differentiated thyroid cancer in a series of Polish patients., PLoS One, 2020. 15 (2)(2): p. e0229264., https://pubmed.ncbi.nlm.nih.gov/32092093/

521. de la Fouchardière, C, Decaussin-Petrucci, M, Berthiller, J, Descotes, F, Lopez, J, Lifante, JC, et.al. Predictive factors of outcome in poorly differentiated thyroid carcinomas., Eur J Cancer, 2018. 92 (): p. 40-47., https://pubmed.ncbi.nlm.nih.gov/29413688/

522. Ho, AS, Luu, M, Barrios, L, Chen, I, Melany, M, Ali, N, et.al. Incidence and Mortality Risk Spectrum Across Aggressive Variants of Papillary Thyroid Carcinoma., JAMA Oncol, 2020. 6 (5)(5): p. 706-713., https://pubmed.ncbi.nlm.nih.gov/32134428/

523. Dralle, H, Sekulla, C, Haerting, J, Timmermann, W, Neumann, HJ, Kruse, E, et.al. Risk factors of paralysis and functional outcome after recurrent laryngeal nerve monitoring in thyroid surgery., Surgery, 2004. 136 (6)(6): p. 1310-22., https://pubmed.ncbi.nlm.nih.gov/15657592/

524. Maneck, M, Dotzenrath, C, Dralle, H, Fahlenbrach, C, Paschke, R, Steinmüller, T, et.al. [Complications after thyroid gland operations in Germany : A routine data analysis of 66,902 AOK patients]., Chirurg, 2017. 88 (1)(1): p. 50-57., https://pubmed.ncbi.nlm.nih.gov/27510155/

525. Adam, MA, Thomas, S, Youngwirth, L, Hyslop, T, Reed, SD, Scheri, RP, et.al. Is There a Minimum Number of Thyroidectomies a Surgeon Should Perform to Optimize Patient Outcomes?, Ann Surg, 2017. 265 (2)(2): p. 402-407., https://pubmed.ncbi.nlm.nih.gov/28059969/

526. Godballe, C, Madsen, AR, Sørensen, CH, Schytte, S, Trolle, W, Helweg-Larsen, J, et.al. Risk factors for recurrent nerve palsy after thyroid surgery: a national study of patients treated at Danish departments of ENT Head and Neck Surgery., Eur Arch Otorhinolaryngol, 2014. 271 (8)(8): p. 2267-76., https://pubmed.ncbi.nlm.nih.gov/24132654/

527. Hauch, A, Al-Qurayshi, Z, Friedlander, P, Kandil, E, Association of socioeconomic status, race, and ethnicity with outcomes of patients undergoing thyroid surgery., JAMA Otolaryngol Head Neck Surg, 2014. 140 (12)(12): p. 1173-83., https://pubmed.ncbi.nlm.nih.gov/25187970/

528. Maneck, M, Dotzenrath, C, Dralle, H, Fahlenbrach, C, Steinmüller, T, Simon, D, et.al. [Case volume and complications after thyroid gland surgery in Germany: an analysis of routine data from 48,387 AOK patients]., Chirurg, 2021. 92 (1)(1): p. 40-48., https://pubmed.ncbi.nlm.nih.gov/32430544/

529. Cirocchi, R, Arezzo, A, D'Andrea, V, Abraha, I, Popivanov, GI, Avenia, N, et.al. Intraoperative neuromonitoring versus visual nerve identification for prevention of recurrent laryngeal nerve injury in adults undergoing thyroid surgery., Cochrane Database Syst Rev, 2019. 1 (1)(1): p. CD012483., https://pubmed.ncbi.nlm.nih.gov/30659577/

530. Justiz, Bundesministerium der, Gesetz zum Schutz vor der schädlichen Wirkung ionisierender Strahlung (Strahlenschutzgesetz - StrlSchG). Strahlenschutzgesetz vom 27. Juni 2017 (BGBl. I S. 1966), das zuletzt durch die Bekanntmachung vom 3. Januar 2022 (BGBl. I S. 15) geändert worden ist, 2017.

531. Justiz, Bundesministerium der, Verordnung zur weiteren Modernisierung des Strahlenschutzrechts, 2018.

532. Strahlenschutzkommission, Therapeutische Verfahren in der Nuklearmedizin, 2022.

533. Eilsberger, F., Kreissl, M. C., Luster, M., Pfestroff, A., [Therapy concepts for thyroid carcinoma], Nuklearmedizin, 2022. 61(3): p. 223-230., https://pubmed.ncbi.nlm.nih.gov/34644802/

534. Krajewska, J., Jarzab, M., Kukulska, A., Czarniecka, A., Roskosz, J., Puch, Z., et.al. Postoperative Radioiodine Treatment within 9 Months from Diagnosis Significantly Reduces the Risk of Relapse in Low-Risk Differentiated Thyroid Carcinoma, Nucl Med Mol Imaging, 2019. 53(5): p. 320-327.

535. Yu, F., Li, X., Ji, Y., Tan, J., Zhang, G., Wang, P., et.al. Delayed Initial Radioiodine Adjuvant Therapy Does Affect Biochemical Response in Intermediate- to High-Risk Differentiated Thyroid Cancer, Front Endocrinol (Lausanne), 2021. 12: p. 743310., https://pubmed.ncbi.nlm.nih.gov/34858329/

536. Schmid, K. W., Synoracki, S., Dralle, H., Wittekind, C., [Proposal for an extended pTNM classification of thyroid carcinoma : Commentary on deficits of the 8th edition of the TNM classification (German version)], Pathologe, 2018. 39(1): p. 49-56.

537. Schmid, K. W., Synoracki, S., Dralle, H., Wittekind, C., Proposal for an extended pTNM classification of thyroid carcinoma, Der Pathologe, 2019. 40(1): p. 18-24., https://doi.org/10.1007/s00292-018-0418-x

538. Tuttle, RM, Tala, H, Shah, J, Leboeuf, R, Ghossein, R, Gonen, M, et.al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system., Thyroid, 2010. 20 (12)(12): p. 1341-9., https://pubmed.ncbi.nlm.nih.gov/21034228/

539. Castagna, MG, Maino, F, Cipri, C, Belardini, V, Theodoropoulou, A, Cevenini, G, et.al. Delayed risk stratification, to include the response to initial treatment (surgery and radioiodine ablation), has better outcome predictivity in differentiated thyroid cancer patients., Eur J Endocrinol, 2011. 165 (3)(3): p. 441-6., https://pubmed.ncbi.nlm.nih.gov/21750043/

540. Vaisman, F, Momesso, D, Bulzico, DA, Pessoa, CH, Dias, F, Corbo, R, et.al. Spontaneous remission in thyroid cancer patients after biochemical incomplete response to initial therapy., Clin Endocrinol (Oxf), 2012. 77 (1)(1): p. 132-8., https://pubmed.ncbi.nlm.nih.gov/22248037/

541. Pitoia, F, Bueno, F, Urciuoli, C, Abelleira, E, Cross, G, Tuttle, RM, Outcomes of patients with differentiated thyroid cancer risk-stratified according to the American thyroid association and Latin American thyroid society risk of recurrence classification systems., Thyroid, 2013. 23 (11)(11): p. 1401-7., https://pubmed.ncbi.nlm.nih.gov/23517313/

542. Li, J., Liang, J., Zhao, T., Lin, Y., Noninferior response in BRAF(V600E) mutant nonmetastatic papillary thyroid carcinoma to radioiodine therapy, Eur J Nucl Med Mol Imaging, 2016. 43(6): p. 1034-9.

543. Orosco, RK, Hussain, T, Noel, JE, Chang, DC, Dosiou, C, Mittra, E, et.al. Radioactive iodine in differentiated thyroid cancer: a national database perspective., Endocr Relat Cancer, 2019. 26 (10)(10): p. 795-802., https://pubmed.ncbi.nlm.nih.gov/31443087/

544. Brierley, J. D., Panzarella, T., Tsang, R. W., Gospodarowicz, M. K., O'Sullivan, B., A comparison of different staging systems predictability of patient outcome. Thyroid carcinoma as an example, Cancer, 1997. 79(12): p. 2414-23., https://pubmed.ncbi.nlm.nih.gov/9191532/

545. Tanase, K., Thies, E. D., Mäder, U., Reiners, C., Verburg, F. A., The TNM system (version 7) is the most accurate staging system for the prediction of loss of life expectancy in differentiated thyroid cancer, Clin Endocrinol (Oxf), 2016. 84(2): p. 284-291.

546. Nixon, I. J., Wang, L. Y., Migliacci, J. C., Eskander, A., Campbell, M. J., Aniss, A., et.al. An International Multi-Institutional Validation of Age 55 Years as a Cutoff for Risk Stratification in the AJCC/UICC Staging System for Well-Differentiated Thyroid Cancer, Thyroid, 2016. 26(3): p. 373-80., https://pubmed.ncbi.nlm.nih.gov/26914539/

547. Tuttle, R. M., Ahuja, S., Avram, A. M., Bernet, V. J., Bourguet, P., Daniels, G. H., et.al. Controversies, Consensus, and Collaboration in the Use of (131)I Therapy in Differentiated Thyroid Cancer: A Joint Statement from the American Thyroid Association, the European Association of Nuclear Medicine, the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association, Thyroid, 2019. 29(4): p. 461-470.

548. Orosco, R. K., Hussain, T., Brumund, K. T., Oh, D. K., Chang, D. C., Bouvet, M., Analysis of age and disease status as predictors of thyroid cancer-specific mortality using the Surveillance, Epidemiology, and End Results database, Thyroid, 2015. 25(1): p. 125-32., https://pubmed.ncbi.nlm.nih.gov/25369076/

549. van Velsen, E. F. S., Visser, W. E., Stegenga, M. T., Mäder, U., Reiners, C., van Kemenade, F. J., et.al. Finding the Optimal Age Cutoff for the UICC/AJCC TNM Staging System in Patients with Papillary or Follicular Thyroid Cancer, Thyroid, 2021. 31(7): p. 1041-1049., https://pubmed.ncbi.nlm.nih.gov/33487121/

550. Luster, M., Aktolun, C., Amendoeira, I., Barczyński, M., Bible, K. C., Duntas, L. H., et.al. European Perspective on 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: Proceedings of an Interactive International Symposium, Thyroid, 2019. 29(1): p. 7-26.

551. Verburg, F. A., Flux, G., Giovanella, L., van Nostrand, D., Muylle, K., Luster, M., Differentiated thyroid cancer patients potentially benefitting from postoperative I-131 therapy: a review of the literature of the past decade, Eur J Nucl Med Mol Imaging, 2020. 47(1): p. 78-83.

552. (IARC), International Agency for Research on Cancer, Cancer incidence in five continents XI:

553. Pontius, L. N., Youngwirth, L. M., Thomas, S. M., Scheri, R. P., Roman, S. A., Sosa, J. A., Lymphovascular invasion is associated with survival for papillary thyroid cancer, Endocr Relat Cancer, 2016. 23(7): p. 555-62.

554. Zhu, G.; Deng, Y.; Pan, L.; Ouyang, W.; Feng, H.; Wu, J.; Chen, P.; Wang, J.; Chen, Y.; Luo, J., Clinical significance of the BRAF V600E mutation in PTC and its effect on radioiodine therapy, Endocrine Connections, 2019. 8: p. 754-763., https://pubmed.ncbi.nlm.nih.gov/31071680/

555. Schmidt, M., Bartenstein, P., Bucerius, J., Dietlein, M., Drzezga, A., Herrmann, K., et.al. Individualized treatment of differentiated thyroid cancer: The value of surgery in combination with radioiodine imaging and therapy - A German position paper from Surgery and Nuclear Medicine, Nuklearmedizin, 2022. 61(2): p. 87-96.

556. Sawka, A. M., Thephamongkhol, K., Brouwers, M., Thabane, L., Browman, G., Gerstein, H. C., Clinical review 170: A systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer, J Clin Endocrinol Metab, 2004. 89(8): p. 3668-76.

557. Sawka, A. M., Brierley, J. D., Tsang, R. W., Thabane, L., Rotstein, L., Gafni, A., et.al. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer, Endocrinol Metab Clin North Am, 2008. 37(2): p. 457-80, x.

558. Sun, Y., Gong, J., Guo, B., Shang, J., Cheng, Y., Xu, H., Association of adjuvant radioactive iodine therapy with survival in node-positive papillary thyroid cancer, Oral Oncology, 2018. 87: p. 152-157., https://pubmed.ncbi.nlm.nih.gov/30527231/

559. Jonklaas, J., Sarlis, N. J., Litofsky, D., Ain, K. B., Bigos, S. T., Brierley, J. D., et.al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy, Thyroid, 2006. 16(12): p. 1229-42., https://pubmed.ncbi.nlm.nih.gov/17199433/

560. Carhill, A. A., Litofsky, D. R., Ross, D. S., Jonklaas, J., Cooper, D. S., Brierley, J. D., et.al. Long-Term Outcomes Following Therapy in Differentiated Thyroid Carcinoma: NTCTCS Registry Analysis 1987-2012, J Clin Endocrinol Metab, 2015. 100(9): p. 3270-9., https://pubmed.ncbi.nlm.nih.gov/26171797/

561. Yang, Z., Flores, J., Katz, S., Nathan, C. A., Mehta, V., Comparison of Survival Outcomes Following Postsurgical Radioactive Iodine Versus External Beam Radiation in Stage IV Differentiated Thyroid Carcinoma, Thyroid, 2017. 27(7): p. 944-952., https://pubmed.ncbi.nlm.nih.gov/28446057/

562. Ruel, E., Thomas, S., Perkins, J. M., Roman, S. A., Sosa, J. A., The Impact of Pathologically Positive Lymph Nodes in the Clinically Negative Neck: An Analysis of 39,301 Patients with Papillary Thyroid Cancer, Annals of Surgical Oncology, 2017. 24(7): p. 1935-1942., https://pubmed.ncbi.nlm.nih.gov/28127652/

563. Tang, J., Kong, D., Cui, Q., Wang, K., Zhang, D., Liao, X., et.al. The role of radioactive iodine therapy in papillary thyroid cancer: an observational study based on SEER, OncoTargets and therapy, 2018. 11: p. 3551-3560., https://pubmed.ncbi.nlm.nih.gov/29950860/

564. Verburg, F. A., Mäder, U., Tanase, K., Thies, E. D., Diessl, S., Buck, A. K., et.al. Life expectancy is reduced in differentiated thyroid cancer patients ≥ 45 years old with extensive local tumor invasion, lateral lymph node, or distant metastases at diagnosis and normal in all other DTC patients, J Clin Endocrinol Metab, 2013. 98(1): p. 172-80.

565. Adam, M. A., Pura, J., Gu, L., Dinan, M. A., Tyler, D. S., Reed, S. D., et.al. Extent of surgery for papillary thyroid cancer is not associated with survival: an analysis of 61,775 patients, Ann Surg, 2014. 260(4): p. 601-5; discussion 605-7., https://www.ncbi.nlm.nih.gov/pubmed/25203876

566. Ruel, E., Thomas, S., Dinan, M., Perkins, J. M., Roman, S. A., Sosa, J. A., Adjuvant radioactive iodine therapy is associated with improved survival for patients with intermediate-risk papillary thyroid cancer, Journal of Clinical Endocrinology & Metabolism, 2015. 100(4): p. 1529-36., https://pubmed.ncbi.nlm.nih.gov/25642591/

567. Liu, X.; Fan, Y.; Liu, Y.; He, X.; Zheng, X.; Tan, J. Jia, Q.; Meng Z., The impact of radioactive iodine treatmenton survival among papillary thyroid cancer patients according to the 7th and 8th editions of the AJCC/TNM staging system: a SEER-based study, Updates in Surgery, 2020. 72: p. 871-884.

568. MacKinney, EC, Kuchta, KM, Winchester, DJ, Khokar, AM, Holoubek, SA, Moo-Young, TA, et.al. Overall survival is improved with total thyroidectomy and radiation for male patients and patients older than 55 with T2N0M0 Stage 1 classic papillary thyroid cancer., Surgery, 2022. 171 (1)(1): p. 197-202., https://pubmed.ncbi.nlm.nih.gov/34666913/

569. Zhao, M.; Shi, X.; Zhang, J.; Deng, S.; Zhou, Y.; Wen, R.; Lu, Y.; Zhang, B., Radioactive Iodine Ablation Can Reduce the Structural Recurrence Rate of Intermediate-Risk Papillary Thyroid Microcarcinoma: A Meta-Analysis, Computational and Mathematical Methods in Medicine, 2022. Volume 2022 | Article ID 8028846:

570. Sutton, W, Canner, JK, Segev, DL, Zeiger, MA, Mathur, A, Treatment Variation in Older Adults With Differentiated Thyroid Cancer., J Surg Res, 2020. 254 (): p. 154-164., https://pubmed.ncbi.nlm.nih.gov/32445931/

571. Harach, H. R., Franssila, K. O., Wasenius, VM, Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study., Cancer, 1985. 56: p. 531-538., https://pubmed.ncbi.nlm.nih.gov/2408737/

572. Hu, G., Zhu, W., Yang, W., Wang, H., Shen, L., Zhang, H., The Effectiveness of Radioactive Iodine Remnant Ablation for Papillary Thyroid Microcarcinoma: A Systematic Review and Meta-analysis, World Journal of Surgery, 2016. 40(1): p. 100-9., https://pubmed.ncbi.nlm.nih.gov/26578322/

573. Baudin, E., Travagli, J. P., Ropers, J., Mancusi, F., Bruno-Bossio, G., Caillou, B., et.al. Microcarcinoma of the thyroid gland: the Gustave-Roussy Institute experience, Cancer, 1998. 83(3): p. 553-9., https://pubmed.ncbi.nlm.nih.gov/9690549/

574. Pillai, S., Gopalan, V., Smith, R. A., Lam, A. K., Diffuse sclerosing variant of papillary thyroid carcinoma--an update of its clinicopathological features and molecular biology, Crit Rev Oncol Hematol, 2015. 94(1): p. 64-73.

575. Elisei, R., Viola, D., Torregrossa, L., Giannini, R., Romei, C., Ugolini, C., et.al. The BRAF(V600E) mutation is an independent, poor prognostic factor for the outcome of patients with low-risk intrathyroid papillary thyroid carcinoma: single-institution results from a large cohort study, J Clin Endocrinol Metab, 2012. 97(12): p. 4390-8., https://pubmed.ncbi.nlm.nih.gov/23066120/

576. Machens, A., Holzhausen, H. J., Dralle, H., The prognostic value of primary tumor size in papillary and follicular thyroid carcinoma, Cancer, 2005. 103(11): p. 2269-73.

577. Malandrino, P., Pellegriti, G., Attard, M., Violi, M. A., Giordano, C., Sciacca, L., et.al. Papillary thyroid microcarcinomas: a comparative study of the characteristics and risk factors at presentation in two cancer registries, J Clin Endocrinol Metab, 2013. 98(4): p. 1427-34.

578. Mehanna, H., Al-Maqbili, T., Carter, B., Martin, E., Campain, N., Watkinson, J., et.al. Differences in the recurrence and mortality outcomes rates of incidental and nonincidental papillary thyroid microcarcinoma: a systematic review and meta-analysis of 21 329 person-years of follow-up, J Clin Endocrinol Metab, 2014. 99(8): p. 2834-43.

579. Shattuck, T. M., Westra, W. H., Ladenson, P. W., Arnold, A., Independent clonal origins of distinct tumor foci in multifocal papillary thyroid carcinoma, N Engl J Med, 2005. 352(23): p. 2406-12.

580. Genpeng, L., Jianyong, L., Jiaying, Y., Ke, J., Zhihui, L., Rixiang, G., et.al. Independent predictors and lymph node metastasis characteristics of multifocal papillary thyroid cancer, Medicine, 2018. 97(5): p. e9619., https://pubmed.ncbi.nlm.nih.gov/29384841/

581. Leboulleux, S., Bournaud, C., Chougnet, C. N., Zerdoud, S., Al Ghuzlan, A., Catargi, B., et.al. Thyroidectomy without Radioiodine in Patients with Low-Risk Thyroid Cancer, N Engl J Med, 2022. 386(10): p. 923-932.

582. Kwon, H, Jeon, MJ, Kim, WG, Park, S, Kim, M, Kim, TY, et.al. Lack of Efficacy of Radioiodine Remnant Ablation for Papillary Thyroid Microcarcinoma: Verification Using Inverse Probability of Treatment Weighting., Ann Surg Oncol, 2017. 24 (9)(9): p. 2596-2602., https://pubmed.ncbi.nlm.nih.gov/28600731/

583. Al-Qahtani, KH, Al Asiri, M, Tunio, MA, Aljohani, NJ, Bayoumi, Y, Fatani, H, et.al. Adjuvant Radioactive iodine 131 ablation in papillary microcarcinoma of thyroid: Saudi Arabian experience [corrected]., J Otolaryngol Head Neck Surg, 2015. 44 (): p. 51., https://pubmed.ncbi.nlm.nih.gov/26621255/

584. Goran, M., Markovic, I., Buta, M., Gavrilovic, D., Cvetkovic, A., Santrac, N., et.al. The influence of papillary thyroid microcarcinomas size on the occurrence of lymph node metastases, J buon, 2019. 24(5): p. 2120-2126., https://pubmed.ncbi.nlm.nih.gov/31786884/

585. Gao, X., Zhang, X., Zhang, Y., Hua, W., Maimaiti, Y., Gao, Z., Is papillary thyroid microcarcinoma an indolent tumor?: A retrospective study on 280 cases treated with radioiodine, Medicine (Baltimore), 2016. 95(40): p. e5067., https://pubmed.ncbi.nlm.nih.gov/27749574/

586. Gong, Y., Li, G., Lei, J., You, J., Jiang, K., Li, Z., et.al. A favorable tumor size to define papillary thyroid microcarcinoma: an analysis of 1176 consecutive cases, Cancer Manag Res, 2018. 10: p. 899-906., https://pubmed.ncbi.nlm.nih.gov/29740219/

587. Al-Qurayshi, Z., Nilubol, N., Tufano, R. P., Kandil, E., Wolf in Sheep's Clothing: Papillary Thyroid Microcarcinoma in the US, J Am Coll Surg, 2020. 230(4): p. 484-491., https://www.ncbi.nlm.nih.gov/pubmed/32220437

588. Huang, Y., Yin, Y., Zhou, W., Risk Factors for Central and Lateral Lymph Node Metastases in Patients With Papillary Thyroid Micro-Carcinoma: Retrospective Analysis on 484 Cases, Front Endocrinol (Lausanne), 2021. 12: p. 640565., https://pubmed.ncbi.nlm.nih.gov/33746905/

589. Tuncel, M., Vrachimis, A., Campenni, A., de Keizer, B., Verburg, F. A., Kreissl, M. C., et.al. To give or not to give? A critical appraisal of a clinical trial on radioiodine treatment, Eur J Nucl Med Mol Imaging, 2022. 49(10): p. 3316-3319.

590. Zhao, H, Gong, Y, Radioactive iodine in low- to intermediate-risk papillary thyroid cancer., Front Endocrinol (Lausanne), 2022. 13 (): p. 960682., https://pubmed.ncbi.nlm.nih.gov/36034423/

591. Schmidt, M., Görges, R., Drzezga, A., Dietlein, M., A Matter of Controversy: Is Radioiodine Therapy Favorable in Differentiated Thyroid Carcinoma?, J Nucl Med, 2018. 59(8): p. 1195-1201.

592. Wang, J. B., Sun, Y. Y., Shi, L. H., Xie, L., Predictive factors for non-small-volume central lymph node metastases (more than 5 or ≥ 2 mm) in clinically node-negative papillary thyroid carcinoma, Medicine (Baltimore), 2019. 98(1): p. e14028., https://pubmed.ncbi.nlm.nih.gov/30608456/

593. Lei, J., Zhong, J., Jiang, K., Li, Z., Gong, R., Zhu, J., Skip lateral lymph node metastasis leaping over the central neck compartment in papillary thyroid carcinoma, Oncotarget, 2017. 8(16): p. 27022-27033.

594. Nie, X., Tan, Z., Ge, M., Skip metastasis in papillary thyroid carcinoma is difficult to predict in clinical practice, BMC Cancer, 2017. 17(1): p. 702.

595. Alzahrani, A. S., Xing, M., Impact of lymph node metastases identified on central neck dissection (CND) on the recurrence of papillary thyroid cancer: potential role of BRAFV600E mutation in defining CND, Endocr Relat Cancer, 2013. 20(1): p. 13-22., https://www.ncbi.nlm.nih.gov/pubmed/23132792

596. Pereira, JA, Jimeno, J, Miquel, J, Iglesias, M, Munné, A, Sancho, JJ, et.al. Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma., Surgery, 2005. 138 (6)(6): p. 1095-100, discussion 1100-1., https://pubmed.ncbi.nlm.nih.gov/16360396/

597. Wang, L. Y., Ganly, I., Nodal metastases in thyroid cancer: prognostic implications and management, Future Oncol, 2016. 12(7): p. 981-94., https://pubmed.ncbi.nlm.nih.gov/26948758/

598. Robinson, T. J., Thomas, S., Dinan, M. A., Roman, S., Sosa, J. A., Hyslop, T., How Many Lymph Nodes Are Enough? Assessing the Adequacy of Lymph Node Yield for Papillary Thyroid Cancer, J Clin Oncol, 2016. 34(28): p. 3434-9.

599. Randolph, G. W., Duh, Q. Y., Heller, K. S., LiVolsi, V. A., Mandel, S. J., Steward, D. L., et.al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension, Thyroid, 2012. 22(11): p. 1144-52.

600. Randolph, GW, Duh, QY, Heller, KS, LiVolsi, VA, Mandel, SJ, Steward, DL, et.al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension., Thyroid, 2012. 22 (11)(11): p. 1144-52., https://pubmed.ncbi.nlm.nih.gov/23083442/

601. Eustatia-Rutten, C. F., Corssmit, E. P., Biermasz, N. R., Pereira, A. M., Romijn, J. A., Smit, J. W., Survival and death causes in differentiated thyroid carcinoma, J Clin Endocrinol Metab, 2006. 91(1): p. 313-9., https://pubmed.ncbi.nlm.nih.gov/16263822/

602. Holoubek, SA, MacKinney, EC, Khokar, AM, Kuchta, KM, Winchester, DJ, Prinz, RA, et.al. Radioactive iodine does not improve overall survival for patients with aggressive variants of papillary thyroid carcinoma less than 2 cm., Surgery, 2022. 171 (1)(1): p. 203-211., https://pubmed.ncbi.nlm.nih.gov/34384604/

603. Gonzalez-Gonzalez, R., Bologna-Molina, R., Carreon-Burciaga, R. G., Gómezpalacio-Gastelum, M., Molina-Frechero, N., Salazar-Rodríguez, S., Papillary thyroid carcinoma: differential diagnosis and prognostic values of its different variants: review of the literature, ISRN Oncol, 2011. 2011: p. 915925., https://pubmed.ncbi.nlm.nih.gov/22432054/

604. Jiang, C., Cheng, T., Zheng, X., Hong, S., Liu, S., Liu, J., et.al. Clinical behaviors of rare variants of papillary thyroid carcinoma are associated with survival: a population-level analysis, Cancer Manag Res, 2018. 10: p. 465-472., https://pubmed.ncbi.nlm.nih.gov/29563836/

605. Lam, A. K., Saremi, N., Cribriform-morular variant of papillary thyroid carcinoma: a distinctive type of thyroid cancer, Endocr Relat Cancer, 2017. 24(4): p. R109-r121.

606. Ito, Y., Miyauchi, A., Ishikawa, H., Hirokawa, M., Kudo, T., Tomoda, C., et.al. Our experience of treatment of cribriform morular variant of papillary thyroid carcinoma; difference in clinicopathological features of FAP-associated and sporadic patients, Endocr J, 2011. 58(8): p. 685-9., https://pubmed.ncbi.nlm.nih.gov/21670544/

607. Yu, X. M., Schneider, D. F., Leverson, G., Chen, H., Sippel, R. S., Follicular variant of papillary thyroid carcinoma is a unique clinical entity: a population-based study of 10,740 cases, Thyroid, 2013. 23(10): p. 1263-8., https://pubmed.ncbi.nlm.nih.gov/23477346/

608. Koo, J. S., Hong, S., Park, C. S., Diffuse sclerosing variant is a major subtype of papillary thyroid carcinoma in the young, Thyroid, 2009. 19(11): p. 1225-31.

609. Fukushima, M., Ito, Y., Hirokawa, M., Akasu, H., Shimizu, K., Miyauchi, A., Clinicopathologic characteristics and prognosis of diffuse sclerosing variant of papillary thyroid carcinoma in Japan: an 18-year experience at a single institution, World J Surg, 2009. 33(5): p. 958-62., https://pubmed.ncbi.nlm.nih.gov/19198928/

610. Regalbuto, C., Malandrino, P., Tumminia, A., Le Moli, R., Vigneri, R., Pezzino, V., A diffuse sclerosing variant of papillary thyroid carcinoma: clinical and pathologic features and outcomes of 34 consecutive cases, Thyroid, 2011. 21(4): p. 383-9.

611. Coca-Pelaz, A., Shah, J. P., Hernandez-Prera, J. C., Ghossein, R. A., Rodrigo, J. P., Hartl, D. M., et.al. Papillary Thyroid Cancer-Aggressive Variants and Impact on Management: A Narrative Review, Adv Ther, 2020. 37(7): p. 3112-3128., https://pubmed.ncbi.nlm.nih.gov/32488657/

612. Nikiforov, Y. E., Erickson, L. A., Nikiforova, M. N., Caudill, C. M., Lloyd, R. V., Solid variant of papillary thyroid carcinoma: incidence, clinical-pathologic characteristics, molecular analysis, and biologic behavior, Am J Surg Pathol, 2001. 25(12): p. 1478-84.

613. Nikiforov, Y., Gnepp, D. R., Fagin, J. A., Thyroid lesions in children and adolescents after the Chernobyl disaster: implications for the study of radiation tumorigenesis, J Clin Endocrinol Metab, 1996. 81(1): p. 9-14.

614. Reiners, C., Biko, J., Haenscheid, H., Hebestreit, H., Kirinjuk, S., Baranowski, O., et.al. Twenty-five years after Chernobyl: outcome of radioiodine treatment in children and adolescents with very high-risk radiation-induced differentiated thyroid carcinoma, J Clin Endocrinol Metab, 2013. 98(7): p. 3039-48.

615. Vuong, H. G., Odate, T., Duong, U. N. P., Mochizuki, K., Nakazawa, T., Katoh, R., et.al. Prognostic importance of solid variant papillary thyroid carcinoma: A systematic review and meta-analysis, Head Neck, 2018. 40(7): p. 1588-1597.

616. Ohashi, R., Kawahara, K., Namimatsu, S., Igarashi, T., Sakatani, T., Sugitani, I., et.al. Clinicopathological significance of a solid component in papillary thyroid carcinoma, Histopathology, 2017. 70(5): p. 775-781.

617. Chang, H., Kim, S. M., Chun, K. W., Kim, B. W., Lee, Y. S., Chang, H. S., et.al. Clinicopathologic features of solid variant papillary thyroid cancer, ANZ J Surg, 2014. 84(5): p. 380-2., https://pubmed.ncbi.nlm.nih.gov/23826897/

618. Cartwright, S., Fingeret, A., Contemporary evaluation and management of tall cell variant of papillary thyroid carcinoma, Curr Opin Endocrinol Diabetes Obes, 2020. 27(5): p. 351-357., https://pubmed.ncbi.nlm.nih.gov/32701516/

619. Kazaure, H. S., Roman, S. A., Sosa, J. A., Aggressive variants of papillary thyroid cancer: incidence, characteristics and predictors of survival among 43,738 patients, Ann Surg Oncol, 2012. 19(6): p. 1874-80.

620. Leung, A. K., Chow, S. M., Law, S. C., Clinical features and outcome of the tall cell variant of papillary thyroid carcinoma, Laryngoscope, 2008. 118(1): p. 32-8.

621. Longheu, A., Canu, G. L., Cappellacci, F., Erdas, E., Medas, F., Calò, P. G., Tall Cell Variant versus Conventional Papillary Thyroid Carcinoma: A Retrospective Analysis in 351 Consecutive Patients, J Clin Med, 2020. 10(1):

622. Xu, J., Zhang, Y., Liu, J., Qiu, S., Wang, M., A population-based study of the three major variants of papillary thyroid carcinoma, J Int Med Res, 2021. 49(2): p. 300060520984618., https://pubmed.ncbi.nlm.nih.gov/33535844/

623. Michels, J. J., Jacques, M., Henry-Amar, M., Bardet, S., Prevalence and prognostic significance of tall cell variant of papillary thyroid carcinoma, Hum Pathol, 2007. 38(2): p. 212-9.

624. Holoubek, S. A., Yan, H., Khokar, A. H., Kuchta, K. M., Winchester, D. J., Prinz, R. A., et.al. Aggressive variants of papillary thyroid microcarcinoma are associated with high-risk features, but not decreased survival, Surgery, 2020. 167(1): p. 19-27., https://pubmed.ncbi.nlm.nih.gov/31627846/

625. Limberg, J., Ullmann, T. M., Stefanova, D., Buicko, J. L., Finnerty, B. M., Zarnegar, R., et.al. Does Aggressive Variant Histology Without Invasive Features Predict Overall Survival in Papillary Thyroid Cancer?: A National Cancer Database Analysis, Ann Surg, 2021. 274(3): p. e276-e281.

626. Regalbuto, C., Malandrino, P., Frasca, F., Pellegriti, G., Le Moli, R., Vigneri, R., et.al. The tall cell variant of papillary thyroid carcinoma: clinical and pathological features and outcomes, J Endocrinol Invest, 2013. 36(4): p. 249-54.

627. Wei, S., Gao, M., Zhao, C., Pan, Y., Li, H., Li, J., et.al. Low expression of sodium iodide symporter expression in aggressive variants of papillary thyroid carcinoma, Int J Clin Oncol, 2014. 19(5): p. 800-4.

628. Silver, C. E., Owen, R. P., Rodrigo, J. P., Rinaldo, A., Devaney, K. O., Ferlito, A., Aggressive variants of papillary thyroid carcinoma, Head Neck, 2011. 33(7): p. 1052-9.

629. Wong, K. S., Higgins, S. E., Marqusee, E., Nehs, M. A., Angell, T., Barletta, J. A., Tall Cell Variant of Papillary Thyroid Carcinoma: Impact of Change in WHO Definition and Molecular Analysis, Endocr Pathol, 2019. 30(1): p. 43-48.

630. Chen, J. H., Faquin, W. C., Lloyd, R. V., Nosé, V., Clinicopathological and molecular characterization of nine cases of columnar cell variant of papillary thyroid carcinoma, Mod Pathol, 2011. 24(5): p. 739-49., https://pubmed.ncbi.nlm.nih.gov/21358618/

631. Nath, M. C., Erickson, L. A., Aggressive Variants of Papillary Thyroid Carcinoma: Hobnail, Tall Cell, Columnar, and Solid, Adv Anat Pathol, 2018. 25(3): p. 172-179.

632. Song, E., Jeon, M. J., Oh, H. S., Han, M., Lee, Y. M., Kim, T. Y., et.al. Do aggressive variants of papillary thyroid carcinoma have worse clinical outcome than classic papillary thyroid carcinoma?, Eur J Endocrinol, 2018. 179(3): p. 135-142.

633. Wang, S., Xiong, Y., Zhao, Q., Song, H., Yi, P., Liu, C., Columnar cell papillary thyroid carcinoma prognosis: findings from the SEER database using propensity score matching analysis, Am J Transl Res, 2019. 11(9): p. 6262-6270., https://pubmed.ncbi.nlm.nih.gov/31632592/

634. Wenig, B. M., Thompson, L. D., Adair, C. F., Shmookler, B., Heffess, C. S., Thyroid papillary carcinoma of columnar cell type: a clinicopathologic study of 16 cases, Cancer, 1998. 82(4): p. 740-53.

635. Asioli, S., Erickson, L. A., Sebo, T. J., Zhang, J., Jin, L., Thompson, G. B., et.al. Papillary thyroid carcinoma with prominent hobnail features: a new aggressive variant of moderately differentiated papillary carcinoma. A clinicopathologic, immunohistochemical, and molecular study of eight cases, Am J Surg Pathol, 2010. 34(1): p. 44-52., https://pubmed.ncbi.nlm.nih.gov/19956062/

636. Mohapatra, D., Naik, S., Das, P., Agrawala, S., Metastatic hobnail variant of papillary thyroid carcinoma: A diagnostic challenge in cell block preparation, Indian J Pathol Microbiol, 2021. 64(2): p. 358-361.

637. Asioli, S., Erickson, L. A., Righi, A., Lloyd, R. V., Papillary thyroid carcinoma with hobnail features: histopathologic criteria to predict aggressive behavior, Hum Pathol, 2013. 44(3): p. 320-8., https://pubmed.ncbi.nlm.nih.gov/23036367/

638. Lubitz, C. C., Economopoulos, K. P., Pawlak, A. C., Lynch, K., Dias-Santagata, D., Faquin, W. C., et.al. Hobnail variant of papillary thyroid carcinoma: an institutional case series and molecular profile, Thyroid, 2014. 24(6): p. 958-65.

639. Donaldson, L. B., Yan, F., Morgan, P. F., Kaczmar, J. M., Fernandes, J. K., Nguyen, S. A., et.al. Hobnail variant of papillary thyroid carcinoma: a systematic review and meta-analysis, Endocrine, 2021. 72(1): p. 27-39., https://pubmed.ncbi.nlm.nih.gov/33025563/

640. Morandi, L.; Righi, A.; Maletta, F.; Rucci, P.; Pagni, F.; Gallo, M.; Rossi, S.; Caporali, L.; Sapino, A.; Lloyd, R.; Asioli, S., Somatic mutation profiling of hobnail variant of papillary thyroid carcinoma., Endocrine-related Cancer, 2017. 24: p. 107-117.

641. Gross, M., Eliashar, R., Ben-Yaakov, A., Weinberger, J. M., Maly, B., Clinicopathologic features and outcome of the oncocytic variant of papillary thyroid carcinoma, Ann Otol Rhinol Laryngol, 2009. 118(5): p. 374-81., https://pubmed.ncbi.nlm.nih.gov/19548388/

642. Herrera, M. F., Hay, I. D., Wu, P. S., Goellner, J. R., Ryan, J. J., Ebersold, J. R., et.al. Hürthle cell (oxyphilic) papillary thyroid carcinoma: a variant with more aggressive biologic behavior, World J Surg, 1992. 16(4): p. 669-74; discussion 774-5., https://pubmed.ncbi.nlm.nih.gov/1413835/

643. Hong, J. H., Yi, H. S., Yi, S., Kim, H. W., Lee, J., Kim, K. S., Implications of oncocytic change in papillary thyroid cancer, Clin Endocrinol (Oxf), 2016. 85(5): p. 797-804., https://pubmed.ncbi.nlm.nih.gov/27234487/

644. Carr, A. A., Yen, T. W. F., Ortiz, D. I., Hunt, B. C., Fareau, G., Massey, B. L., et.al. Patients with Oncocytic Variant Papillary Thyroid Carcinoma Have a Similar Prognosis to Matched Classical Papillary Thyroid Carcinoma Controls, Thyroid, 2018. 28(11): p. 1462-1467., https://pubmed.ncbi.nlm.nih.gov/30215297/

645. Liu, C., Zhao, Q., Zeng, W., Chen, C., Ming, J., Wang, S., et.al. Do patients with oxyphilic cell papillary thyroid carcinoma have a poor prognosis? Analysis of the surveillance, epidemiology, and end results database 2004-2013 with propensity score matching, Oncotarget, 2017. 8(44): p. 77075-77085., https://pubmed.ncbi.nlm.nih.gov/29100371/

646. Wenter, V., Jellinek, A., Unterrainer, M., Ahmaddy, F., Lehner, S., Albert, N. L., et.al. Long-term outcome of rare oncocytic papillary (Hürthle cell) thyroid carcinoma following (adjuvant) initial radioiodine therapy, Eur J Nucl Med Mol Imaging, 2019. 46(12): p. 2526-2535.

647. Goffredo, P., Sosa, J. A., Roman, S. A., Differentiated thyroid cancer presenting with distant metastases: a population analysis over two decades, World Journal of Surgery, 2013. 37(7): p. 1599-605., https://pubmed.ncbi.nlm.nih.gov/23525600/

648. Beckner, M. E., Heffess, C. S., Oertel, J. E., Oxyphilic papillary thyroid carcinomas, Am J Clin Pathol, 1995. 103(3): p. 280-7., https://pubmed.ncbi.nlm.nih.gov/7872249/

649. Cipriani, N. A., Nagar, S., Kaplan, S. P., White, M. G., Antic, T., Sadow, P. M., et.al. Follicular Thyroid Carcinoma: How Have Histologic Diagnoses Changed in the Last Half-Century and What Are the Prognostic Implications?, Thyroid, 2015. 25(11): p. 1209-16., https://pubmed.ncbi.nlm.nih.gov/26440366/

650. Yamazaki, H., Katoh, R., Sugino, K., Matsuzu, K., Masaki, C., Akaishi, J., et.al. Encapsulated Angioinvasive Follicular Thyroid Carcinoma: Prognostic Impact of the Extent of Vascular Invasion, Ann Surg Oncol, 2022., https://pubmed.ncbi.nlm.nih.gov/35169976/

651. O'Neill, C. J., Vaughan, L., Learoyd, D. L., Sidhu, S. B., Delbridge, L. W., Sywak, M. S., Management of follicular thyroid carcinoma should be individualised based on degree of capsular and vascular invasion, Eur J Surg Oncol, 2011. 37(2): p. 181-5.

652. Ito, Y., Hirokawa, M., Masuoka, H., Yabuta, T., Kihara, M., Higashiyama, T., et.al. Prognostic factors of minimally invasive follicular thyroid carcinoma: extensive vascular invasion significantly affects patient prognosis, Endocr J, 2013. 60(5): p. 637-42., https://pubmed.ncbi.nlm.nih.gov/23327839/

653. D'Avanzo, A., Treseler, P., Ituarte, P. H., Wong, M., Streja, L., Greenspan, F. S., et.al. Follicular thyroid carcinoma: histology and prognosis, Cancer, 2004. 100(6): p. 1123-9., https://pubmed.ncbi.nlm.nih.gov/15022277/

654. Peth, S., Hummel, R., Schreckenberger, M., Schad, A., Raabe, R., Weber, T., [Is there an indication for thyroidectomy in cases of minimally invasive follicular thyroid carcinoma?], Chirurg, 2022. 93(5): p. 509-512.

655. Wu, M. H., Lee, Y. Y., Lu, Y. L., Lin, S. F., Risk Factors and Prognosis for Metastatic Follicular Thyroid Cancer, Front Endocrinol (Lausanne), 2022. 13: p. 791826., https://pubmed.ncbi.nlm.nih.gov/35299967/

656. Janovitz, T., Barletta, J. A., Clinically Relevant Prognostic Parameters in Differentiated Thyroid Carcinoma, Endocr Pathol, 2018. 29(4): p. 357-364., https://pubmed.ncbi.nlm.nih.gov/30238434/

657. Vogrin, A., Besic, H., Besic, N., Music, M. M., Recurrence rate in regional lymph nodes in 737 patients with follicular or Hürthle cell neoplasms, Radiol Oncol, 2016. 50(3): p. 269-73.

658. Oluic, B., Paunovic, I., Loncar, Z., Djukic, V., Diklic, A., Jovanovic, M., et.al. Survival and prognostic factors for survival, cancer specific survival and disease free interval in 239 patients with Hurthle cell carcinoma: a single center experience, BMC Cancer, 2017. 17(1): p. 371.

659. Hundahl, S. A., Fleming, I. D., Fremgen, A. M., Menck, H. R., A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995 [see commetns], Cancer, 1998. 83(12): p. 2638-48., https://pubmed.ncbi.nlm.nih.gov/9874472/

660. Haigh, P. I., Urbach, D. R., The treatment and prognosis of Hürthle cell follicular thyroid carcinoma compared with its non-Hürthle cell counterpart, Surgery, 2005. 138(6): p. 1152-7; discussion 1157-8., https://pubmed.ncbi.nlm.nih.gov/16360403/

661. Sugino, K., Kameyama, K., Ito, K., Nagahama, M., Kitagawa, W., Shibuya, H., et.al. Does Hürthle cell carcinoma of the thyroid have a poorer prognosis than ordinary follicular thyroid carcinoma?, Ann Surg Oncol, 2013. 20(9): p. 2944-50.

662. Lopez-Penabad, L., Chiu, A. C., Hoff, A. O., Schultz, P., Gaztambide, S., Ordoñez, N. G., et.al. Prognostic factors in patients with Hürthle cell neoplasms of the thyroid, Cancer, 2003. 97(5): p. 1186-94.

663. Jillard, C. L., Youngwirth, L., Scheri, R. P., Roman, S., Sosa, J. A., Radioactive Iodine Treatment Is Associated with Improved Survival for Patients with Hürthle Cell Carcinoma, Thyroid, 2016. 26(7): p. 959-64., https://pubmed.ncbi.nlm.nih.gov/27150319/

664. Xu, L., Zou, Q., Jiao, J., Zhang, Y., Postoperative radioiodine therapy impact on survival in poorly differentiated thyroid carcinoma: a population-based study, Nucl Med Commun, 2022. 43(2): p. 145-151., https://pubmed.ncbi.nlm.nih.gov/34711774/

665. Ibrahimpasic, T., Ghossein, R., Carlson, D. L., Nixon, I., Palmer, F. L., Shaha, A. R., et.al. Outcomes in patients with poorly differentiated thyroid carcinoma, J Clin Endocrinol Metab, 2014. 99(4): p. 1245-52., https://pubmed.ncbi.nlm.nih.gov/24512493/

666. Ibrahimpasic, T., Ghossein, R., Shah, J. P., Ganly, I., Poorly Differentiated Carcinoma of the Thyroid Gland: Current Status and Future Prospects, Thyroid, 2019. 29(3): p. 311-321., https://pubmed.ncbi.nlm.nih.gov/30747050/

667. Park, E. K., Chung, J. K., Lim, I. H., Park, D. J., Lee, D. S., Lee, M. C., et.al. Recurrent/metastatic thyroid carcinomas false negative for serum thyroglobulin but positive by posttherapy I-131 whole body scans, Eur J Nucl Med Mol Imaging, 2009. 36(2): p. 172-9.

668. Robenshtok, E., Grewal, R. K., Fish, S., Sabra, M., Tuttle, R. M., A low postoperative nonstimulated serum thyroglobulin level does not exclude the presence of radioactive iodine avid metastatic foci in intermediate-risk differentiated thyroid cancer patients, Thyroid, 2013. 23(4): p. 436-42.

669. Prabhu, M., Samson, S., Reddy, A., Venkataramanarao, S. H., Chandrasekhar, N. H., Pillai, V., et.al. Role of Preablative Stimulated Thyroglobulin in Prediction of Nodal and Distant Metastasis on Iodine Whole-Body Scan, Indian J Nucl Med, 2018. 33(2): p. 93-98.

670. Giovanella, L., Suriano, S., Ceriani, L., Verburg, F. A., Undetectable thyroglobulin in patients with differentiated thyroid carcinoma and residual radioiodine uptake on a postablation whole-body scan, Clin Nucl Med, 2011. 36(2): p. 109-12., https://pubmed.ncbi.nlm.nih.gov/21220971/

671. Matrone, A., Gambale, C., Piaggi, P., Viola, D., Giani, C., Agate, L., et.al. Postoperative Thyroglobulin and Neck Ultrasound in the Risk Restratification and Decision to Perform 131I Ablation, J Clin Endocrinol Metab, 2017. 102(3): p. 893-902.

672. Campennì, A., Giovanella, L., Pignata, S. A., Vento, A., Alibrandi, A., Sturiale, L., et.al. Undetectable or low (<1 ng/ml) postsurgical thyroglobulin values do not rule out metastases in early stage differentiated thyroid cancer patients, Oncotarget, 2018. 9(25): p. 17491-17500., https://pubmed.ncbi.nlm.nih.gov/29707123/

673. Mallick, U., Harmer, C., Yap, B., Wadsley, J., Clarke, S., Moss, L., et.al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer, New England journal of medicine, 2012. 366(18): p. 1674-1685., https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00814146/full, https://www.nejm.org/doi/pdf/10.1056/NEJMoa1109589?articleTools=true

674. Maxon, H. R., Thomas, S. R., Hertzberg, V. S., Kereiakes, J. G., Chen, I. W., Sperling, M. I., et.al. Relation between effective radiation dose and outcome of radioiodine therapy for thyroid cancer, N Engl J Med, 1983. 309(16): p. 937-41.

675. Flux, G. D., Haq, M., Chittenden, S. J., Buckley, S., Hindorf, C., Newbold, K., et.al. A dose-effect correlation for radioiodine ablation in differentiated thyroid cancer, Eur J Nucl Med Mol Imaging, 2010. 37(2): p. 270-5., https://pubmed.ncbi.nlm.nih.gov/19760413/

676. Jentzen, W., Verschure, F., van Zon, A., van de Kolk, R., Wierts, R., Schmitz, J., et.al. 124I PET Assessment of Response of Bone Metastases to Initial Radioiodine Treatment of Differentiated Thyroid Cancer, J Nucl Med, 2016. 57(10): p. 1499-1504., https://pubmed.ncbi.nlm.nih.gov/27199362/

677. Klubo-Gwiezdzinska, J., Van Nostrand, D., Atkins, F., Burman, K., Jonklaas, J., Mete, M., et.al. Efficacy of dosimetric versus empiric prescribed activity of 131I for therapy of differentiated thyroid cancer, J Clin Endocrinol Metab, 2011. 96(10): p. 3217-25.

678. Hänscheid, H., Canzi, C., Eschner, W., Flux, G., Luster, M., Strigari, L., et.al. EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry II. Dosimetry prior to radioiodine therapy of benign thyroid diseases, Eur J Nucl Med Mol Imaging, 2013. 40(7): p. 1126-34., https://pubmed.ncbi.nlm.nih.gov/23576099/

679. Pacini, F., Brianzoni, E., Durante, C., Elisei, R., Ferdeghini, M., Fugazzola, L., et.al. Recommendations for post-surgical thyroid ablation in differentiated thyroid cancer: a 2015 position statement of the Italian Society of Endocrinology, J Endocrinol Invest, 2016. 39(3): p. 341-7.

680. Robinson, P. S., Barker, P., Campbell, A., Henson, P., Surveyor, I., Young, P. R., Iodine-131 in breast milk following therapy for thyroid carcinoma, J Nucl Med, 1994. 35(11): p. 1797-801.

681. National Research Council, Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2The National Academies Press, 2006., https://nap.nationalacademies.org/catalog/11340/health-risks-from-exposure-to-low-levels-of-ionizing-radiation

682. Schlumberger, M., De Vathaire, F., Ceccarelli, C., Delisle, M. J., Francese, C., Couette, J. E., et.al. Exposure to radioactive iodine-131 for scintigraphy or therapy does not preclude pregnancy in thyroid cancer patients, J Nucl Med, 1996. 37(4): p. 606-12.

683. Metallo, M., Groza, L., Brunaud, L., Klein, M., Weryha, G., Feigerlova, E., Long-Term Quality of Life and Pregnancy Outcomes of Differentiated Thyroid Cancer Survivors Treated by Total Thyroidectomy and I(131) during Adolescence and Young Adulthood, Int J Endocrinol, 2016. 2016: p. 7586482.

684. Kim, H. O., Lee, K., Lee, S. M., Seo, G. H., Association Between Pregnancy Outcomes and Radioactive Iodine Treatment After Thyroidectomy Among Women With Thyroid Cancer, JAMA Intern Med, 2020. 180(1): p. 54-61.

685. Howell, R. W., Wessels, B. W., Loevinger, R., Watson, E. E., Bolch, W. E., Brill, A. B., et.al. The MIRD perspective 1999. Medical Internal Radiation Dose Committee, J Nucl Med, 1999. 40(1): p. 3s-10s., https://pubmed.ncbi.nlm.nih.gov/9935082/

686. Mazzaferri, E. L., Gonadal damage from 131I therapy for thyroid cancer, Clin Endocrinol (Oxf), 2002. 57(3): p. 313-4.

687. Pacini, F., Gasperi, M., Fugazzola, L., Ceccarelli, C., Lippi, F., Centoni, R., et.al. Testicular function in patients with differentiated thyroid carcinoma treated with radioiodine, J Nucl Med, 1994. 35(9): p. 1418-22.

688. Wichers, M., Benz, E., Palmedo, H., Biersack, H. J., Grünwald, F., Klingmüller, D., Testicular function after radioiodine therapy for thyroid carcinoma, Eur J Nucl Med, 2000. 27(5): p. 503-7.

689. Hyer, S., Vini, L., O'Connell, M., Pratt, B., Harmer, C., Testicular dose and fertility in men following I(131) therapy for thyroid cancer, Clin Endocrinol (Oxf), 2002. 56(6): p. 755-8., https://pubmed.ncbi.nlm.nih.gov/12072044/

690. Sarkar, S. D., Beierwaltes, W. H., Gill, S. P., Cowley, B. J., Subsequent fertility and birth histories of children and adolescents treated with 131I for thyroid cancer, J Nucl Med, 1976. 17(6): p. 460-4.

691. Rosário, P. W., Barroso, A. L., Rezende, L. L., Padrão, E. L., Borges, M. A., Guimarães, V. C., et.al. Testicular function after radioiodine therapy in patients with thyroid cancer, Thyroid, 2006. 16(7): p. 667-70.

692. Canale, D., Ceccarelli, C., Caglieresi, C., Moscatelli, A., Gavioli, S., Santini, P., et.al. Effects of radioiodine treatment for differentiated thyroid cancer on testis function, Clin Endocrinol (Oxf), 2015. 82(2): p. 295-9., https://pubmed.ncbi.nlm.nih.gov/25138547/

693. Piek, MW, Postma, EL, van Leeuwaarde, R, de Boer, JP, Bos, AME, Lok, C, et.al. The Effect of Radioactive Iodine Therapy on Ovarian Function and Fertility in Female Thyroid Cancer Patients: A Systematic Review and Meta-Analysis., Thyroid, 2021. 31 (4)(4): p. 658-668., https://pubmed.ncbi.nlm.nih.gov/33012254/

694. Zhang, L, Huang, Y, Zheng, Y, Cai, L, Wen, J, Chen, G, The effect of I-131 therapy on pregnancy outcomes after thyroidectomy in patients with differentiated thyroid carcinoma: a meta-analysis., Endocrine, 2021. 73 (2)(2): p. 301-307., https://pubmed.ncbi.nlm.nih.gov/34009542/

695. Sawka, A. M., Ibrahim-Zada, I., Galacgac, P., Tsang, R. W., Brierley, J. D., Ezzat, S., et.al. Dietary iodine restriction in preparation for radioactive iodine treatment or scanning in well-differentiated thyroid cancer: a systematic review, Thyroid, 2010. 20(10): p. 1129-38.

696. Pluijmen, M. J., Eustatia-Rutten, C., Goslings, B. M., Stokkel, M. P., Arias, A. M., Diamant, M., et.al. Effects of low-iodide diet on postsurgical radioiodide ablation therapy in patients with differentiated thyroid carcinoma, Clin Endocrinol (Oxf), 2003. 58(4): p. 428-35.

697. Sohn, S. Y., Choi, J. Y., Jang, H. W., Kim, H. J., Jin, S. M., Kim, S. W., et.al. Association between excessive urinary iodine excretion and failure of radioactive iodine thyroid ablation in patients with papillary thyroid cancer, Thyroid, 2013. 23(6): p. 741-7.

698. Dobrenic, M., Huic, D., Zuvic, M., Grosev, D., Petrovic, R., Samardzic, T., Usefulness of low iodine diet in managing patients with differentiated thyroid cancer - initial results, Radiol Oncol, 2011. 45(3): p. 189-95., https://pubmed.ncbi.nlm.nih.gov/22933955/

699. Barbaro, D., Boni, G., Meucci, G., Simi, U., Lapi, P., Orsini, P., et.al. Radioiodine treatment with 30 mCi after recombinant human thyrotropin stimulation in thyroid cancer: effectiveness for postsurgical remnants ablation and possible role of iodine content in L-thyroxine in the outcome of ablation, J Clin Endocrinol Metab, 2003. 88(9): p. 4110-5., https://pubmed.ncbi.nlm.nih.gov/12970272/

700. Lan, W., Renjie, W., Qichang, W., Feiyue, T., Qingjie, M., Bin, J., Preoperative Use of Intravenous Contrast Media Is Associated With Decreased Excellent Response Rates in Intermediate-Risk DTC Patients Who Subsequently Receive Total Thyroidectomy and Low-Dose RAI Therapy, Front Oncol, 2020. 10: p. 1297.

701. Petrulea, M. S., Lencu, C., Piciu, D., Lisencu, C. I., Georgescu, C. E., Challenges of thyroid cancer management in amiodarone-treated patients: a case report, Clujul Med, 2015. 88(4): p. 550-4.

702. Puchalski, A. R., Chopra, I. J., Radioiodine treatment of differentiated thyroid cancer despite history of 'iodine allergy', Endocrinol Diabetes Metab Case Rep, 2014. 2014: p. 130084.

703. Nakada, K., Ishibashi, T., Takei, T., Hirata, K., Shinohara, K., Katoh, S., et.al. Does lemon candy decrease salivary gland damage after radioiodine therapy for thyroid cancer?, J Nucl Med, 2005. 46(2): p. 261-6.

704. Jentzen, W., Hobbs, R. F., Stahl, A., Knust, J., Sgouros, G., Bockisch, A., Pre-therapeutic (124)I PET(/CT) dosimetry confirms low average absorbed doses per administered (131)I activity to the

salivary glands in radioiodine therapy of differentiated thyroid cancer, Eur J Nucl Med Mol Imaging, 2010. 37(5): p. 884-95., https://pubmed.ncbi.nlm.nih.gov/20069293/

705. Jentzen, W., Balschuweit, D., Schmitz, J., Freudenberg, L., Eising, E., Hilbel, T., et.al. The influence of saliva flow stimulation on the absorbed radiation dose to the salivary glands during radioiodine therapy of thyroid cancer using 124I PET(/CT) imaging, Eur J Nucl Med Mol Imaging, 2010. 37(12): p. 2298-306., https://pubmed.ncbi.nlm.nih.gov/20625723/

706. Fu, H., Ma, C., Tang, L., Wu, F., Liu, B., Wang, H., Recombinant human thyrotropin versus thyroid hormone withdrawal in radioiodine remnant ablation for differentiated thyroid cancer: a meta-analysis, The Quarterly Journal of Nuclear Medicine & Molecular Imaging, 2015. 59(1): p. 121-8., https://pubmed.ncbi.nlm.nih.gov/24844252/

707. Verburg, FA, Stokkel, MP, Düren, C, Verkooijen, RB, Mäder, U, van Isselt, JW, et.al. No survival difference after successful (131)I ablation between patients with initially low-risk and high-risk differentiated thyroid cancer., Eur J Nucl Med Mol Imaging, 2010. 37 (2)(2): p. 276-83., https://pubmed.ncbi.nlm.nih.gov/20091165/

708. Gomes-Lima, CJ, Chittimoju, S, Wehbeh, L, Dia, S, Pagadala, P, Al-Jundi, M, et.al. Metastatic Differentiated Thyroid Cancer Survival Is Unaffected by Mode of Preparation for , J Endocr Soc, 2022. 6 (5)(5): p. bvac032., https://pubmed.ncbi.nlm.nih.gov/35356009/

709. Schlumberger, M., Catargi, B., Borget, I., Deandreis, D., Zerdoud, S., Bridji, B., et.al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer, N Engl J Med, 2012. 366(18): p. 1663-73.

710. Jentzen, W, Hoppenbrouwers, J, van Leeuwen, P, van der Velden, D, van de Kolk, R, Poeppel, TD, et.al. Assessment of lesion response in the initial radioiodine treatment of differentiated thyroid cancer using 124I PET imaging., J Nucl Med, 2014. 55 (11)(11): p. 1759-65., https://pubmed.ncbi.nlm.nih.gov/25332440/

711. Ma, C, Feng, F, Wang, S, Fu, H, Wu, S, Ye, Z, et.al. Chinese Data of Efficacy of Low- and High-Dose Iodine-131 for the Ablation of Thyroid Remnant., Thyroid, 2017. 27 (6)(6): p. 832-837., https://pubmed.ncbi.nlm.nih.gov/28401794/

712. Qu, Y, Huang, R, Li, L, Low- and high-dose radioiodine therapy for low-/intermediate-risk differentiated thyroid cancer: a preliminary clinical trial., Ann Nucl Med, 2017. 31 (1)(1): p. 71-83., https://pubmed.ncbi.nlm.nih.gov/27757803/

713. Shengguang, Y, Ji-Eun, C, Lijuan, HL, I-131 for Remnant Ablation in Differentiated Thyroid Cancer After Thyroidectomy: A Meta-Analysis of Randomized Controlled Evidence., Med Sci Monit, 2016. 22 (): p. 2439-50., https://pubmed.ncbi.nlm.nih.gov/27406262/

714. Jin, Y, Ruan, M, Cheng, L, Fu, H, Liu, M, Sheng, S, et.al. Radioiodine Uptake and Thyroglobulin-Guided Radioiodine Remnant Ablation in Patients with Differentiated Thyroid Cancer: A Prospective, Randomized, Open-Label, Controlled Trial., Thyroid, 2019. 29 (1)(1): p. 101-110., https://pubmed.ncbi.nlm.nih.gov/30560716/

715. Vrachimis, A., Riemann, B., Gerss, J., Maier, T., Schober, O., Peace of mind for patients with differentiated thyroid cancer?, Nuklearmedizin, 2013. 52(4): p. 115-20.

716. Abdulrezzak, U., Tutus, A., Isik, I., Kurt, Y., Kula, M., Quantitative comparison of low dose and standard dose radioiodine therapy effectiveness in patients with low risk differentiated thyroid cancer, Q J Nucl Med Mol Imaging, 2017. 61(3): p. 314-322., https://www.ncbi.nlm.nih.gov/pubmed/25600659

717. Elrasad, S. A. A., Abdelhafeez, Y., Husseini, M. A., Amin, R. A. A., Elrefaei, S., Thyroid remnant ablation of differentiated thyroid carcinoma: a comparison of ablation success with high and low doses of radioiodine (I-131), European journal of nuclear medicine and molecular imaging., 2015.

42(1 SUPPL. 1): p. S328., https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01136120/full, https://link.springer.com/content/pdf/10.1007%2Fs00259-015-3198-z.pdf

718. Schlumberger, M, Leboulleux, S, Catargi, B, Deandreis, D, Zerdoud, S, Bardet, S, et.al. Outcome after ablation in patients with low-risk thyroid cancer (ESTIMABL1): 5-year follow-up results of a randomised, phase 3, equivalence trial., Lancet Diabetes Endocrinol, 2018. 6 (8)(8): p. 618-626., https://pubmed.ncbi.nlm.nih.gov/29807824/

719. Andresen, N. S., Buatti, J. M., Tewfik, H. H., Pagedar, N. A., Anderson, C. M., Watkins, J. M., Radioiodine Ablation following Thyroidectomy for Differentiated Thyroid Cancer: Literature Review of Utility, Dose, and Toxicity, Eur Thyroid J, 2017. 6(4): p. 187-196., https://pubmed.ncbi.nlm.nih.gov/28868259/

720. Jentzen, W., Moldovan, A. S., Ruhlmann, M., Görges, R., Bockisch, A., Rosenbaum-Krumme, S., Lowest effective 131I activity for thyroid remnant ablation of differentiated thyroid cancer patients. Dosimetry-based model for estimation, Nuklearmedizin, 2015. 54(3): p. 137-43., https://pubmed.ncbi.nlm.nih.gov/25987357/

721. Verburg, F. A., Mäder, U., Reiners, C., Hänscheid, H., Long-term survival in differentiated thyroid cancer is worse after low-activity initial post-surgical 131I therapy in both high- and low-risk patients, J Clin Endocrinol Metab, 2014. 99(12): p. 4487-96.

722. Kukulska, A., Krajewska, J., Gawkowska-Suwinska, M., Puch, Z., Paliczka-Cieslik, E., Roskosz, J., et.al. Radioiodine thyroid remnant ablation in patients with differentiated thyroid carcinoma (DTC): prospective comparison of long-term outcomes of treatment with 30, 60 and 100 mCi, Thyroid research, 2010. 3(1): p. 9., https://pubmed.ncbi.nlm.nih.gov/21040579/

723. Miller, J. E., Al-Attar, N. C., Brown, O. H., Shaughness, G. G., Rosculet, N. P., Avram, A. M., et.al. Location and Causation of Residual Lymph Node Metastasis After Surgical Treatment of Regionally Advanced Differentiated Thyroid Cancer, Thyroid, 2018. 28(5): p. 593-600.

724. Spanu, A., Nuvoli, S., Marongiu, A., Gelo, I., Mele, L., Piras, B., et.al. Neck lymph node metastasis detection in patients with differentiated thyroid carcinoma (DTC) in long-term follow-up: a (131)I-SPECT/CT study, BMC Cancer, 2020. 20(1): p. 239.

725. Avram, A. M., Fig, L. M., Frey, K. A., Gross, M. D., Wong, K. K., Preablation 131-I scans with SPECT/CT in postoperative thyroid cancer patients: what is the impact on staging?, J Clin Endocrinol Metab, 2013. 98(3): p. 1163-71., https://pubmed.ncbi.nlm.nih.gov/23430789/

726. Avram, A. M., Dewaraja, Y. K., Thyroid Cancer Radiotheragnostics: the case for activity adjusted (131)I therapy, Clin Transl Imaging, 2018. 6(5): p. 335-346., https://pubmed.ncbi.nlm.nih.gov/30911535/

727. Szujo, S., Sira, L., Bajnok, L., Bodis, B., Gyory, F., Nemes, O., et.al. The impact of post-radioiodine therapy SPECT/CT on early risk stratification in differentiated thyroid cancer; a bi-institutional study, Oncotarget, 2017. 8(45): p. 79825-79834.

728. Avram, Anca M., Zukotynski, Katherine, Nadel, Helen Ruth, Giovanella, Luca, Management of Differentiated Thyroid Cancer: The Standard of Care, Journal of Nuclear Medicine, 2022. 63(2): p. 189-195., https://jnm.snmjournals.org/content/jnumed/63/2/189.full.pdf

729. Banerjee, M., Wiebel, J. L., Guo, C., Gay, B., Haymart, M. R., Use of imaging tests after primary treatment of thyroid cancer in the United States: population based retrospective cohort study evaluating death and recurrence, Bmj, 2016. 354: p. i3839., https://pubmed.ncbi.nlm.nih.gov/27443325/

730. Giovanella, L, Castellana, M, Trimboli, P, Unstimulated high-sensitive thyroglobulin is a powerful prognostic predictor in patients with thyroid cancer., Clin Chem Lab Med, 2019. 58 (1)(1): p. 130-137., https://pubmed.ncbi.nlm.nih.gov/31444962/

731. Bundesministerium für Umwelt, Naturschutz, nukleare Sicherheit und Verbraucherschutz, Richtlinie zur Strahlenschutzverordnung, 2011.

732. Verburg, F. A., Stokkel, M. P., Düren, C., Verkooijen, R. B., Mäder, U., van Isselt, J. W., et.al. No survival difference after successful (131)I ablation between patients with initially low-risk and high-risk differentiated thyroid cancer, Eur J Nucl Med Mol Imaging, 2010. 37(2): p. 276-83.

733. Görges, R, Brandt-Mainz, K, Freudenberg, L, Frilling, A, Grimm, W, Bockisch, A, [Continously increasing sensitivity in thyroid cancer aftercare in the course of three generations of thyroglobulin IMAs]., Nuklearmedizin, 2003. 42 (4)(4): p. 157-66., https://pubmed.ncbi.nlm.nih.gov/12937694/

734. Zöphel, K, Wunderlich, G, Smith, BR, Serum thyroglobulin measurements with a high sensitivity enzyme-linked immunosorbent assay: is there a clinical benefit in patients with differentiated thyroid carcinoma?, Thyroid, 2003. 13 (9)(9): p. 861-5., https://pubmed.ncbi.nlm.nih.gov/14588100/

735. Kita, T., Yokoyama, K., Higuchi, T., Kinuya, S., Taki, J., Nakajima, K., et.al. Multifactorial analysis on the short-term side effects occurring within 96 hours after radioiodine-131 therapy for differentiated thyroid carcinoma, Ann Nucl Med, 2004. 18(4): p. 345-9.

736. Pashnehsaz, M., Takavar, A., Izadyar, S., Zakariaee, S. S., Mahmoudi, M., Paydar, R., et.al. Gastrointestinal Side Effects of the Radioiodine Therapy for the Patients with Differentiated Thyroid Carcinoma Two Days after Prescription, World J Nucl Med, 2016. 15(3): p. 173-8.

737. Van Nostrand, D., Neutze, J., Atkins, F., Side effects of "rational dose" iodine-131 therapy for metastatic well-differentiated thyroid carcinoma, J Nucl Med, 1986. 27(10): p. 1519-27.

738. Clement, S. C., Peeters, R. P., Ronckers, C. M., Links, T. P., van den Heuvel-Eibrink, M. M., Nieveen van Dijkum, E. J., et.al. Intermediate and long-term adverse effects of radioiodine therapy for differentiated thyroid carcinoma--a systematic review, Cancer Treat Rev, 2015. 41(10): p. 925-34., https://pubmed.ncbi.nlm.nih.gov/26421813/

739. Lu, L., Shan, F., Li, W., Lu, H., Short-Term Side Effects after Radioiodine Treatment in Patients with Differentiated Thyroid Cancer, Biomed Res Int, 2016. 2016: p. 4376720.

740. Alexander, C., Bader, J. B., Schaefer, A., Finke, C., Kirsch, C. M., Intermediate and long-term side effects of high-dose radioiodine therapy for thyroid carcinoma, J Nucl Med, 1998. 39(9): p. 1551-4., https://www.ncbi.nlm.nih.gov/pubmed/9744341

741. Mendoza, A., Shaffer, B., Karakla, D., Mason, M. E., Elkins, D., Goffman, T. E., Quality of life with well-differentiated thyroid cancer: treatment toxicities and their reduction, Thyroid, 2004. 14(2): p. 133-40.

742. Hyer, S., Kong, A., Pratt, B., Harmer, C., Salivary gland toxicity after radioiodine therapy for thyroid cancer, Clin Oncol (R Coll Radiol), 2007. 19(1): p. 83-6., https://pubmed.ncbi.nlm.nih.gov/17305259/

743. Adramerinas, M, Andreadis, D, Vahtsevanos, K, Poulopoulos, A, Pazaitou-Panayiotou, K, Sialadenitis as a complication of radioiodine therapy in patients with thyroid cancer: where do we stand?, Hormones (Athens), 2021. 20 (4)(4): p. 669-678., https://pubmed.ncbi.nlm.nih.gov/34143403/

744. Rosário, P. W., Maia, F. F., Barroso, A., Padrão, E. L., Rezende, L., Purisch, S., [Sialoadenitis following ablative therapy with high doses of radioiodine for treatment of differentiated thyroid cancer], Arq Bras Endocrinol Metabol, 2004. 48(2): p. 310-4.

745. Rosario, P. W., Calsolari, M. R., Salivary and lacrimal gland dysfunction after remnant ablation with radioactive iodine in patients with differentiated thyroid carcinoma prepared with recombinant human thyrotropin, Thyroid, 2013. 23(5): p. 617-9.

746. Dietlein, M., Drzezga, A., [Taste dysfunction (dysgeusia) and radioiodine therapy of thyroid cancer - be aware of side effects by antidepressants and sedatives. Vorschädigung durch Antidepressiva

und Sedativa beachten], Nuklearmedizin, 2017. 56(4): p. 125-131., https://pubmed.ncbi.nlm.nih.gov/28715040/

747. Fard-Esfahani, A., Mirshekarpour, H., Fallahi, B., Eftekhari, M., Saghari, M., Beiki, D., et.al. The effect of high-dose radioiodine treatment on lacrimal gland function in patients with differentiated thyroid carcinoma, Clin Nucl Med, 2007. 32(9): p. 696-9., https://pubmed.ncbi.nlm.nih.gov/17710021/

748. Grünwald, F., Schomburg, A., Menzel, C., Steinecker, S., Späth, G., Bockisch, A., et.al. [Changes in the blood picture after radioiodine therapy of thyroid cancer], Med Klin (Munich), 1994. 89(10): p. 522-8., https://pubmed.ncbi.nlm.nih.gov/7808352/

749. Datz, F. L., Cerebral edema following iodine-131 therapy for thyroid carcinoma metastatic to the brain, J Nucl Med, 1986. 27(5): p. 637-40., https://pubmed.ncbi.nlm.nih.gov/3712081/

750. Holmquest, D. L., Lake, P., Sudden hemorrhage in metastatic thyroid carcinoma of the brain during treatment with iodine-131, J Nucl Med, 1976. 17(4): p. 307-9., https://pubmed.ncbi.nlm.nih.gov/3632/

751. Orita, Y., Sugitani, I., Matsuura, M., Ushijima, M., Tsukahara, K., Fujimoto, Y., et.al. Prognostic factors and the therapeutic strategy for patients with bone metastasis from differentiated thyroid carcinoma, Surgery, 2010. 147(3): p. 424-31.

752. An, Y. S., Yoon, J. K., Lee, S. J., Song, H. S., Yoon, S. H., Jo, K. S., Symptomatic late-onset sialadenitis after radioiodine therapy in thyroid cancer, Ann Nucl Med, 2013. 27(4): p. 386-91., https://www.ncbi.nlm.nih.gov/pubmed/23389626

753. Jeong, SY, Kim, HW, Lee, SW, Ahn, BC, Lee, J, Salivary gland function 5 years after radioactive iodine ablation in patients with differentiated thyroid cancer: direct comparison of pre- and postablation scintigraphies and their relation to xerostomia symptoms., Thyroid, 2013. 23 (5)(5): p. 609-16., https://pubmed.ncbi.nlm.nih.gov/23153322/

754. Klein Hesselink, E. N., Brouwers, A. H., de Jong, J. R., van der Horst-Schrivers, A. N., Coppes, R. P., Lefrandt, J. D., et.al. Effects of Radioiodine Treatment on Salivary Gland Function in Patients with Differentiated Thyroid Carcinoma: A Prospective Study, J Nucl Med, 2016. 57(11): p. 1685-1691.

755. Solans, R., Bosch, J. A., Galofré, P., Porta, F., Roselló, J., Selva-O'Callagan, A., et.al. Salivary and lacrimal gland dysfunction (sicca syndrome) after radioiodine therapy, J Nucl Med, 2001. 42(5): p. 738-43.

756. Wu, J. Q., Feng, H. J., Ouyang, W., Sun, Y. G., Chen, P., Wang, J., et.al. Systematic evaluation of salivary gland damage following I-131 therapy in differentiated thyroid cancer patients by quantitative scintigraphy and clinical follow-up, Nucl Med Commun, 2015. 36(8): p. 819-26., https://pubmed.ncbi.nlm.nih.gov/25932534/

757. Jonklaas, J., Nasal symptoms after radioiodine therapy: a rarely described side effect with similar frequency to lacrimal dysfunction, Thyroid, 2014. 24(12): p. 1806-14., https://pubmed.ncbi.nlm.nih.gov/25090584/

758. Molinaro, E., Leboeuf, R., Shue, B., Martorella, A. J., Fleisher, M., Larson, S., et.al. Mild decreases in white blood cell and platelet counts are present one year after radioactive iodine remnant ablation, Thyroid, 2009. 19(10): p. 1035-41.

759. Prinsen, H. T., Klein Hesselink, E. N., Brouwers, A. H., Plukker, J. T., Sluiter, W. J., van der Horst-Schrivers, A. N., et.al. Bone Marrow Function After (131)I Therapy in Patients With Differentiated Thyroid Carcinoma, J Clin Endocrinol Metab, 2015. 100(10): p. 3911-7.

760. Nappi, C, Klain, M, Cantoni, V, Green, R, Piscopo, L, Volpe, F, et.al. Risk of primary breast cancer in patients with differentiated thyroid cancer undergoing radioactive iodine therapy: a systematic

review and meta-analysis., Eur J Nucl Med Mol Imaging, 2022. 49 (5)(5): p. 1630-1639., https://pubmed.ncbi.nlm.nih.gov/34820683/

761. Reinecke, MJ, Ahlers, G, Burchert, A, Eilsberger, F, Flux, GD, Marlowe, RJ, et.al. Second primary malignancies induced by radioactive iodine treatment of differentiated thyroid carcinoma - a critical review and evaluation of the existing evidence., Eur J Nucl Med Mol Imaging, 2022. 49 (9)(9): p. 3247-3256., https://pubmed.ncbi.nlm.nih.gov/35320386/

762. Mattsson, S, Johansson, L, Leide Svegborn, S, Liniecki, J, Noßke, D, Riklund, KÅ, et.al. Radiation Dose to Patients from Radiopharmaceuticals: a Compendium of Current Information Related to Frequently Used Substances., Ann ICRP, 2015. 44 (2 Suppl)(2 Suppl): p. 7-321., https://pubmed.ncbi.nlm.nih.gov/26069086/

763. Silva-Vieira, M., Carrilho Vaz, S., Esteves, S., Ferreira, T. C., Limbert, E., Salgado, L., et.al. Second Primary Cancer in Patients with Differentiated Thyroid Cancer: Does Radioiodine Play a Role?, Thyroid, 2017. 27(8): p. 1068-1076.

764. Teng, C. J., Hu, Y. W., Chen, S. C., Yeh, C. M., Chiang, H. L., Chen, T. J., et.al. Use of Radioactive Iodine for Thyroid Cancer and Risk of Second Primary Malignancy: A Nationwide Population-Based Study, J Natl Cancer Inst, 2016. 108(2):

765. Molenaar, R. J., Pleyer, C., Radivoyevitch, T., Sidana, S., Godley, A., Advani, A. S., et.al. Risk of developing chronic myeloid neoplasms in well-differentiated thyroid cancer patients treated with radioactive iodine, Leukemia, 2018. 32(4): p. 952-959., https://pubmed.ncbi.nlm.nih.gov/29104287/

766. Molenaar, R. J., Sidana, S., Radivoyevitch, T., Advani, A. S., Gerds, A. T., Carraway, H. E., et.al. Risk of Hematologic Malignancies After Radioiodine Treatment of Well-Differentiated Thyroid Cancer, Journal of Clinical Oncology, 2018. 36(18): p. 1831-1839., https://pubmed.ncbi.nlm.nih.gov/29252123/

767. Rubino, C., de Vathaire, F., Dottorini, M. E., Hall, P., Schvartz, C., Couette, J. E., et.al. Second primary malignancies in thyroid cancer patients, Br J Cancer, 2003. 89(9): p. 1638-44.

768. Seo, G. H., Cho, Y. Y., Chung, J. H., Kim, S. W., Increased Risk of Leukemia After Radioactive Iodine Therapy in Patients with Thyroid Cancer: A Nationwide, Population-Based Study in Korea, Thyroid, 2015. 25(8): p. 927-34.

769. Bhattacharyya, N., Chien, W., Risk of second primary malignancy after radioactive iodine treatment for differentiated thyroid carcinoma, Ann Otol Rhinol Laryngol, 2006. 115(8): p. 607-10., https://pubmed.ncbi.nlm.nih.gov/16944659/

770. Hall, P., Holm, L. E., Lundell, G., Bjelkengren, G., Larsson, L. G., Lindberg, S., et.al. Cancer risks in thyroid cancer patients, Br J Cancer, 1991. 64(1): p. 159-63., https://pubmed.ncbi.nlm.nih.gov/1854616/

771. Marti, J. L., Jain, K. S., Morris, L. G., Increased risk of second primary malignancy in pediatric and young adult patients treated with radioactive iodine for differentiated thyroid cancer, Thyroid, 2015. 25(6): p. 681-7., https://pubmed.ncbi.nlm.nih.gov/25851829/

772. Sawka, A. M., Thabane, L., Parlea, L., Ibrahim-Zada, I., Tsang, R. W., Brierley, J. D., et.al. Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis, Thyroid, 2009. 19(5): p. 451-7.

773. Seo, GH, Kong, KA, Kim, BS, Kang, SY, Moon, BS, Yoon, HJ, et.al. Radioactive Iodine Treatment for Children and Young Adults with Thyroid Cancer in South Korea: A Population-based Study., J Clin Endocrinol Metab, 2021. 106 (7)(7): p. e2580-e2588., https://pubmed.ncbi.nlm.nih.gov/33755732/

774. Rall, J. E., Alpers, J. B., Lewallen, C. G., Sonenberg, M., Berman, M., Rawson, R. W., Radiation pneumonitis and fibrosis: a complication of radioiodine treatment of pulmonary metastases from cancer of the thyroid, J Clin Endocrinol Metab, 1957. 17(11): p. 1263-76.

775. Dietlein, M., Drzezga, A., [Ablative Radioiodtherapie bei niedrigem und intermediarem Rezidivrisiko. Hohere Uberlebensrate beim Schilddrusenkarzinom], Nuclear-Medizin, 2016. 55(3): p. 71-6., https://pubmed.ncbi.nlm.nih.gov/27350003/

776. Benua, R. S., Cicale, N. R., Sonenberg, M., Rawson, R. W., The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer, Am J Roentgenol Radium Ther Nucl Med, 1962. 87: p. 171-82., https://pubmed.ncbi.nlm.nih.gov/13867399/

777. Chen, L., Shen, Y., Luo, Q., Yu, Y., Lu, H., Zhu, R., Pulmonary fibrosis following radioiodine therapy of pulmonary metastases from differentiated thyroid carcinoma, Thyroid, 2010. 20(3): p. 337-40., https://pubmed.ncbi.nlm.nih.gov/20187786/

778. Sgouros, G., Song, H., Ladenson, P. W., Wahl, R. L., Lung toxicity in radioiodine therapy of thyroid carcinoma: development of a dose-rate method and dosimetric implications of the 80-mCi rule, J Nucl Med, 2006. 47(12): p. 1977-84.

779. Silberstein, E. B., Alavi, A., Balon, H. R., Clarke, S. E., Divgi, C., Gelfand, M. J., et.al. The SNMMI practice guideline for therapy of thyroid disease with 131I 3.0, J Nucl Med, 2012. 53(10): p. 1633-51.

780. Bledsoe, T. J., Nath, S. K., Decker, R. H., Radiation Pneumonitis, Clin Chest Med, 2017. 38(2): p. 201-208., https://pubmed.ncbi.nlm.nih.gov/28477633/

781. Hanania, A. N., Mainwaring, W., Ghebre, Y. T., Hanania, N. A., Ludwig, M., Radiation-Induced Lung Injury: Assessment and Management, Chest, 2019. 156(1): p. 150-162., https://pubmed.ncbi.nlm.nih.gov/30998908/

782. Fard-Esfahani, A., Emami-Ardekani, A., Fallahi, B., Fard-Esfahani, P., Beiki, D., Hassanzadeh-Rad, A., et.al. Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma, Nucl Med Commun, 2014. 35(8): p. 808-17., https://pubmed.ncbi.nlm.nih.gov/24751702/

783. Hebestreit, H., Biko, J., Drozd, V., Demidchik, Y., Burkhardt, A., Trusen, A., et.al. Pulmonary fibrosis in youth treated with radioiodine for juvenile thyroid cancer and lung metastases after Chernobyl, Eur J Nucl Med Mol Imaging, 2011. 38(9): p. 1683-90., https://pubmed.ncbi.nlm.nih.gov/21626048/

784. Kim, KJ, Song, JE, Kim, JY, Bae, JH, Kim, NH, Yoo, HJ, et.al. Effects of radioactive iodine treatment on cardiovascular disease in thyroid cancer patients: a nationwide cohort study., Ann Transl Med, 2020. 8 (19)(19): p. 1235., https://pubmed.ncbi.nlm.nih.gov/33178767/

785. Albano, D., Bertagna, F., Panarotto, M. B., Giubbini, R., Early and late adverse effects of radioiodine for pediatric differentiated thyroid cancer, Pediatr Blood Cancer, 2017. 64(11):, https://www.ncbi.nlm.nih.gov/pubmed/28436606

786. Brown, A. P., Chen, J., Hitchcock, Y. J., Szabo, A., Shrieve, D. C., Tward, J. D., The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer, J Clin Endocrinol Metab, 2008. 93(2): p. 504-15., https://pubmed.ncbi.nlm.nih.gov/18029468/

787. Shalet, S. M., Tsatsoulis, A., Whitehead, E., Read, G., Vulnerability of the human Leydig cell to radiation damage is dependent upon age, J Endocrinol, 1989. 120(1): p. 161-5.

788. Rivkees, S. A., Mazzaferri, E. L., Verburg, F. A., Reiners, C., Luster, M., Breuer, C. K., et.al. The treatment of differentiated thyroid cancer in children: emphasis on surgical approach and radioactive iodine therapy, Endocr Rev, 2011. 32(6): p. 798-826.

789. Maier, TM, Schober, O, Gerß, J, Görlich, D, Wenning, C, Schaefers, M, et.al. Differentiated thyroid cancer patients more than 60 years old paradoxically show an increased life expectancy., J Nucl Med, 2015. 56 (2)(2): p. 190-5., https://pubmed.ncbi.nlm.nih.gov/25613533/

790. Zaydfudim, V, Feurer, ID, Griffin, MR, Phay, JE, The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma., Surgery, 2008. 144 (6)(6): p. 1070-7; discussion 1077-8., https://pubmed.ncbi.nlm.nih.gov/19041020/

791. Wang, TS, Cheung, K, Farrokhyar, F, Roman, SA, Sosa, JA, A meta-analysis of the effect of prophylactic central compartment neck dissection on locoregional recurrence rates in patients with papillary thyroid cancer., Ann Surg Oncol, 2013. 20 (11)(11): p. 3477-83., https://pubmed.ncbi.nlm.nih.gov/23846784/

792. Lang, BH, Ng, SH, Lau, LL, Cowling, BJ, Wong, KP, Wan, KY, A systematic review and meta-analysis of prophylactic central neck dissection on short-term locoregional recurrence in papillary thyroid carcinoma after total thyroidectomy., Thyroid, 2013. 23 (9)(9): p. 1087-98., https://pubmed.ncbi.nlm.nih.gov/23402640/

793. Pacini, F, Molinaro, E, Castagna, MG, Agate, L, Elisei, R, Ceccarelli, C, et.al. Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma., J Clin Endocrinol Metab, 2003. 88 (8)(8): p. 3668-73., https://pubmed.ncbi.nlm.nih.gov/12915653/

794. Torlontano, M, Crocetti, U, Augello, G, D'Aloiso, L, Bonfitto, N, Varraso, A, et.al. Comparative evaluation of recombinant human thyrotropin-stimulated thyroglobulin levels, 131I whole-body scintigraphy, and neck ultrasonography in the follow-up of patients with papillary thyroid microcarcinoma who have not undergone radioiodine therapy., J Clin Endocrinol Metab, 2006. 91 (1)(1): p. 60-3., https://pubmed.ncbi.nlm.nih.gov/16219716/

795. Matrone, A, Gambale, C, Piaggi, P, Viola, D, Giani, C, Agate, L, et.al. Postoperative Thyroglobulin and Neck Ultrasound in the Risk Restratification and Decision to Perform 131I Ablation., J Clin Endocrinol Metab, 2017. 102 (3)(3): p. 893-902., https://pubmed.ncbi.nlm.nih.gov/27929713/

796. Ko, MS, Lee, JH, Shong, YK, Gong, GY, Baek, JH, Normal and abnormal sonographic findings at the thyroidectomy sites in postoperative patients with thyroid malignancy., AJR Am J Roentgenol, 2010. 194 (6)(6): p. 1596-609., https://pubmed.ncbi.nlm.nih.gov/20489102/

797. Chua, WY, Langer, JE, Jones, LP, Surveillance Neck Sonography After Thyroidectomy for Papillary Thyroid Carcinoma: Pitfalls in the Diagnosis of Locally Recurrent and Metastatic Disease., J Ultrasound Med, 2017. 36 (7)(7): p. 1511-1530., https://pubmed.ncbi.nlm.nih.gov/28393379/

798. Kobaly, K, Mandel, SJ, Langer, JE, Clinical review: Thyroid cancer mimics on surveillance neck sonography., J Clin Endocrinol Metab, 2015. 100 (2)(2): p. 371-5., https://pubmed.ncbi.nlm.nih.gov/25375984/

799. Shin, JH, Han, BK, Ko, EY, Kang, SS, Sonographic findings in the surgical bed after thyroidectomy: comparison of recurrent tumors and nonrecurrent lesions., J Ultrasound Med, 2007. 26 (10)(10): p. 1359-66., https://pubmed.ncbi.nlm.nih.gov/17901139/

800. Melo, M, da Rocha, AG, Vinagre, J, Batista, R, Peixoto, J, Tavares, C, et.al. TERT promoter mutations are a major indicator of poor outcome in differentiated thyroid carcinomas., J Clin Endocrinol Metab, 2014. 99 (5)(5): p. E754-65., https://pubmed.ncbi.nlm.nih.gov/24476079/

801. Malandrino, P, Latina, A, Marescalco, S, Spadaro, A, Regalbuto, C, Fulco, RA, et.al. Risk-adapted management of differentiated thyroid cancer assessed by a sensitive measurement of basal serum thyroglobulin., J Clin Endocrinol Metab, 2011. 96 (6)(6): p. 1703-9., https://pubmed.ncbi.nlm.nih.gov/21450986/

802. Kowalska, A, Walczyk, A, Pałyga, I, Gąsior-Perczak, D, Gadawska-Juszczyk, K, Szymonek, M, et.al. The Delayed Risk Stratification System in the Risk of Differentiated Thyroid Cancer Recurrence., PLoS One, 2016. 11 (4)(4): p. e0153242., https://pubmed.ncbi.nlm.nih.gov/27078258/

803. Hong, CM, Lee, WK, Jeong, SY, Lee, SW, Ahn, BC, Lee, J, Superiority of delayed risk stratification in differentiated thyroid cancer after total thyroidectomy and radioactive iodine ablation., Nucl Med Commun, 2014. 35 (11)(11): p. 1119-26., https://pubmed.ncbi.nlm.nih.gov/25144561/

804. Lee, SG, Lee, WK, Lee, HS, Moon, J, Lee, CR, Kang, SW, et.al. Practical Performance of the 2015 American Thyroid Association Guidelines for Predicting Tumor Recurrence in Patients with Papillary Thyroid Cancer in South Korea., Thyroid, 2017. 27 (2)(2): p. 174-181., https://pubmed.ncbi.nlm.nih.gov/27750028/

805. Nascimento, C, Borget, I, Al Ghuzlan, A, Deandreis, D, Chami, L, Travagli, JP, et.al. Persistent disease and recurrence in differentiated thyroid cancer patients with undetectable postoperative stimulated thyroglobulin level., Endocr Relat Cancer, 2011. 18 (2)(2): p. R29-40., https://pubmed.ncbi.nlm.nih.gov/21183629/

806. van Velsen, EFS, Stegenga, MT, van Kemenade, FJ, Kam, BLR, van Ginhoven, TM, Visser, WE, et.al. Evaluating the 2015 American Thyroid Association Risk Stratification System in High-Risk Papillary and Follicular Thyroid Cancer Patients., Thyroid, 2019. 29 (8)(8): p. 1073-1079., https://pubmed.ncbi.nlm.nih.gov/31140385/

807. Grani, G, Zatelli, MC, Alfò, M, Montesano, T, Torlontano, M, Morelli, S, et.al. Real-World Performance of the American Thyroid Association Risk Estimates in Predicting 1-Year Differentiated Thyroid Cancer Outcomes: A Prospective Multicenter Study of 2000 Patients., Thyroid, 2021. 31 (2)(2): p. 264-271., https://pubmed.ncbi.nlm.nih.gov/32475305/

808. Vaisman, F, Tala, H, Grewal, R, Tuttle, RM, In differentiated thyroid cancer, an incomplete structural response to therapy is associated with significantly worse clinical outcomes than only an incomplete thyroglobulin response., Thyroid, 2011. 21 (12)(12): p. 1317-22., https://pubmed.ncbi.nlm.nih.gov/22136267/

809. Shen, FC, Hsieh, CJ, Huang, IC, Chang, YH, Wang, PW, Dynamic Risk Estimates of Outcome in Chinese Patients with Well-Differentiated Thyroid Cancer After Total Thyroidectomy and Radioactive Iodine Remnant Ablation., Thyroid, 2017. 27 (4)(4): p. 531-536., https://pubmed.ncbi.nlm.nih.gov/28007013/

810. Trimboli, P, Zilioli, V, Imperiali, M, Ceriani, L, Giovanella, L, High-sensitive basal serum thyroglobulin 6-12 months after thyroid ablation is strongly associated with early response to therapy and event-free survival in patients with low-to-intermediate risk differentiated thyroid carcinomas., Eur J Endocrinol, 2017. 176 (5)(5): p. 497-504., https://pubmed.ncbi.nlm.nih.gov/28137736/

811. Malandrino, P, Tumino, D, Russo, M, Marescalco, S, Fulco, RA, Frasca, F, Surveillance of patients with differentiated thyroid cancer and indeterminate response: a longitudinal study on basal thyroglobulin trend., J Endocrinol Invest, 2019. 42 (10)(10): p. 1223-1230., https://pubmed.ncbi.nlm.nih.gov/30963467/

812. Lee, YM, Cho, JW, Hong, SJ, Yoon, JH, Dynamic risk stratification in papillary thyroid carcinoma measuring 1 to 4 cm., J Surg Oncol, 2018. 118 (4)(4): p. 636-643., https://pubmed.ncbi.nlm.nih.gov/30114339/

813. Kim, TH, Ki, CS, Kim, HS, Kim, K, Choe, JH, Kim, JH, et.al. Refining Dynamic Risk Stratification and Prognostic Groups for Differentiated Thyroid Cancer With TERT Promoter Mutations., J Clin Endocrinol Metab, 2017. 102 (5)(5): p. 1757-1764., https://pubmed.ncbi.nlm.nih.gov/28323925/

814. Filetti, S, Durante, C, Hartl, D, Leboulleux, S, Locati, LD, Newbold, K, et.al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†., Ann Oncol, 2019. 30 (12)(12): p. 1856-1883., https://pubmed.ncbi.nlm.nih.gov/31549998/

815. Wiersinga, WM, Duntas, L, Fadeyev, V, Nygaard, B, Vanderpump, MP, 2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism., Eur Thyroid J, 2012. 1 (2)(2): p. 55-71., https://pubmed.ncbi.nlm.nih.gov/24782999/

816. Rajput, R, Chatterjee, S, Rajput, M, Can Levothyroxine Be Taken as Evening Dose? Comparative Evaluation of Morning versus Evening Dose of Levothyroxine in Treatment of Hypothyroidism., J Thyroid Res, 2011. 2011 (): p. 505239., https://pubmed.ncbi.nlm.nih.gov/21785690/

817. Bolk, N, Visser, TJ, Nijman, J, Jongste, IJ, Tijssen, JG, Berghout, A, Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial., Arch Intern Med, 2010. 170 (22)(22): p. 1996-2003., https://pubmed.ncbi.nlm.nih.gov/21149757/

818. Ku, EJ, Yoo, WS, Lee, EK, Ahn, HY, Woo, SH, Hong, JH, et.al. Effect of TSH Suppression Therapy on Bone Mineral Density in Differentiated Thyroid Cancer: A Systematic Review and Meta-analysis., J Clin Endocrinol Metab, 2021. 106 (12)(12): p. 3655-3667., https://pubmed.ncbi.nlm.nih.gov/34302730/

819. Kwak, D, Ha, J, Won, Y, Kwon, Y, Park, S, Effects of thyroid-stimulating hormone suppression after thyroidectomy for thyroid cancer on bone mineral density in postmenopausal women: a systematic review and meta-analysis., BMJ Open, 2021. 11 (5)(5): p. e043007., https://pubmed.ncbi.nlm.nih.gov/33986046/

820. Bauer, DC, Ettinger, B, Nevitt, MC, Stone, KL, Risk for fracture in women with low serum levels of thyroid-stimulating hormone., Ann Intern Med, 2001. 134 (7)(7): p. 561-8., https://pubmed.ncbi.nlm.nih.gov/12803168/

821. Hawkins Carranza, F, Guadalix Iglesias, S, Luisa De Mingo Domínguez, M, Martín-Arriscado Arroba, C, López Álvarez, B, Allo Miguel, G, et.al. Trabecular bone deterioration in differentiated thyroid cancer: Impact of long-term TSH suppressive therapy., Cancer Med, 2020. 9 (16)(16): p. 5746-5755., https://pubmed.ncbi.nlm.nih.gov/32583973/

822. Flynn, RW, Bonellie, SR, Jung, RT, MacDonald, TM, Morris, AD, Leese, GP, Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy., J Clin Endocrinol Metab, 2010. 95 (1)(1): p. 186-93., https://pubmed.ncbi.nlm.nih.gov/19906785/

823. Smit, JW, Eustatia-Rutten, CF, Corssmit, EP, Pereira, AM, Frölich, M, Bleeker, GB, et.al. Reversible diastolic dysfunction after long-term exogenous subclinical hyperthyroidism: a randomized, placebo-controlled study., J Clin Endocrinol Metab, 2005. 90 (11)(11): p. 6041-7., https://pubmed.ncbi.nlm.nih.gov/16131580/

824. Mercuro, G, Panzuto, MG, Bina, A, Leo, M, Cabula, R, Petrini, L, et.al. Cardiac function, physical exercise capacity, and quality of life during long-term thyrotropin-suppressive therapy with levothyroxine: effect of individual dose tailoring., J Clin Endocrinol Metab, 2000. 85 (1)(1): p. 159-64., https://pubmed.ncbi.nlm.nih.gov/10634380/

825. McGriff, NJ, Csako, G, Gourgiotis, L, Lori C, G, Pucino, F, Sarlis, NJ, Effects of thyroid hormone suppression therapy on adverse clinical outcomes in thyroid cancer., Ann Med, 2002. 34 (7-8)(7-8): p. 554-64., https://pubmed.ncbi.nlm.nih.gov/12553495/

826. Hovens, GC, Stokkel, MP, Kievit, J, Corssmit, EP, Pereira, AM, Romijn, JA, et.al. Associations of serum thyrotropin concentrations with recurrence and death in differentiated thyroid cancer., J Clin Endocrinol Metab, 2007. 92 (7)(7): p. 2610-5., https://pubmed.ncbi.nlm.nih.gov/17426094/

827. Diessl, S, Holzberger, B, Mäder, U, Grelle, I, Smit, JW, Buck, AK, et.al. Impact of moderate vs stringent TSH suppression on survival in advanced differentiated thyroid carcinoma., Clin Endocrinol (Oxf), 2012. 76 (4)(4): p. 586-92., https://pubmed.ncbi.nlm.nih.gov/22059804/

828. Cady, B, Rossi, R, An expanded view of risk-group definition in differentiated thyroid carcinoma., Surgery, 1988. 104 (6)(6): p. 947-53., https://pubmed.ncbi.nlm.nih.gov/3194846/

829. Sugitani, I, Fujimoto, Y, Does postoperative thyrotropin suppression therapy truly decrease recurrence in papillary thyroid carcinoma? A randomized controlled trial., J Clin Endocrinol Metab, 2010. 95 (10)(10): p. 4576-83., https://pubmed.ncbi.nlm.nih.gov/20660039/

830. Ritter, A, Mizrachi, A, Bachar, G, Vainer, I, Shimon, I, Hirsch, D, et.al. Detecting Recurrence Following Lobectomy for Thyroid Cancer: Role of Thyroglobulin and Thyroglobulin Antibodies., J Clin Endocrinol Metab, 2020. 105 (6)(6):, https://pubmed.ncbi.nlm.nih.gov/32219303/

831. van Dijk, SPJ, Coerts, HI, Loncar, I, Verhoef, C, Kruijff, S, Engelsman, AF, et.al. Deescalating Follow-up After Hemithyroidectomy for Patients With Low-risk Papillary Thyroid Microcarcinoma., JAMA Otolaryngol Head Neck Surg, 2023. 149 (1)(1): p. 42-48., https://pubmed.ncbi.nlm.nih.gov/36416850/

832. Giovanella, L, Ceriani, L, Garo, ML, Is thyroglobulin a reliable biomarker of differentiated thyroid cancer in patients treated by lobectomy? A systematic review and meta-analysis., Clin Chem Lab Med, 2022. 60 (7)(7): p. 1091-1100., https://pubmed.ncbi.nlm.nih.gov/35475431/

833. Rosario, PW, Mourão, GF, Calsolari, MR, Definition of the Response to Initial Therapy with Radioiodine in Patients with Differentiated Thyroid Carcinoma: Basal or Stimulated Thyroglobulin?, Horm Metab Res, 2019. 51 (10)(10): p. 634-638., https://pubmed.ncbi.nlm.nih.gov/31578049/

834. Bögershausen, LR, Giovanella, L, Stief, T, Luster, M, Verburg, FA, Long-term predictive value of highly sensitive thyroglobulin measurement., Clin Endocrinol (Oxf), 2023. 98 (4)(4): p. 622-628., https://pubmed.ncbi.nlm.nih.gov/36263618/

835. Jeon, MJ, Kim, M, Park, S, Oh, HS, Kim, TY, Kim, WB, et.al. A Follow-Up Strategy for Patients with an Excellent Response to Initial Therapy for Differentiated Thyroid Carcinoma: Less Is Better., Thyroid, 2018. 28 (2)(2): p. 187-192., https://pubmed.ncbi.nlm.nih.gov/29179642/

836. Leenhardt, L, Borson-Chazot, F, Calzada, M, Carnaille, B, Charrié, A, Cochand-Priollet, B, et.al. Good practice guide for cervical ultrasound scan and echo-guided techniques in treating differentiated thyroid cancer of vesicular origin., Ann Endocrinol (Paris), 2011. 72 (3)(3): p. 173-97., https://pubmed.ncbi.nlm.nih.gov/21641577/

837. Pacella, CM, Bizzarri, G, Spiezia, S, Bianchini, A, Guglielmi, R, Crescenzi, A, et.al. Thyroid tissue: US-guided percutaneous laser thermal ablation., Radiology, 2004. 232 (1)(1): p. 272-80., https://pubmed.ncbi.nlm.nih.gov/15155898/

838. Kamaya, A, Gross, M, Akatsu, H, Jeffrey, RB, Recurrence in the thyroidectomy bed: sonographic findings., AJR Am J Roentgenol, 2011. 196 (1)(1): p. 66-70., https://pubmed.ncbi.nlm.nih.gov/21178048/

839. Peiling Yang, S, Bach, AM, Tuttle, RM, Fish, SA, Frequent screening with serial neck ultrasound is more likely to identify false-positive abnormalities than clinically significant disease in the surveillance of intermediate risk papillary thyroid cancer patients without suspicious findings on follow-up ultrasound evaluation., J Clin Endocrinol Metab, 2015. 100 (4)(4): p. 1561-7., https://pubmed.ncbi.nlm.nih.gov/25632970/

840. Yang, SP, Bach, AM, Tuttle, RM, Fish, SA, SERIAL NECK ULTRASOUND IS MORE LIKELY TO IDENTIFY FALSE-POSITIVE ABNORMALITIES THAN CLINICALLY SIGNIFICANT DISEASE IN LOW-RISK PAPILLARY THYROID CANCER PATIENTS., Endocr Pract, 2015. 21 (12)(12): p. 1372-9., https://pubmed.ncbi.nlm.nih.gov/26372300/

841. Sek, KS, Tsang, I, Lee, XY, Albaqmi, OH, Morosan Allo, YJ, Rosmarin, MC, et.al. Frequent neck US in papillary thyroid cancer likely detects non-actionable findings., Clin Endocrinol (Oxf), 2021. 94 (3)(3): p. 504-512., https://pubmed.ncbi.nlm.nih.gov/32886805/

842. Grani, G, Ramundo, V, Falcone, R, Lamartina, L, Montesano, T, Biffoni, M, et.al. Thyroid Cancer Patients With No Evidence of Disease: The Need for Repeat Neck Ultrasound., J Clin Endocrinol Metab, 2019. 104 (11)(11): p. 4981-4989., https://pubmed.ncbi.nlm.nih.gov/31206157/

843. Verburg, FA, Mäder, U, Giovanella, L, Luster, M, Reiners, C, Low or Undetectable Basal Thyroglobulin Levels Obviate the Need for Neck Ultrasound in Differentiated Thyroid Cancer Patients After Total Thyroidectomy and , Thyroid, 2018. 28 (6)(6): p. 722-728., https://pubmed.ncbi.nlm.nih.gov/29665748/

844. Ross, DS, Litofsky, D, Ain, KB, Bigos, T, Brierley, JD, Cooper, DS, et.al. Recurrence after treatment of micropapillary thyroid cancer., Thyroid, 2009. 19 (10)(10): p. 1043-8., https://pubmed.ncbi.nlm.nih.gov/19772419/

845. Brassard, M, Borget, I, Edet-Sanson, A, Giraudet, AL, Mundler, O, Toubeau, M, et.al. Long-term follow-up of patients with papillary and follicular thyroid cancer: a prospective study on 715 patients., J Clin Endocrinol Metab, 2011. 96 (5)(5): p. 1352-9., https://pubmed.ncbi.nlm.nih.gov/21389143/

846. Durante, C, Montesano, T, Torlontano, M, Attard, M, Monzani, F, Tumino, S, et.al. Papillary thyroid cancer: time course of recurrences during postsurgery surveillance., J Clin Endocrinol Metab, 2013. 98 (2)(2): p. 636-42., https://pubmed.ncbi.nlm.nih.gov/23293334/

847. Hay, ID, Johnson, TR, Kaggal, S, Reinalda, MS, Iniguez-Ariza, NM, Grant, CS, et.al. Papillary Thyroid Carcinoma (PTC) in Children and Adults: Comparison of Initial Presentation and Long-Term Postoperative Outcome in 4432 Patients Consecutively Treated at the Mayo Clinic During Eight Decades (1936-2015)., World J Surg, 2018. 42 (2)(2): p. 329-342., https://pubmed.ncbi.nlm.nih.gov/29030676/

848. Hwangbo, Y, Kim, JM, Park, YJ, Lee, EK, Lee, YJ, Park, DJ, et.al. Long-Term Recurrence of Small Papillary Thyroid Cancer and Its Risk Factors in a Korean Multicenter Study., J Clin Endocrinol Metab, 2017. 102 (2)(2): p. 625-633., https://pubmed.ncbi.nlm.nih.gov/27732329/

849. Dehbi, HM, Mallick, U, Wadsley, J, Newbold, K, Harmer, C, Hackshaw, A, Recurrence after low-dose radioiodine ablation and recombinant human thyroid-stimulating hormone for differentiated thyroid cancer (HiLo): long-term results of an open-label, non-inferiority randomised controlled trial., Lancet Diabetes Endocrinol, 2019. 7 (1)(1): p. 44-51., https://pubmed.ncbi.nlm.nih.gov/30501974/

850. Elisei, R, Molinaro, E, Agate, L, Bottici, V, Masserini, L, Ceccarelli, C, et.al. Are the clinical and pathological features of differentiated thyroid carcinoma really changed over the last 35 years? Study on 4187 patients from a single Italian institution to answer this question., J Clin Endocrinol Metab, 2010. 95 (4)(4): p. 1516-27., https://pubmed.ncbi.nlm.nih.gov/20156922/

851. Durante, C, Montesano, T, Attard, M, Torlontano, M, Monzani, F, Costante, G, et.al. Long-term surveillance of papillary thyroid cancer patients who do not undergo postoperative radioiodine remnant ablation: is there a role for serum thyroglobulin measurement?, J Clin Endocrinol Metab, 2012. 97 (8)(8): p. 2748-53., https://pubmed.ncbi.nlm.nih.gov/22679061/

852. Verburg, FA, Schmidt, M, Kreissl, MC, Grünwald, F, Lassmann, M, Hänscheid, H, et.al. [Procedural guideline for Iodine-131 whole-body scintigraphy in differentiated thyroid carcinoma (version 5)]., Nuklearmedizin, 2019. 58 (3)(3): p. 228-241., https://pubmed.ncbi.nlm.nih.gov/31035298/

853. de Meer, SG, Vriens, MR, Zelissen, PM, Borel Rinkes, IH, de Keizer, B, The role of routine diagnostic radioiodine whole-body scintigraphy in patients with high-risk differentiated thyroid cancer., J Nucl Med, 2011. 52 (1)(1): p. 56-9., https://pubmed.ncbi.nlm.nih.gov/21149483/

854. Spencer, CA, Clinical review: Clinical utility of thyroglobulin antibody (TgAb) measurements for patients with differentiated thyroid cancers (DTC)., J Clin Endocrinol Metab, 2011. 96 (12)(12): p. 3615-27., https://pubmed.ncbi.nlm.nih.gov/21917876/

855. Verburg, FA, Luster, M, Cupini, C, Chiovato, L, Duntas, L, Elisei, R, et.al. Implications of thyroglobulin antibody positivity in patients with differentiated thyroid cancer: a clinical position statement., Thyroid, 2013. 23 (10)(10): p. 1211-25., https://pubmed.ncbi.nlm.nih.gov/23692026/

856. Côrtes, MCS, Rosario, PW, Oliveira, LFF, Calsolari, MR, Clinical Impact of Detectable Antithyroglobulin Antibodies Below the Reference Limit (Borderline) in Patients with Papillary Thyroid Carcinoma with Undetectable Serum Thyroglobulin and Normal Neck Ultrasonography After Ablation: A Prospective Study., Thyroid, 2018. 28 (2)(2): p. 229-235., https://pubmed.ncbi.nlm.nih.gov/29325506/

857. Lee, ZJO, Eslick, GD, Edirimanne, S, Investigating Antithyroglobulin Antibody As a Prognostic Marker for Differentiated Thyroid Cancer: A Meta-Analysis and Systematic Review., Thyroid, 2020. 30 (11)(11): p. 1601-1612., https://pubmed.ncbi.nlm.nih.gov/32345152/

858. Zavala, LF, Barra, MI, Olmos, R, Tuttle, M, González, H, Droppelmann, N, et.al. In properly selected patients with differentiated thyroid cancer, antithyroglobulin antibodies decline after thyroidectomy and their sole presence should not be an indication for radioiodine ablation., Arch Endocrinol Metab, 2019. 63 (3)(3): p. 293-299., https://pubmed.ncbi.nlm.nih.gov/31038590/

859. Hilditch, TE, Dempsey, MF, Bolster, AA, McMenemin, RM, Reed, NS, Self-stunning in thyroid ablation: evidence from comparative studies of diagnostic 131I and 123I., Eur J Nucl Med Mol Imaging, 2002. 29 (6)(6): p. 783-8., https://pubmed.ncbi.nlm.nih.gov/12029552/

860. Lassmann, M, Luster, M, Hänscheid, H, Reiners, C, Impact of 131I diagnostic activities on the biokinetics of thyroid remnants., J Nucl Med, 2004. 45 (4)(4): p. 619-25., https://pubmed.ncbi.nlm.nih.gov/15073258/

861. Wu, D, Ylli, D, Heimlich, SL, Burman, KD, Wartofsky, L, Van Nostrand, D, (124)I Positron Emission Tomography/Computed Tomography Versus Conventional Radioiodine Imaging in Differentiated Thyroid Cancer: A Review., Thyroid, 2019. 29 (11)(11): p. 1523-1535., https://pubmed.ncbi.nlm.nih.gov/31452449/

862. Giostra, A, Richetta, E, Pasquino, M, Miranti, A, Cutaia, C, Brusasco, G, et.al. Red marrow and blood dosimetry in (131)I treatment of metastatic thyroid carcinoma: pre-treatment versus in-therapy results., Phys Med Biol, 2016. 61 (11)(11): p. 4316-26., https://pubmed.ncbi.nlm.nih.gov/27200493/

863. Salvatori, M, Rufini, V, Reale, F, Samanes Gajate, AM, Maussier, ML, Revelli, L, et.al. Radio-guided surgery for lymph node recurrences of differentiated thyroid cancer., World J Surg, 2003. 27 (7)(7): p. 770-5., https://pubmed.ncbi.nlm.nih.gov/14509503/

864. Vrachimis, A, Riemann, B, Mäder, U, Reiners, C, Verburg, FA, Endogenous TSH levels at the time of , Eur J Nucl Med Mol Imaging, 2016. 43 (2)(2): p. 224-231., https://pubmed.ncbi.nlm.nih.gov/26493309/

865. Edmonds, CJ, Hayes, S, Kermode, JC, Thompson, BD, Measurement of serum TSH and thyroid hormones in the management of treatment of thyroid carcinoma with radioiodine., Br J Radiol, 1977. 50 (599)(599): p. 799-807., https://pubmed.ncbi.nlm.nih.gov/588901/

866. Qichang, W, Lin, B, Gege, Z, Youjia, Z, Qingjie, M, Renjie, W, et.al. Diagnostic performance of 18F-FDG-PET/CT in DTC patients with thyroglobulin elevation and negative iodine scintigraphy: a meta-

analysis., Eur J Endocrinol, 2019. 181 (2)(2): p. 93-102., https://pubmed.ncbi.nlm.nih.gov/31117054/

867. Ma, C, Xie, J, Lou, Y, Gao, Y, Zuo, S, Wang, X, The role of TSH for 18F-FDG-PET in the diagnosis of recurrence and metastases of differentiated thyroid carcinoma with elevated thyroglobulin and negative scan: a meta-analysis., Eur J Endocrinol, 2010. 163 (2)(2): p. 177-83., https://pubmed.ncbi.nlm.nih.gov/20484385/

868. Kim, SJ, Lee, SW, Pak, K, Shim, SR, Diagnostic performance of PET in thyroid cancer with elevated anti-Tg Ab., Endocr Relat Cancer, 2018. 25 (6)(6): p. 643-652., https://pubmed.ncbi.nlm.nih.gov/29559552/

869. Grabellus, F, Nagarajah, J, Bockisch, A, Schmid, KW, Sheu, SY, Glucose transporter 1 expression, tumor proliferation, and iodine/glucose uptake in thyroid cancer with emphasis on poorly differentiated thyroid carcinoma., Clin Nucl Med, 2012. 37 (2)(2): p. 121-7., https://pubmed.ncbi.nlm.nih.gov/22228332/

870. Deandreis, D, Al Ghuzlan, A, Leboulleux, S, Lacroix, L, Garsi, JP, Talbot, M, et.al. Do histological, immunohistochemical, and metabolic (radioiodine and fluorodeoxyglucose uptakes) patterns of metastatic thyroid cancer correlate with patient outcome?, Endocr Relat Cancer, 2011. 18 (1)(1): p. 159-69., https://pubmed.ncbi.nlm.nih.gov/21118976/

871. Robbins, RJ, Wan, Q, Grewal, RK, Reibke, R, Gonen, M, Strauss, HW, et.al. Real-time prognosis for metastatic thyroid carcinoma based on 2-[18F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning., J Clin Endocrinol Metab, 2006. 91 (2)(2): p. 498-505., https://pubmed.ncbi.nlm.nih.gov/16303836/

872. Phan, HT, Jager, PL, Paans, AM, Plukker, JT, Sturkenboom, MG, Sluiter, WJ, et.al. The diagnostic value of 124I-PET in patients with differentiated thyroid cancer., Eur J Nucl Med Mol Imaging, 2008. 35 (5)(5): p. 958-65., https://pubmed.ncbi.nlm.nih.gov/18175115/

873. Van Nostrand, D, Moreau, S, Bandaru, VV, Atkins, F, Chennupati, S, Mete, M, et.al. (124)I positron emission tomography versus (131)I planar imaging in the identification of residual thyroid tissue and/or metastasis in patients who have well-differentiated thyroid cancer., Thyroid, 2010. 20 (8)(8): p. 879-83., https://pubmed.ncbi.nlm.nih.gov/20615132/

874. Gulec, SA, Kuker, RA, Goryawala, M, Fernandez, C, Perez, R, Khan-Ghany, A, et.al. (124)I PET/CT in Patients with Differentiated Thyroid Cancer: Clinical and Quantitative Image Analysis., Thyroid, 2016. 26 (3)(3): p. 441-8., https://pubmed.ncbi.nlm.nih.gov/26857905/

875. Kist, JW, de Keizer, B, van der Vlies, M, Brouwers, AH, Huysmans, DA, van der Zant, FM, et.al. 124I PET/CT to Predict the Outcome of Blind 131I Treatment in Patients with Biochemical Recurrence of Differentiated Thyroid Cancer: Results of a Multicenter Diagnostic Cohort Study (THYROPET)., J Nucl Med, 2016. 57 (5)(5): p. 701-7., https://pubmed.ncbi.nlm.nih.gov/26609180/

876. Pettinato, C, Spezi, E, Nanni, C, Grassetto, G, Monari, F, Allegri, V, et.al. Pretherapeutic dosimetry in patients affected by metastatic thyroid cancer using 124I PET/CT sequential scans for 131I treatment planning., Clin Nucl Med, 2014. 39 (8)(8): p. e367-74., https://pubmed.ncbi.nlm.nih.gov/24978332/

877. Jentzen, W, Freudenberg, L, Eising, EG, Sonnenschein, W, Knust, J, Bockisch, A, Optimized 124I PET dosimetry protocol for radioiodine therapy of differentiated thyroid cancer., J Nucl Med, 2008. 49 (6)(6): p. 1017-23., https://pubmed.ncbi.nlm.nih.gov/18483099/

878. Jentzen, W, Weise, R, Kupferschläger, J, Freudenberg, L, Brandau, W, Bares, R, et.al. Iodine-124 PET dosimetry in differentiated thyroid cancer: recovery coefficient in 2D and 3D modes for PET(/CT) systems., Eur J Nucl Med Mol Imaging, 2008. 35 (3)(3): p. 611-23., https://pubmed.ncbi.nlm.nih.gov/17929014/

879. Eschmann, SM, Reischl, G, Bilger, K, Kupferschläger, J, Thelen, MH, Dohmen, BM, et.al. Evaluation of dosimetry of radioiodine therapy in benign and malignant thyroid disorders by means of iodine-124 and PET., Eur J Nucl Med Mol Imaging, 2002. 29 (6)(6): p. 760-7., https://pubmed.ncbi.nlm.nih.gov/12029549/

880. Freudenberg, LS, Jentzen, W, Görges, R, Petrich, T, Marlowe, RJ, Knust, J, et.al. 124I-PET dosimetry in advanced differentiated thyroid cancer: therapeutic impact., Nuklearmedizin, 2007. 46 (4)(4): p. 121-8., https://pubmed.ncbi.nlm.nih.gov/17690789/

881. Klagge, A, Krause, K, Schierle, K, Steinert, F, Dralle, H, Fuhrer, D, Somatostatin receptor subtype expression in human thyroid tumours., Horm Metab Res, 2010. 42 (4)(4): p. 237-40., https://pubmed.ncbi.nlm.nih.gov/20094970/

882. Woelfl, S, Bogner, S, Huber, H, Salaheddin-Nassr, S, Hatzl, M, Decristoforo, C, et.al. Expression of somatostatin receptor subtype 2 and subtype 5 in thyroid malignancies., Nuklearmedizin, 2014. 53 (5)(5): p. 179-85., https://pubmed.ncbi.nlm.nih.gov/24967740/

883. Almeida, LS, Araújo, MC, Zantut-Wittmann, DE, Assumpção, LV, Souza, TF, Silva, CM, et.al. Effect of thyroid-stimulating hormone in 68Ga-DOTATATE PET/CT of radioiodine-refractory thyroid carcinoma: a pilot study., Nucl Med Commun, 2018. 39 (5)(5): p. 441-450., https://pubmed.ncbi.nlm.nih.gov/29543624/

884. Kundu, P, Lata, S, Sharma, P, Singh, H, Malhotra, A, Bal, C, Prospective evaluation of (68)Ga-DOTA-NOC PET-CT in differentiated thyroid cancer patients with raised thyroglobulin and negative (131)I-whole body scan: comparison with (18)F-FDG PET-CT., Eur J Nucl Med Mol Imaging, 2014. 41 (7)(7): p. 1354-62., https://pubmed.ncbi.nlm.nih.gov/24562651/

885. Jhaveri, KS, Fischer, SE, Hosseini-Nik, H, Sreeharsha, B, Menezes, RJ, Gallinger, S, et.al. Prospective comparison of gadoxetic acid-enhanced liver MRI and contrast-enhanced CT with histopathological correlation for preoperative detection of colorectal liver metastases following chemotherapy and potential impact on surgical plan., HPB (Oxford), 2017. 19 (11)(11): p. 992-1000., https://pubmed.ncbi.nlm.nih.gov/28760631/

886. AWMF, S1-Leitlinie 064-009, Atemwegserkrankung – Bildgebende Diagnostik, 2017., https://register.awmf.org/de/leitlinien/detail/064-009

887. Bundesärztekammer, Leitlinie der Bundesärztekammer zur Qualitätssicherung in der ComputertomographieDeutsches Ärzteblatt, 2022., 10.3238/arztebl.2022.LL_Qualitätssicherung_Computertomographie

888. McLoughlin, LC, O'Kelly, F, O'Brien, C, Sheikh, M, Feeney, J, Torreggiani, W, et.al. The improved accuracy of planar bone scintigraphy by adding single photon emission computed tomography (SPECT-CT) to detect skeletal metastases from prostate cancer., Ir J Med Sci, 2016. 185 (1)(1): p. 101-5., https://pubmed.ncbi.nlm.nih.gov/25394725/

889. Lee, H, Lee, WW, Park, SY, Kim, SE, F-18 Sodium Fluoride Positron Emission Tomography/Computed Tomography for Detection of Thyroid Cancer Bone Metastasis Compared with Bone Scintigraphy., Korean J Radiol, 2016. 17 (2)(2): p. 281-8., https://pubmed.ncbi.nlm.nih.gov/26957915/

890. Jambor, I, Kuisma, A, Ramadan, S, Huovinen, R, Sandell, M, Kajander, S, et.al. Prospective evaluation of planar bone scintigraphy, SPECT, SPECT/CT, 18F-NaF PET/CT and whole body 1.5T MRI, including DWI, for the detection of bone metastases in high risk breast and prostate cancer patients: SKELETA clinical trial., Acta Oncol, 2016. 55 (1)(1): p. 59-67., https://pubmed.ncbi.nlm.nih.gov/25833330/

891. Teyateeti, A, Tocharoenchai, C, Muangsomboon, K, Komoltri, C, Pusuwan, P, A Comparison of Accuracy of Planar and Evolution SPECT/CT Bone Imaging in Differentiating Benign from Metastatic

Bone Lesions., J Med Assoc Thai, 2017. 100 (1)(1): p. 100-10., https://pubmed.ncbi.nlm.nih.gov/29911774/

892. Strobel, K, Burger, C, Seifert, B, Husarik, DB, Soyka, JD, Hany, TF, Characterization of focal bone lesions in the axial skeleton: performance of planar bone scintigraphy compared with SPECT and SPECT fused with CT., AJR Am J Roentgenol, 2007. 188 (5)(5): p. W467-74., https://pubmed.ncbi.nlm.nih.gov/17449746/

893. Sedonja, I, Budihna, NV, The benefit of SPECT when added to planar scintigraphy in patients with bone metastases in the spine., Clin Nucl Med, 1999. 24 (6)(6): p. 407-13., https://pubmed.ncbi.nlm.nih.gov/10361935/

894. Even-Sapir, E, Metser, U, Mishani, E, Lievshitz, G, Lerman, H, Leibovitch, I, The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP Planar bone scintigraphy, single- and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT., J Nucl Med, 2006. 47 (2)(2): p. 287-97., https://pubmed.ncbi.nlm.nih.gov/16455635/

895. Schirrmeister, H, Glatting, G, Hetzel, J, Nüssle, K, Arslandemir, C, Buck, AK, et.al. Prospective evaluation of the clinical value of planar bone scans, SPECT, and (18)F-labeled NaF PET in newly diagnosed lung cancer., J Nucl Med, 2001. 42 (12)(12): p. 1800-4., https://pubmed.ncbi.nlm.nih.gov/11752076/

896. Gurkan, G, Sarikaya, I, Sarikaya, A, Semiquantitative assessment of osteoblastic, osteolytic, and mixed lytic-sclerotic bone lesions on fluorodeoxyglucose positron emission tomography/computed tomography and bone scintigraphy., World J Nucl Med, 2019. 18 (2)(2): p. 132-136., https://pubmed.ncbi.nlm.nih.gov/31040743/

897. Chua, S, Gnanasegaran, G, Cook, GJ, Miscellaneous cancers (lung, thyroid, renal cancer, myeloma, and neuroendocrine tumors): role of SPECT and PET in imaging bone metastases., Semin Nucl Med, 2009. 39 (6)(6): p. 416-30., https://pubmed.ncbi.nlm.nih.gov/19801221/

898. Utsunomiya, D, Shiraishi, S, Imuta, M, Tomiguchi, S, Kawanaka, K, Morishita, S, et.al. Added value of SPECT/CT fusion in assessing suspected bone metastasis: comparison with scintigraphy alone and nonfused scintigraphy and CT., Radiology, 2006. 238 (1)(1): p. 264-71., https://pubmed.ncbi.nlm.nih.gov/16304081/

899. Beck, M., , Kuwert, T., Wertigkeit der SPECT/CT in der skelettszintigrafischen Diagnostik., in Der Nuklearmediziner, 2016. p. 8 - 21., https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0042-100693

900. Palmedo, H, Marx, C, Ebert, A, Kreft, B, Ko, Y, Türler, A, et.al. Whole-body SPECT/CT for bone scintigraphy: diagnostic value and effect on patient management in oncological patients., Eur J Nucl Med Mol Imaging, 2014. 41 (1)(1): p. 59-67., https://pubmed.ncbi.nlm.nih.gov/23974666/

901. Löfgren, J, Mortensen, J, Rasmussen, SH, Madsen, C, Loft, A, Hansen, AE, et.al. A Prospective Study Comparing , J Nucl Med, 2017. 58 (11)(11): p. 1778-1785., https://pubmed.ncbi.nlm.nih.gov/28798033/

902. Tenenbaum, F, Schlumberger, M, Bonnin, F, Lumbroso, J, Aubert, B, Benali, H, et.al. Usefulness of technetium-99m hydroxymethylene diphosphonate scans in localizing bone metastases of differentiated thyroid carcinoma., Eur J Nucl Med, 1993. 20 (12)(12): p. 1168-74., https://pubmed.ncbi.nlm.nih.gov/8299652/

903. Pacini, F, Fugazzola, L, Lippi, F, Ceccarelli, C, Centoni, R, Miccoli, P, et.al. Detection of thyroglobulin in fine needle aspirates of nonthyroidal neck masses: a clue to the diagnosis of metastatic differentiated thyroid cancer., J Clin Endocrinol Metab, 1992. 74 (6)(6): p. 1401-4., https://pubmed.ncbi.nlm.nih.gov/1592886/

904. Frasoldati, A, Toschi, E, Zini, M, Flora, M, Caroggio, A, Dotti, C, et.al. Role of thyroglobulin measurement in fine-needle aspiration biopsies of cervical lymph nodes in patients with differentiated thyroid cancer., Thyroid, 1999. 9 (2)(2): p. 105-11., https://pubmed.ncbi.nlm.nih.gov/10090308/

905. Torres, MR, Nóbrega Neto, SH, Rosas, RJ, Martins, AL, Ramos, AL, da Cruz, TR, Thyroglobulin in the washout fluid of lymph-node biopsy: what is its role in the follow-up of differentiated thyroid carcinoma?, Thyroid, 2014. 24 (1)(1): p. 7-18., https://pubmed.ncbi.nlm.nih.gov/24044517/

906. Cunha, N, Rodrigues, F, Curado, F, Ilhéu, O, Cruz, C, Naidenov, P, et.al. Thyroglobulin detection in fine-needle aspirates of cervical lymph nodes: a technique for the diagnosis of metastatic differentiated thyroid cancer., Eur J Endocrinol, 2007. 157 (1)(1): p. 101-7., https://pubmed.ncbi.nlm.nih.gov/17609408/

907. Jeon, SJ, Kim, E, Park, JS, Son, KR, Baek, JH, Kim, YS, et.al. Diagnostic benefit of thyroglobulin measurement in fine-needle aspiration for diagnosing metastatic cervical lymph nodes from papillary thyroid cancer: correlations with US features., Korean J Radiol, 2009. 10 (2)(2): p. 106-11., https://pubmed.ncbi.nlm.nih.gov/19270855/

908. Sigstad, E, Heilo, A, Paus, E, Holgersen, K, Grøholt, KK, Jørgensen, LH, et.al. The usefulness of detecting thyroglobulin in fine-needle aspirates from patients with neck lesions using a sensitive thyroglobulin assay., Diagn Cytopathol, 2007. 35 (12)(12): p. 761-7., https://pubmed.ncbi.nlm.nih.gov/18008339/

909. Grani, G, Fumarola, A, Thyroglobulin in lymph node fine-needle aspiration washout: a systematic review and meta-analysis of diagnostic accuracy., J Clin Endocrinol Metab, 2014. 99 (6)(6): p. 1970-82., https://pubmed.ncbi.nlm.nih.gov/24617715/

910. AWMF, S2k-Leitlinie Operative Therapie benigner Schilddrüsenerkrankungen, 2021., https://register.awmf.org/assets/guidelines/088-007l_S2k_operative_Therapie_benigner_Schilddruesenerkrankungen_2022-06_1_01.pdf

911. Cusano, NE, Rubin, MR, McMahon, DJ, Irani, D, Anderson, L, Levy, E, et.al. PTH(1-84) is associated with improved quality of life in hypoparathyroidism through 5 years of therapy., J Clin Endocrinol Metab, 2014. 99 (10)(10): p. 3694-9., https://pubmed.ncbi.nlm.nih.gov/24978675/

912. Sikjaer, T, Rolighed, L, Hess, A, Fuglsang-Frederiksen, A, Mosekilde, L, Rejnmark, L, Effects of PTH(1-84) therapy on muscle function and quality of life in hypoparathyroidism: results from a randomized controlled trial., Osteoporos Int, 2014. 25 (6)(6): p. 1717-26., https://pubmed.ncbi.nlm.nih.gov/24687385/

913. Mannstadt, M, Clarke, BL, Vokes, T, Brandi, ML, Ranganath, L, Fraser, WD, et.al. Efficacy and safety of recombinant human parathyroid hormone (1-84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study., Lancet Diabetes Endocrinol, 2013. 1 (4)(4): p. 275-83., https://pubmed.ncbi.nlm.nih.gov/24622413/

914. Sikjaer, T, Rejnmark, L, Rolighed, L, Heickendorff, L, Mosekilde, L, The effect of adding PTH(1-84) to conventional treatment of hypoparathyroidism: a randomized, placebo-controlled study., J Bone Miner Res, 2011. 26 (10)(10): p. 2358-70., https://pubmed.ncbi.nlm.nih.gov/21773992/

915. Orloff, LA, Wiseman, SM, Bernet, VJ, Fahey, TJ, Shaha, AR, Shindo, ML, et.al. American Thyroid Association Statement on Postoperative Hypoparathyroidism: Diagnosis, Prevention, and Management in Adults., Thyroid, 2018. 28 (7)(7): p. 830-841., https://pubmed.ncbi.nlm.nih.gov/29848235/

916. Bollerslev, J, Rejnmark, L, Marcocci, C, Shoback, DM, Sitges-Serra, A, van Biesen, W, et.al. European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults., Eur J Endocrinol, 2015. 173 (2)(2): p. G1-20., https://pubmed.ncbi.nlm.nih.gov/26160136/

917. Khan, AA, Bilezikian, JP, Brandi, ML, Clarke, BL, Gittoes, NJ, Pasieka, JL, et.al. Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop., J Bone Miner Res, 2022. 37 (12)(12): p. 2568-2585., https://pubmed.ncbi.nlm.nih.gov/36054621/

918. Bilezikian, JP, Khan, A, Potts, JT, Brandi, ML, Clarke, BL, Shoback, D, et.al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research., J Bone Miner Res, 2011. 26 (10)(10): p. 2317-37., https://pubmed.ncbi.nlm.nih.gov/21812031/

919. Stack, BC, Bimston, DN, Bodenner, DL, Brett, EM, Dralle, H, Orloff, LA, et.al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY DISEASE STATE CLINICAL REVIEW: POSTOPERATIVE HYPOPARATHYROIDISM--DEFINITIONS AND MANAGEMENT., Endocr Pract, 2015. 21 (6)(6): p. 674-85., https://pubmed.ncbi.nlm.nih.gov/26135962/

920. Franch-Arcas, G, González-Sánchez, C, Aguilera-Molina, YY, Rozo-Coronel, O, Estévez-Alonso, JS, Muñoz-Herrera, Á, Is there a case for selective, rather than routine, preoperative laryngoscopy in thyroid surgery?, Gland Surg, 2015. 4 (1)(1): p. 8-18., https://pubmed.ncbi.nlm.nih.gov/25713775/

921. Sittel, C, Stennert, E, Thumfart, WF, Dapunt, U, Eckel, HE, Prognostic value of laryngeal electromyography in vocal fold paralysis., Arch Otolaryngol Head Neck Surg, 2001. 127 (2)(2): p. 155-60., https://pubmed.ncbi.nlm.nih.gov/11177032/

922. Farrag, TY, Samlan, RA, Lin, FR, Tufano, RP, The utility of evaluating true vocal fold motion before thyroid surgery., Laryngoscope, 2006. 116 (2)(2): p. 235-8., https://pubmed.ncbi.nlm.nih.gov/16467711/

923. Birben, B, Özden, S, Er, S, Saylam, B, Is Vocal Cord Assessment before Total Thyroidectomy Required for All Patients?, Am Surg, 2019. 85 (11)(11): p. 1265-1268., https://pubmed.ncbi.nlm.nih.gov/31775969/

924. Chandrasekhar, SS, Randolph, GW, Seidman, MD, Rosenfeld, RM, Angelos, P, Barkmeier-Kraemer, J, et.al. Clinical practice guideline: improving voice outcomes after thyroid surgery., Otolaryngol Head Neck Surg, 2013. 148 (6 Suppl)(6 Suppl): p. S1-37., https://pubmed.ncbi.nlm.nih.gov/23733893/

925. Musholt, TJ, Musholt, PB, Garm, J, Napiontek, U, Keilmann, A, Changes of the speaking and singing voice after thyroid or parathyroid surgery., Surgery, 2006. 140 (6)(6): p. 978-88; discussion 988-9., https://pubmed.ncbi.nlm.nih.gov/17188147/

926. Kletzien, H, Macdonald, CL, Orne, J, Francis, DO, Leverson, G, Wendt, E, et.al. Comparison Between Patient-Perceived Voice Changes and Quantitative Voice Measures in the First Postoperative Year After Thyroidectomy: A Secondary Analysis of a Randomized Clinical Trial., JAMA Otolaryngol Head Neck Surg, 2018. 144 (11)(11): p. 995-1003., https://pubmed.ncbi.nlm.nih.gov/29710208/

927. Hayward, NJ, Grodski, S, Yeung, M, Johnson, WR, Serpell, J, Recurrent laryngeal nerve injury in thyroid surgery: a review., ANZ J Surg, 2013. 83 (1-2)(1-2): p. 15-21., https://pubmed.ncbi.nlm.nih.gov/22989215/

928. Schneider, R, Machens, A, Lorenz, K, Dralle, H, Intraoperative nerve monitoring in thyroid surgery-shifting current paradigms., Gland Surg, 2020. 9 (Suppl 2)(Suppl 2): p. S120-S128., https://pubmed.ncbi.nlm.nih.gov/32175252/

929. Verdolini-Marston, K, Burke, MK, Lessac, A, Glaze, L, Caldwell, E, Preliminary study of two methods of treatment for laryngeal nodules., J Voice, 1995. 9 (1)(1): p. 74-85., https://pubmed.ncbi.nlm.nih.gov/7757153/

930. Fu, S, Theodoros, DG, Ward, EC, Intensive versus traditional voice therapy for vocal nodules: perceptual, physiological, acoustic and aerodynamic changes., J Voice, 2015. 29 (2)(2): p. 260.e31-44., https://pubmed.ncbi.nlm.nih.gov/25311594/

931. da Cunha Pereira, G, de Oliveira Lemos, I, Dalbosco Gadenz, C, Cassol, M, Effects of Voice Therapy on Muscle Tension Dysphonia: A Systematic Literature Review., J Voice, 2018. 32 (5)(5): p. 546-552., https://pubmed.ncbi.nlm.nih.gov/28739332/

932. Yu, WV, Wu, CW, Speech therapy after thyroidectomy., Gland Surg, 2017. 6 (5)(5): p. 501-509., https://pubmed.ncbi.nlm.nih.gov/29142841/

933. Hess, MM, Fleischer, S, Laryngeal framework surgery: current strategies., Curr Opin Otolaryngol Head Neck Surg, 2016. 24 (6)(6): p. 505-509., https://pubmed.ncbi.nlm.nih.gov/27585082/

934. Kraus, DH, Orlikoff, RF, Rizk, SS, Rosenberg, DB, Arytenoid adduction as an adjunct to type I thyroplasty for unilateral vocal cord paralysis., Head Neck, 1999. 21 (1)(1): p. 52-9., https://pubmed.ncbi.nlm.nih.gov/9890351/

935. Müller, AH, Förster, G, [Reinnervation and neurostimulation of the larynx]., HNO, 2013. 61 (2)(2): p. 102-7., https://pubmed.ncbi.nlm.nih.gov/23241856/

936. Tucker, HM, Long-term preservation of voice improvement following surgical medialization and reinnervation for unilateral vocal fold paralysis., J Voice, 1999. 13 (2)(2): p. 251-6., https://pubmed.ncbi.nlm.nih.gov/10442756/

937. Mueller, AH, Hagen, R, Pototschnig, C, Foerster, G, Grossmann, W, Baumbusch, K, et.al. Laryngeal pacing for bilateral vocal fold paralysis: Voice and respiratory aspects., Laryngoscope, 2017. 127 (8)(8): p. 1838-1844., https://pubmed.ncbi.nlm.nih.gov/27943294/

938. Lee, DH, Lee, SY, Lee, M, Seok, J, Park, SJ, Jin, YJ, et.al. Natural Course of Unilateral Vocal Fold Paralysis and Optimal Timing of Permanent Treatment., JAMA Otolaryngol Head Neck Surg, 2020. 146 (1)(1): p. 30-35., https://pubmed.ncbi.nlm.nih.gov/31750869/

939. Tan, LG, Nan, L, Thumboo, J, Sundram, F, Tan, LK, Health-related quality of life in thyroid cancer survivors., Laryngoscope, 2007. 117 (3)(3): p. 507-10., https://pubmed.ncbi.nlm.nih.gov/17334313/

940. Hoftijzer, HC, Heemstra, KA, Corssmit, EP, van der Klaauw, AA, Romijn, JA, Smit, JW, Quality of life in cured patients with differentiated thyroid carcinoma., J Clin Endocrinol Metab, 2008. 93 (1)(1): p. 200-3., https://pubmed.ncbi.nlm.nih.gov/17956954/

941. Gamper, EM, Wintner, LM, Rodrigues, M, Buxbaum, S, Nilica, B, Singer, S, et.al. Persistent quality of life impairments in differentiated thyroid cancer patients: results from a monitoring programme., Eur J Nucl Med Mol Imaging, 2015. 42 (8)(8): p. 1179-88., https://pubmed.ncbi.nlm.nih.gov/25771905/

942. Eustatia-Rutten, CF, Corssmit, EP, Pereira, AM, Frölich, M, Bax, JJ, Romijn, JA, et.al. Quality of life in longterm exogenous subclinical hyperthyroidism and the effects of restoration of euthyroidism, a randomized controlled trial., Clin Endocrinol (Oxf), 2006. 64 (3)(3): p. 284-91., https://pubmed.ncbi.nlm.nih.gov/16487438/

943. Schultz, PN, Stava, C, Vassilopoulou-Sellin, R, Health profiles and quality of life of 518 survivors of thyroid cancer., Head Neck, 2003. 25 (5)(5): p. 349-56., https://pubmed.ncbi.nlm.nih.gov/12692870/

944. Diamond-Rossi, SA, Jonklaas, J, Jensen, RE, Kuo, C, Stearns, S, Esposito, G, et.al. Looking under the hood of "the Cadillac of cancers:" radioactive iodine-related craniofacial side effects among patients with thyroid cancer., J Cancer Surviv, 2020. 14 (6)(6): p. 847-857., https://pubmed.ncbi.nlm.nih.gov/32506220/

945. Husson, O, Mols, F, van de Poll-Franse, L, de Vries, J, Schep, G, Thong, MS, Variation in fatigue among 6011 (long-term) cancer survivors and a normative population: a study from the population-based PROFILES registry., Support Care Cancer, 2015. 23 (7)(7): p. 2165-74., https://pubmed.ncbi.nlm.nih.gov/25556703/

946. Husson, O, Nieuwlaat, WA, Oranje, WA, Haak, HR, van de Poll-Franse, LV, Mols, F, Fatigue among short- and long-term thyroid cancer survivors: results from the population-based PROFILES registry., Thyroid, 2013. 23 (10)(10): p. 1247-55., https://pubmed.ncbi.nlm.nih.gov/23578315/

947. Alhashemi, A, Jones, JM, Goldstein, DP, Mina, DS, Thabane, L, Sabiston, CM, et.al. An Exploratory Study of Fatigue and Physical Activity in Canadian Thyroid Cancer Patients., Thyroid, 2017. 27 (9)(9): p. 1156-1163., https://pubmed.ncbi.nlm.nih.gov/28712348/

948. Vigário, Pdos S, Chachamovitz, DS, Cordeiro, MF, Teixeira, Pde F, de Castro, CL, de Oliveira, FP, et.al. Effects of physical activity on body composition and fatigue perception in patients on thyrotropin-suppressive therapy for differentiated thyroid carcinoma., Thyroid, 2011. 21 (7)(7): p. 695-700., https://pubmed.ncbi.nlm.nih.gov/21615309/

949. Ricarte-Filho, J, Ganly, I, Rivera, M, Katabi, N, Fu, W, Shaha, A, et.al. Papillary thyroid carcinomas with cervical lymph node metastases can be stratified into clinically relevant prognostic categories using oncogenic BRAF, the number of nodal metastases, and extra-nodal extension., Thyroid, 2012. 22 (6)(6): p. 575-84., https://pubmed.ncbi.nlm.nih.gov/22471242/

950. Ronga, G, Toteda, M, D'Apollo, R, De Cristofaro, F, Filesi, M, Acqualagna, G, et.al. Lymph node metastases from differentiated thyroid carcinoma: does radioiodine still play a role?, Clin Ter, 2012. 163 (5)(5): p. 377-81., https://pubmed.ncbi.nlm.nih.gov/23099964/

951. Trybek, T, Kowalska, A, Does the presence of regional lymph node metastases have any impact on the complete remission rate in patients with distant metastases of papillary thyroid carcinoma (PTC), treated by radioiodine therapy?, Endokrynol Pol, 2010. 61 (5)(5): p. 443-5., https://pubmed.ncbi.nlm.nih.gov/21049455/

952. Cao, C. J., Dou, C. Y., Lian, J., Luan, Z. S., Zhou, W., Xie, W., et.al. Clinical outcomes and associated factors of radioiodine-131 treatment in differentiated thyroid cancer with cervical lymph node metastasis, Oncology Letters, 2018. 15(5): p. 8141-8148., https://pubmed.ncbi.nlm.nih.gov/29740497/

953. Ilhan, H., Mustafa, M., Bartenstein, P., Kuwert, T., Schmidt, D., Rate of elimination of radioiodine-avid lymph node metastases of differentiated thyroid carcinoma by postsurgical radioiodine ablation. A bicentric study, Nuklearmedizin, 2016. 55(6): p. 221-227., https://pubmed.ncbi.nlm.nih.gov/27588323/

954. Wu, X, Gu, H, Gao, Y, Li, B, Fan, R, Clinical outcomes and prognostic factors of radioiodine ablation therapy for lymph node metastases from papillary thyroid carcinoma., Nucl Med Commun, 2018. 39 (1)(1): p. 22-27., https://pubmed.ncbi.nlm.nih.gov/29135721/

955. He, Y., Pan, M. Z., Huang, J. M., Xie, P., Zhang, F., Wei, L. G., Iodine-131: An Effective Method for Treating Lymph Node Metastases of Differentiated Thyroid Cancer, Med Sci Monit, 2016. 22: p. 4924-4928., https://pubmed.ncbi.nlm.nih.gov/27974741/

956. Wojtczak, B, Sutkowski, K, Kaliszewski, K, Barczyński, M, Bolanowski, M, Thyroid reoperation using intraoperative neuromonitoring., Endocrine, 2017. 58 (3)(3): p. 458-466., https://pubmed.ncbi.nlm.nih.gov/29052179/

957. Sedlmaier, A, Steinmüller, T, Hermanns, M, Nawka, T, Weikert, S, Sedlmaier, B, et.al. Continuous versus intermittent intraoperative neuromonitoring in complex benign thyroid surgery: A retrospective analysis and prospective follow-up., Clin Otolaryngol, 2019. 44 (6)(6): p. 1071-1079., https://pubmed.ncbi.nlm.nih.gov/31565844/

958. Sabra, M. M., Dominguez, J. M., Grewal, R. K., Larson, S. M., Ghossein, R. A., Tuttle, R. M., et.al. Clinical outcomes and molecular profile of differentiated thyroid cancers with radioiodine-avid distant metastases, J Clin Endocrinol Metab, 2013. 98(5): p. E829-36.

959. Higashi, T., Nishii, R., Yamada, S., Nakamoto, Y., Ishizu, K., Kawase, S., et.al. Delayed initial radioactive iodine therapy resulted in poor survival in patients with metastatic differentiated thyroid carcinoma: a retrospective statistical analysis of 198 cases, J Nucl Med, 2011. 52(5): p. 683-9., https://pubmed.ncbi.nlm.nih.gov/21498534/

960. Shokoohi, A., Berthelet, E., Gill, S., Prisman, E., Sexsmith, G., Tran, E., et.al. Treatment for Recurrent Differentiated Thyroid Cancer: A Canadian Population Based Experience, Cureus, 2020. 12(2): p. e7122.

961. Ywata de Carvalho, A., Kohler, H. F., Gomes, C. C., Vartanian, J. G., Kowalski, L. P., Predictive factors for recurrence of papillary thyroid carcinoma: analysis of 4,085 patients, Acta Otorhinolaryngol Ital, 2021. 41(3): p. 236-242., https://pubmed.ncbi.nlm.nih.gov/34264917/

962. Cho, S. W., Choi, H. S., Yeom, G. J., Lim, J. A., Moon, J. H., Park, D. J., et.al. Long-term prognosis of differentiated thyroid cancer with lung metastasis in Korea and its prognostic factors, Thyroid, 2014. 24(2): p. 277-86., https://pubmed.ncbi.nlm.nih.gov/23758653/

963. Sampson, E., Brierley, J. D., Le, L. W., Rotstein, L., Tsang, R. W., Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis, Cancer, 2007. 110(7): p. 1451-6.

964. Nixon, I. J., Whitcher, M. M., Palmer, F. L., Tuttle, R. M., Shaha, A. R., Shah, J. P., et.al. The impact of distant metastases at presentation on prognosis in patients with differentiated carcinoma of the thyroid gland, Thyroid, 2012. 22(9): p. 884-9.

965. Lin, J. D., Hsueh, C., Chao, T. C., Long-Term Follow-Up of the Therapeutic Outcomes for Papillary Thyroid Carcinoma With Distant Metastasis, Medicine, 2015. 94(26): p. e1063., http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medc&AN=26131826, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4504566/pdf/medi-94-e1063.pdf

966. Jung, C. K., Lee, S., Bae, J. S., Lim, D. J., Late-onset distant metastases confer poor prognosis in patients with well-differentiated thyroid cancer, Gland Surg, 2020. 9(5): p. 1857-1866.

967. Lin, J. D., Kuo, S. F., Huang, B. Y., Lin, S. F., Chen, S. T., The efficacy of radioactive iodine for the treatment of well-differentiated thyroid cancer with distant metastasis, Nuclear Medicine Communications, 2018. 39(12): p. 1091-1096., https://pubmed.ncbi.nlm.nih.gov/30180044/

968. Schlumberger, M., Challeton, C., De Vathaire, F., Travagli, J. P., Gardet, P., Lumbroso, J. D., et.al. Radioactive iodine treatment and external radiotherapy for lung and bone metastases from thyroid carcinoma, J Nucl Med, 1996. 37(4): p. 598-605.

969. Durante, C., Haddy, N., Baudin, E., Leboulleux, S., Hartl, D., Travagli, J. P., et.al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy, J Clin Endocrinol Metab, 2006. 91(8): p. 2892-9., https://pubmed.ncbi.nlm.nih.gov/16684830/

970. Ito, Y., Masuoka, H., Fukushima, M., Inoue, H., Kihara, M., Tomoda, C., et.al. Prognosis and prognostic factors of patients with papillary carcinoma showing distant metastasis at surgery (M1 patients) in Japan, Endocr J, 2010. 57(6): p. 523-31., https://pubmed.ncbi.nlm.nih.gov/20379035/

971. Li, C., Wu, Q., Sun, S., Radioactive Iodine Therapy in Patients With Thyroid Carcinoma With Distant Metastases: A SEER-Based Study, Cancer Control, 2020. 27(1): p. 1073274820914661.

972. Kim, H., Kim, H. I., Kim, S. W., Jung, J., Jeon, M. J., Kim, W. G., et.al. Prognosis of Differentiated Thyroid Carcinoma with Initial Distant Metastasis: A Multicenter Study in Korea, Endocrinol Metab (Seoul), 2018. 33(2): p. 287-295.

973. Madani, A, Jozaghi, Y, Tabah, R, How, J, Mitmaker, E, Rare metastases of well-differentiated thyroid cancers: a systematic review., Ann Surg Oncol, 2015. 22 (2)(2): p. 460-6., https://pubmed.ncbi.nlm.nih.gov/25192681/

974. Mihailovic, JM, Stefanovic, LJ, Malesevic, MD, Erak, MD, Tesanovic, DD, Metastatic differentiated thyroid carcinoma: clinical management and outcome of disease in patients with initial and late distant metastases., Nucl Med Commun, 2009. 30 (7)(7): p. 558-64., https://pubmed.ncbi.nlm.nih.gov/19436230/

975. Zhang, XY, Sun, JW, Qiu, ZL, Wang, Y, Chen, XY, Zhao, JH, et.al. Clinical outcomes and prognostic factors in patients with no less than three distant organ system metastases from differentiated thyroid carcinoma., Endocrine, 2019. 66 (2)(2): p. 254-265., https://pubmed.ncbi.nlm.nih.gov/31317522/

976. Zunino, A, Pitoia, F, Faure, E, Reyes, A, Sala, M, Sklate, R, et.al. Unusual metastases from differentiated thyroid carcinoma: analysis of 36 cases., Endocrine, 2019. 65 (3)(3): p. 630-636., https://pubmed.ncbi.nlm.nih.gov/31327159/

977. Sabra, M. M., Ghossein, R., Tuttle, R. M., Time Course and Predictors of Structural Disease Progression in Pulmonary Metastases Arising from Follicular Cell-Derived Thyroid Cancer, Thyroid, 2016. 26(4): p. 518-24.

978. Ohkuwa, K., Sugino, K., Nagahama, M., Kitagawa, W., Matsuzu, K., Suzuki, A., et.al. Risk stratification in differentiated thyroid cancer with RAI-avid lung metastases, Endocr Connect, 2021. 10(8): p. 825-833.

979. Casara, D., Rubello, D., Saladini, G., Masarotto, G., Favero, A., Girelli, M. E., et.al. Different features of pulmonary metastases in differentiated thyroid cancer: natural history and multivariate statistical analysis of prognostic variables, J Nucl Med, 1993. 34(10): p. 1626-31., https://pubmed.ncbi.nlm.nih.gov/8410272/

980. Song, H. J., Qiu, Z. L., Shen, C. T., Wei, W. J., Luo, Q. Y., Pulmonary metastases in differentiated thyroid cancer: efficacy of radioiodine therapy and prognostic factors, European Journal of Endocrinology, 2015. 173(3): p. 399-408., https://pubmed.ncbi.nlm.nih.gov/26104753/

981. Zhang, X., Liu, D. S., Luan, Z. S., Zhang, F., Liu, X. H., Zhou, W., et.al. Efficacy of radioiodine therapy for treating 20 patients with pulmonary metastases from differentiated thyroid cancer and a meta-analysis of the current literature, Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico, 2018. 20(7): p. 928-935., https://pubmed.ncbi.nlm.nih.gov/29119458/

982. Wang, C., Zhang, R., Wang, R., Meng, Z., Zhang, G., Dong, F., et.al. Predictive Value of Thyroglobulin Changes for the Curative Effect of Radioiodine Therapy in Patients With Metastatic Differentiated Thyroid Carcinoma, Front Endocrinol (Lausanne), 2021. 12: p. 667544., https://pubmed.ncbi.nlm.nih.gov/34040584/

983. Yang, J., Zheng, R., Liang, M., Jia, Y., Lin, L., Geng, J., et.al. Association of the Cumulative Dose of Radioactive Iodine Therapy With Overall Survival in Patients With Differentiated Thyroid Cancer and Pulmonary Metastases, Front Oncol, 2019. 9: p. 558., https://pubmed.ncbi.nlm.nih.gov/31316914/

984. Kim, M, Kim, WG, Park, S, Kwon, H, Jeon, MJ, Lee, JJ, et.al. Initial Size of Metastatic Lesions Is Best Prognostic Factor in Patients with Metastatic Differentiated Thyroid Carcinoma Confined to the Lung., Thyroid, 2017. 27 (1)(1): p. 49-58., https://pubmed.ncbi.nlm.nih.gov/27750021/

985. Lin, J. D., Chao, T. C., Hsueh, C., Follicular thyroid carcinomas with lung metastases: a 23-year retrospective study, Endocr J, 2004. 51(2): p. 219-25.

986. Sabra, M. M., Sherman, E. J., Tuttle, R. M., Tumor volume doubling time of pulmonary metastases predicts overall survival and can guide the initiation of multikinase inhibitor therapy in patients with metastatic, follicular cell-derived thyroid carcinoma, Cancer, 2017. 123(15): p. 2955-2964.

987. Kim, D. H., Jung, J. H., Son, S. H., Kim, C. Y., Hong, C. M., Jeong, S. Y., et.al. Difference of clinical and radiological characteristics according to radioiodine avidity in pulmonary metastases of differentiated thyroid cancer, Nucl Med Mol Imaging, 2014. 48(1): p. 55-62.

988. Long, B., Yang, M., Yang, Z., Yi, H., Li, L., Assessment of radioiodine therapy efficacy for treatment of differentiated thyroid cancer patients with pulmonary metastasis undetected by chest computed tomography, Oncol Lett, 2016. 11(2): p. 965-968.

989. Pawelczak, M, David, R, Franklin, B, Kessler, M, Lam, L, Shah, B, Outcomes of children and adolescents with well-differentiated thyroid carcinoma and pulmonary metastases following ^{131}I treatment: a systematic review., Thyroid, 2010. 20 (10)(10): p. 1095-101., https://pubmed.ncbi.nlm.nih.gov/20860418/

990. Zhang, XY, Song, HJ, Qiu, ZL, Shen, CT, Chen, XY, Sun, ZK, et.al. Pulmonary metastases in children and adolescents with papillary thyroid cancer in China: prognostic factors and outcomes from treatment with , Endocrine, 2018. 62 (1)(1): p. 149-158., https://pubmed.ncbi.nlm.nih.gov/30022382/

991. Slook, O, Levy, S, Slutzky-Shraga, I, Tsvetov, G, Robenshtok, E, Shimon, I, et.al. LONG-TERM OUTCOMES AND PROGNOSTIC FACTORS IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA AND BONE METASTASES., Endocr Pract, 2019. 25 (5)(5): p. 427-437., https://pubmed.ncbi.nlm.nih.gov/30657361/

992. Qi, L., Zhang, W., Ren, X., Xu, R., Liu, C., Tu, C., et.al. Incidence and Predictors of Synchronous Bone Metastasis in Newly Diagnosed Differentiated Thyroid Cancer: A Real-World Population-Based Study, Front Surg, 2022. 9: p. 778303.

993. Iñiguez-Ariza, N. M., Bible, K. C., Clarke, B. L., Bone metastases in thyroid cancer, J Bone Oncol, 2020. 21: p. 100282., https://pubmed.ncbi.nlm.nih.gov/32154098/

994. Varadarajan, VV, Pace, EK, Patel, V, Sawhney, R, Amdur, RJ, Dziegielewski, PT, Follicular thyroid carcinoma metastasis to the facial skeleton: a systematic review., BMC Cancer, 2017. 17 (1)(1): p. 225., https://pubmed.ncbi.nlm.nih.gov/28351395/

995. Halnan, K. E., Roberts, P. H., Paraplegia caused by spinal metastasis from thyroid cancer, Br Med J, 1967. 3(5564): p. 534-6., https://pubmed.ncbi.nlm.nih.gov/6038321/

996. Ramadan, S, Ugas, MA, Berwick, RJ, Notay, M, Cho, H, Jerjes, W, et.al. Spinal metastasis in thyroid cancer., Head Neck Oncol, 2012. 4 (): p. 39., https://pubmed.ncbi.nlm.nih.gov/22730910/

997. Califano, I, Deutsch, S, Löwenstein, A, Cabezón, C, Pitoia, F, Outcomes of patients with bone metastases from differentiated thyroid cancer., Arch Endocrinol Metab, 2018. 62 (1)(1): p. 14-20., https://pubmed.ncbi.nlm.nih.gov/29694635/

998. Petrich, T., Widjaja, A., Musholt, T. J., Hofmann, M., Brunkhorst, T., Ehrenheim, C., et.al. Outcome after radioiodine therapy in 107 patients with differentiated thyroid carcinoma and initial bone metastases: side-effects and influence of age, Eur J Nucl Med, 2001. 28(2): p. 203-8.

999. Robenshtok, E., Farooki, A., Grewal, R. K., Tuttle, R. M., Natural history of small radioiodine-avid bone metastases that have no structural correlate on imaging studies, Endocrine, 2014. 47(1): p. 266-72.

1000. Osborne, J. R., Kondraciuk, J. D., Rice, S. L., Zhou, X., Knezevic, A., Spratt, D. E., et.al. Thyroid Cancer Brain Metastasis: Survival and Genomic Characteristics of a Large Tertiary Care Cohort, Clin Nucl Med, 2019. 44(7): p. 544-549.

1001. Mazziotti, G, Formenti, AM, Panarotto, MB, Arvat, E, Chiti, A, Cuocolo, A, et.al. Real-life management and outcome of thyroid carcinoma-related bone metastases: results from a nationwide multicenter experience., Endocrine, 2018. 59 (1)(1): p. 90-101., https://pubmed.ncbi.nlm.nih.gov/29110129/

1002. Kato, S., Demura, S., Shinmura, K., Yokogawa, N., Shimizu, T., Tsuchiya, H., Current Management of Bone Metastases from Differentiated Thyroid Cancer, Cancers (Basel), 2021. 13(17):

1003. Shen, J., Wang, S., Zhao, X., Shao, X., Jiang, X., Dai, Y., et.al. Skull metastasis from follicular thyroid carcinoma: report of three cases and review of literature, Int J Clin Exp Pathol, 2015. 8(11): p. 15285-93., https://pubmed.ncbi.nlm.nih.gov/26823882/

1004. Shimmura, H., Mori, E., Sekine, R., Tei, M., Otori, N., Metastasis of Papillary Thyroid Carcinoma to the Maxillary Sinus: Case Report and Review of the Literature, Case Rep Otolaryngol, 2020. 2020: p. 4056901.

1005. Deandreis, D, Rubino, C, Tala, H, Leboulleux, S, Terroir, M, Baudin, E, et.al. Comparison of Empiric Versus Whole-Body/-Blood Clearance Dosimetry-Based Approach to Radioactive Iodine Treatment in Patients with Metastases from Differentiated Thyroid Cancer., J Nucl Med, 2017. 58 (5)(5): p. 717-722., https://pubmed.ncbi.nlm.nih.gov/27738010/

1006. Hong, YW, Lin, JD, Yu, MC, Hsu, CC, Lin, YS, Outcomes and prognostic factors in thyroid cancer patients with cranial metastases: A retrospective cohort study of 4,683 patients., Int J Surg, 2018. 55 (): p. 182-187., https://pubmed.ncbi.nlm.nih.gov/29883619/

1007. Wu, T., Jiao, Z., Li, Y., Peng, J., Yao, F., Chen, W., et.al. Brain Metastases From Differentiated Thyroid Carcinoma: A Retrospective Study of 22 Patients, Front Endocrinol (Lausanne), 2021. 12: p. 730025., https://pubmed.ncbi.nlm.nih.gov/34603207/

1008. Simões-Pereira, J., Macedo, D., Bugalho, M. J., Clinical outcomes of a cohort of patients with central nervous system metastases from thyroid cancer, Endocr Connect, 2016. 5(6): p. 82-88.

1009. Slutzky-Shraga, I., Gorshtein, A., Popovitzer, A., Robenshtok, E., Tsvetov, G., Akirov, A., et.al. Clinical characteristics and disease outcome of patients with non-medullary thyroid cancer and brain metastases, Oncol Lett, 2018. 15(1): p. 672-676.

1010. Gomes-Lima, C. J., Wu, D., Rao, S. N., Punukollu, S., Hritani, R., Zeymo, A., et.al. Brain Metastases From Differentiated Thyroid Carcinoma: Prevalence, Current Therapies, and Outcomes, J Endocr Soc, 2019. 3(2): p. 359-371., https://pubmed.ncbi.nlm.nih.gov/30706042/

1011. Guelho, D., Ribeiro, C., Melo, M., Carrilho, F., Long-term survival in a patient with brain metastases of papillary thyroid carcinoma, BMJ Case Rep, 2016. 2016:, https://pubmed.ncbi.nlm.nih.gov/26961557/

1012. Vrachimis, A, Schmid, KW, Jürgens, H, Schober, O, Weckesser, M, Riemann, B, Cerebral metastases from thyroid carcinoma: complete remission following radioiodine treatment., Dtsch Arztebl Int, 2013. 110 (50)(50): p. 861-6., https://pubmed.ncbi.nlm.nih.gov/24399028/

1013. Spitzweg, C, Bible, KC, Hofbauer, LC, Morris, JC, Advanced radioiodine-refractory differentiated thyroid cancer: the sodium iodide symporter and other emerging therapeutic targets., Lancet Diabetes Endocrinol, 2014. 2 (10)(10): p. 830-42., https://pubmed.ncbi.nlm.nih.gov/24898835/

1014. Fugazzola, L, Elisei, R, Fuhrer, D, Jarzab, B, Leboulleux, S, Newbold, K, et.al. 2019 European Thyroid Association Guidelines for the Treatment and Follow-Up of Advanced Radioiodine-

Refractory Thyroid Cancer., Eur Thyroid J, 2019. 8 (5)(5): p. 227-245., https://pubmed.ncbi.nlm.nih.gov/31768334/

1015. Filetti, S, Durante, C, Hartl, DM, Leboulleux, S, Locati, LD, Newbold, K, et.al. ESMO Clinical Practice Guideline update on the use of systemic therapy in advanced thyroid cancer., Ann Oncol, 2022. 33 (7)(7): p. 674-684., https://pubmed.ncbi.nlm.nih.gov/35491008/

1016. Schutz, FA, Je, Y, Richards, CJ, Choueiri, TK, Meta-analysis of randomized controlled trials for the incidence and risk of treatment-related mortality in patients with cancer treated with vascular endothelial growth factor tyrosine kinase inhibitors., J Clin Oncol, 2012. 30 (8)(8): p. 871-7., https://pubmed.ncbi.nlm.nih.gov/22312105/

1017. Brose, MS, Nutting, CM, Jarzab, B, Elisei, R, Siena, S, Bastholt, L, et.al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial., Lancet, 2014. 384 (9940)(9940): p. 319-28., https://pubmed.ncbi.nlm.nih.gov/24768112/

1018. Schlumberger, M, Tahara, M, Wirth, LJ, Robinson, B, Brose, MS, Elisei, R, et.al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer., N Engl J Med, 2015. 372 (7)(7): p. 621-30., https://pubmed.ncbi.nlm.nih.gov/25671254/

1019. Brose, MS, Robinson, B, Sherman, SI, Krajewska, J, Lin, CC, Vaisman, F, et.al. Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial., Lancet Oncol, 2021. 22 (8)(8): p. 1126-1138., https://pubmed.ncbi.nlm.nih.gov/34237250/

1020. Brose, MS, Robinson, BG, Sherman, SI, Jarzab, B, Lin, CC, Vaisman, F, et.al. Cabozantinib for previously treated radioiodine-refractory differentiated thyroid cancer: Updated results from the phase 3 COSMIC-311 trial., Cancer, 2022. 128 (24)(24): p. 4203-4212., https://pubmed.ncbi.nlm.nih.gov/36259380/

1021. Brose, MS, Worden, FP, Newbold, KL, Guo, M, Hurria, A, Effect of Age on the Efficacy and Safety of Lenvatinib in Radioiodine-Refractory Differentiated Thyroid Cancer in the Phase III SELECT Trial., J Clin Oncol, 2017. 35 (23)(23): p. 2692-2699., https://pubmed.ncbi.nlm.nih.gov/28613956/

1022. Hanna, GJ, Busaidy, NL, Chau, NG, Wirth, LJ, Barletta, JA, Calles, A, et.al. Genomic Correlates of Response to Everolimus in Aggressive Radioiodine-refractory Thyroid Cancer: A Phase II Study., Clin Cancer Res, 2018. 24 (7)(7): p. 1546-1553., https://pubmed.ncbi.nlm.nih.gov/29301825/

1023. Bible, KC, Suman, VJ, Molina, JR, Smallridge, RC, Maples, WJ, Menefee, ME, et.al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study., Lancet Oncol, 2010. 11 (10)(10): p. 962-72., https://pubmed.ncbi.nlm.nih.gov/20851682/

1024. Leboulleux, S, Bastholt, L, Krause, T, de la Fouchardiere, C, Tennvall, J, Awada, A, et.al. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial., Lancet Oncol, 2012. 13 (9)(9): p. 897-905., https://pubmed.ncbi.nlm.nih.gov/22898678/

1025. Brose MS, , Fagin JA, , Wirth LJ, , Elisei R, , Sugitani I, , Wu Y, et al., Impact of TSH levels on response to vandetanib in patients with locally advanced or metastatic differentiated thyroid cancer (DTC) who are refractory or unsuitable for radioiodine (RAI) therapy: a phase III study (VERIFY)Thyroid, 2016.

1026. Carr, LL, Mankoff, DA, Goulart, BH, Eaton, KD, Capell, PT, Kell, EM, et.al. Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid cancer and metastatic medullary carcinoma of the thyroid with functional imaging correlation., Clin Cancer Res, 2010. 16 (21)(21): p. 5260-8., https://pubmed.ncbi.nlm.nih.gov/20847059/

1027. Cohen, E., Needles, B., Cullen, K., Wong, S., III, J., Ivy, S., et.al. Phase 2 study of sunitinib in refractory thyroid cancer, 2008/05/20. 26: p. 6025 - 6025.

1028. Cohen, EE, Rosen, LS, Vokes, EE, Kies, MS, Forastiere, AA, Worden, FP, et.al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study., J Clin Oncol, 2008. 26 (29)(29): p. 4708-13., https://pubmed.ncbi.nlm.nih.gov/18541897/

1029. Locati, LD, Licitra, L, Agate, L, Ou, SH, Boucher, A, Jarzab, B, et.al. Treatment of advanced thyroid cancer with axitinib: Phase 2 study with pharmacokinetic/pharmacodynamic and quality-of-life assessments., Cancer, 2014. 120 (17)(17): p. 2694-703., https://pubmed.ncbi.nlm.nih.gov/24844950/

1030. Rao, SN, Cabanillas, ME, Navigating Systemic Therapy in Advanced Thyroid Carcinoma: From Standard of Care to Personalized Therapy and Beyond., J Endocr Soc, 2018. 2 (10)(10): p. 1109-1130., https://pubmed.ncbi.nlm.nih.gov/30250937/

1031. Sherman, Eric Jeffrey, Wirth, Lori J., Shah, Manisha H., Cabanillas, Maria E., Robinson, Bruce, Laskin, Janessa J., et.al. Selpercatinib efficacy and safety in patients with RET-altered thyroid cancer: A clinical trial update.Wolters Kluwer, Journal of Clinical Oncology, 2021. 39(15_suppl): p. 6073 - 6073., https://doi.org/10.1200/JCO.2021.39.15_suppl.6073

1032. Wirth, LJ, Sherman, E, Robinson, B, Solomon, B, Kang, H, Lorch, J, et.al. Efficacy of Selpercatinib in , N Engl J Med, 2020. 383 (9)(9): p. 825-835., https://pubmed.ncbi.nlm.nih.gov/32846061/

1033. Wirth, LJ, Brose, MS, Subbiah, V, Worden, F, Solomon, B, Robinson, B, et.al. Durability of Response With Selpercatinib in Patients With , J Clin Oncol, 2024. 42 (27)(27): p. 3187-3195., https://pubmed.ncbi.nlm.nih.gov/39094065/

1034. Subbiah, V, Hu, MI, Wirth, LJ, Schuler, M, Mansfield, AS, Curigliano, G, et.al. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study., Lancet Diabetes Endocrinol, 2021. 9 (8)(8): p. 491-501., https://pubmed.ncbi.nlm.nih.gov/34118198/

1035. Waguespack, SG, Drilon, A, Lin, JJ, Brose, MS, McDermott, R, Almubarak, M, et.al. Efficacy and safety of larotrectinib in patients with TRK fusion-positive thyroid carcinoma., Eur J Endocrinol, 2022. 186 (6)(6): p. 631-643., https://pubmed.ncbi.nlm.nih.gov/35333737/

1036. Bazhenova, Lyudmila, Liu, S.V., Lin, J.J., Lu, S., Drilon, Alexander Edward, Chawla, S.P., et.al. 533P Efficacy and safety of entrectinib in patients with locally advanced/metastatic NTRK fusion-positive (NTRK-fp) solid tumours, 2021/09/01. 32: p. S598 - S599.

1037. Demeure, MJ, Aziz, M, Rosenberg, R, Gurley, SD, Bussey, KJ, Carpten, JD, Whole-genome sequencing of an aggressive BRAF wild-type papillary thyroid cancer identified EML4-ALK translocation as a therapeutic target., World J Surg, 2014. 38 (6)(6): p. 1296-305., https://pubmed.ncbi.nlm.nih.gov/24633422/

1038. Lee, H, Krishnan, V, Wirth, LJ, Nucera, C, Venturina, M, Sadow, PM, et.al. Case Report of , Thyroid, 2022. 32 (12)(12): p. 1580-1585., https://pubmed.ncbi.nlm.nih.gov/36150036/

1039. Zhu, L, Ma, S, Xia, B, Remarkable response to alectinib for metastatic papillary thyroid cancer with STRN-ALK fusion: A case report., Front Oncol, 2022. 12 (): p. 1009076., https://pubmed.ncbi.nlm.nih.gov/36439495/

1040. Busaidy, NL, Konda, B, Wei, L, Wirth, LJ, Devine, C, Daniels, GA, et.al. Dabrafenib Versus Dabrafenib + Trametinib in , Thyroid, 2022. 32 (10)(10): p. 1184-1192., https://pubmed.ncbi.nlm.nih.gov/35658604/

1041. Falchook, GS, Millward, M, Hong, D, Naing, A, Piha-Paul, S, Waguespack, SG, et.al. BRAF inhibitor dabrafenib in patients with metastatic BRAF-mutant thyroid cancer., Thyroid, 2015. 25 (1)(1): p. 71-7., https://pubmed.ncbi.nlm.nih.gov/25285888/

1042. Brose, MS, Cabanillas, ME, Cohen, EE, Wirth, LJ, Riehl, T, Yue, H, et.al. Vemurafenib in patients with BRAF(V600E)-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: a non-randomised, multicentre, open-label, phase 2 trial., Lancet Oncol, 2016. 17 (9)(9): p. 1272-82., https://pubmed.ncbi.nlm.nih.gov/27460442/

1043. Lee, YA, Lee, H, Im, SW, Song, YS, Oh, DY, Kang, HJ, et.al. NTRK and RET fusion-directed therapy in pediatric thyroid cancer yields a tumor response and radioiodine uptake., J Clin Invest, 2021. 131 (18)(18):, https://pubmed.ncbi.nlm.nih.gov/34237031/

1044. Werner, RA, Sayehli, C, Hänscheid, H, Higuchi, T, Serfling, SE, Fassnacht, M, et.al. Successful combination of selpercatinib and radioiodine after pretherapeutic dose estimation in RET-altered thyroid carcinoma., Eur J Nucl Med Mol Imaging, 2023. 50 (6)(6): p. 1833-1834., https://pubmed.ncbi.nlm.nih.gov/36522435/

1045. Groussin, L, Theodon, H, Bessiene, L, Bricaire, L, Bonnet-Serrano, F, Cochand-Priollet, B, et.al. Redifferentiating Effect of Larotrectinib in , Thyroid, 2022. 32 (5)(5): p. 594-598., https://pubmed.ncbi.nlm.nih.gov/35171708/

1046. Groussin, L, Bessiene, L, Arrondeau, J, Garinet, S, Cochand-Priollet, B, Lupo, A, et.al. None, Thyroid, 2021. 31 (10)(10): p. 1603-1604., https://pubmed.ncbi.nlm.nih.gov/34405703/

1047. Rothenberg, SM, McFadden, DG, Palmer, EL, Daniels, GH, Wirth, LJ, Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib., Clin Cancer Res, 2015. 21 (5)(5): p. 1028-35., https://pubmed.ncbi.nlm.nih.gov/25549723/

1048. Dunn, LA, Sherman, EJ, Baxi, SS, Tchekmedyian, V, Grewal, RK, Larson, SM, et.al. Vemurafenib Redifferentiation of BRAF Mutant, RAI-Refractory Thyroid Cancers., J Clin Endocrinol Metab, 2019. 104 (5)(5): p. 1417-1428., https://pubmed.ncbi.nlm.nih.gov/30256977/

1049. Leboulleux, Sophie, Cao, Christine Do, Zerdoud, Slimane, Attard, Marie, Bournaud, Claire, Benisvy, Danielle, et.al. MERAIODE: A Redifferentiation Phase II Trial With Trametinib and Dabrafenib Followed by Radioactive Iodine Administration for Metastatic Radioactive Iodine Refractory Differentiated Thyroid Cancer Patients With a BRAFV600E Mutation (NCT 03244956), 2021. 5(Supplement_1): p. A876 - A876., https://doi.org/10.1210/jendso/bvab048.1789

1050. Mehnert J, , Varga A, , Brose M, , Aggarwal R, , Lin C, , Prawira A, et al., Pembrolizumab for advanced paillary and follicular thyroid cancer: preliminary results from the phase 1b KEYNOTE-028 studyJ Clin Oncol, 2016. 33(Suppl 15):

1051. Dierks C, , Miething C, , Thomusch O, , von Bubnoff N, , Duyster J., Lenvatinib and pembrolizumab as save and effective combination treatment in 8 patients with metastasized anaplastic thyroid cancer (ATC) and poorly differentiated thyroid cancerAnnals of Oncology, 2018. 29 (Suppl_8): p. viii645 - viii8.

1052. Dierks, C, Seufert, J, Aumann, K, Ruf, J, Klein, C, Kiefer, S, et.al. Combination of Lenvatinib and Pembrolizumab Is an Effective Treatment Option for Anaplastic and Poorly Differentiated Thyroid Carcinoma., Thyroid, 2021. 31 (7)(7): p. 1076-1085., https://pubmed.ncbi.nlm.nih.gov/33509020/

1053. Haugen, Bryan, French, Jena, Worden, Francis, Konda, Bhavana, Sherman, Eric, Dadu, Ramona, et.al. Lenvatinib plus pembrolizumab combination therapy in patients with radioiodine-refractory (RAIR), progressive differentiated thyroid cancer (DTC): Results of a multicenter phase II international thyroid oncology group trial., 2020/05/20. 38: p. 6512 - 6512.

1054. Haugen, B., French, J.D., Worden, F., Konda, B., Sherman, E.J., Dadu, R., et.al. 1917P Pembrolizumab salvage add-on therapy in patients with radioiodine-refractory (RAIR), progressive differentiated thyroid cancer (DTC) progressing on lenvatinib: Results of a multicenter phase II International Thyroid Oncology Group Trial, 2020/09/01. 31: p. S1086 - S1087.

1055. Choksi, P, Papaleontiou, M, Guo, C, Worden, F, Banerjee, M, Haymart, M, Skeletal Complications and Mortality in Thyroid Cancer: A Population-Based Study., J Clin Endocrinol Metab, 2017. 102 (4)(4): p. 1254-1260., https://pubmed.ncbi.nlm.nih.gov/28324052/

1056. Vitale, G, Fonderico, F, Martignetti, A, Caraglia, M, Ciccarelli, A, Nuzzo, V, et.al. Pamidronate improves the quality of life and induces clinical remission of bone metastases in patients with thyroid cancer., Br J Cancer, 2001. 84 (12)(12): p. 1586-90., https://pubmed.ncbi.nlm.nih.gov/11401309/

1057. Coleman, R, Woodward, E, Brown, J, Cameron, D, Bell, R, Dodwell, D, et.al. Safety of zoledronic acid and incidence of osteonecrosis of the jaw (ONJ) during adjuvant therapy in a randomised phase III trial (AZURE: BIG 01-04) for women with stage II/III breast cancer., Breast Cancer Res Treat, 2011. 127 (2)(2): p. 429-38., https://pubmed.ncbi.nlm.nih.gov/21394500/

1058. Wardley, A, Davidson, N, Barrett-Lee, P, Hong, A, Mansi, J, Dodwell, D, et.al. Zoledronic acid significantly improves pain scores and quality of life in breast cancer patients with bone metastases: a randomised, crossover study of community vs hospital bisphosphonate administration., Br J Cancer, 2005. 92 (10)(10): p. 1869-76., https://pubmed.ncbi.nlm.nih.gov/15870721/

1059. Orita, Y, Sugitani, I, Toda, K, Manabe, J, Fujimoto, Y, Zoledronic acid in the treatment of bone metastases from differentiated thyroid carcinoma., Thyroid, 2011. 21 (1)(1): p. 31-5., https://pubmed.ncbi.nlm.nih.gov/21058881/

1060. Meijer, JA, Bakker, LE, Valk, GD, de Herder, WW, de Wilt, JH, Netea-Maier, RT, et.al. Radioactive iodine in the treatment of medullary thyroid carcinoma: a controlled multicenter study., Eur J Endocrinol, 2013. 168 (5)(5): p. 779-86., https://pubmed.ncbi.nlm.nih.gov/23462866/

1061. Kebebew, E, Greenspan, FS, Clark, OH, Woeber, KA, Grunwell, J, Extent of disease and practice patterns for medullary thyroid cancer., J Am Coll Surg, 2005. 200 (6)(6): p. 890-6., https://pubmed.ncbi.nlm.nih.gov/15922202/

1062. Roman, S, Lin, R, Sosa, JA, Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases., Cancer, 2006. 107 (9)(9): p. 2134-42., https://pubmed.ncbi.nlm.nih.gov/17019736/

1063. Machens, A, Hinze, R, Thomusch, O, Dralle, H, Pattern of nodal metastasis for primary and reoperative thyroid cancer., World J Surg, 2002. 26 (1)(1): p. 22-8., https://pubmed.ncbi.nlm.nih.gov/11898029/

1064. Raue, F, Frank-Raue, K, Epidemiology and Clinical Presentation of Medullary Thyroid Carcinoma., Recent Results Cancer Res, 2015. 204 (): p. 61-90., https://pubmed.ncbi.nlm.nih.gov/26494384/

1065. Randle, RW, Balentine, CJ, Leverson, GE, Havlena, JA, Sippel, RS, Schneider, DF, et.al. Trends in the presentation, treatment, and survival of patients with medullary thyroid cancer over the past 30 years., Surgery, 2017. 161 (1)(1): p. 137-146., https://pubmed.ncbi.nlm.nih.gov/27842913/

1066. Raue, F, German medullary thyroid carcinoma/multiple endocrine neoplasia registry. German MTC/MEN Study Group. Medullary Thyroid Carcinoma/Multiple Endocrine Neoplasia Type 2., Langenbecks Arch Surg, 1998. 383 (5)(5): p. 334-6., https://pubmed.ncbi.nlm.nih.gov/9860226/

1067. Opsahl, EM, Akslen, LA, Schlichting, E, Aas, T, Brauckhoff, K, Hagen, AI, et.al. Trends in Diagnostics, Surgical Treatment, and Prognostic Factors for Outcomes in Medullary Thyroid Carcinoma

in Norway: A Nationwide Population-Based Study., Eur Thyroid J, 2019. 8 (1)(1): p. 31-40., https://pubmed.ncbi.nlm.nih.gov/30800639/

1068. Frank-Raue, K, Machens, A, Leidig-Bruckner, G, Rondot, S, Haag, C, Schulze, E, et.al. Prevalence and clinical spectrum of nonsecretory medullary thyroid carcinoma in a series of 839 patients with sporadic medullary thyroid carcinoma., Thyroid, 2013. 23 (3)(3): p. 294-300., https://pubmed.ncbi.nlm.nih.gov/22946486/

1069. Elisei, R, Bottici, V, Luchetti, F, Di Coscio, G, Romei, C, Grasso, L, et.al. Impact of routine measurement of serum calcitonin on the diagnosis and outcome of medullary thyroid cancer: experience in 10,864 patients with nodular thyroid disorders., J Clin Endocrinol Metab, 2004. 89 (1)(1): p. 163-8., https://pubmed.ncbi.nlm.nih.gov/14715844/

1070. Machens, A, Dralle, H, Surgical cure rates of sporadic medullary thyroid cancer in the era of calcitonin screening., Eur J Endocrinol, 2016. 175 (3)(3): p. 219-28., https://pubmed.ncbi.nlm.nih.gov/27334331/

1071. Machens, A, Dralle, H, Biomarker-based risk stratification for previously untreated medullary thyroid cancer., J Clin Endocrinol Metab, 2010. 95 (6)(6): p. 2655-63., https://pubmed.ncbi.nlm.nih.gov/20339026/

1072. Chambon, G, Alovisetti, C, Idoux-Louche, C, Reynaud, C, Rodier, M, Guedj, AM, et.al. The use of preoperative routine measurement of basal serum thyrocalcitonin in candidates for thyroidectomy due to nodular thyroid disorders: results from 2733 consecutive patients., J Clin Endocrinol Metab, 2011. 96 (1)(1): p. 75-81., https://pubmed.ncbi.nlm.nih.gov/20881258/

1073. Costante, G, Meringolo, D, Durante, C, Bianchi, D, Nocera, M, Tumino, S, et.al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules., J Clin Endocrinol Metab, 2007. 92 (2)(2): p. 450-5., https://pubmed.ncbi.nlm.nih.gov/17119000/

1074. Herrmann, BL, Schmid, KW, Goerges, R, Kemen, M, Mann, K, Calcitonin screening and pentagastrin testing: predictive value for the diagnosis of medullary carcinoma in nodular thyroid disease., Eur J Endocrinol, 2010. 162 (6)(6): p. 1141-5., https://pubmed.ncbi.nlm.nih.gov/20332126/

1075. Eckelt, F, Vogel, M, Geserick, M, Kirsten, T, Bae, YJ, Baber, R, et.al. Calcitonin measurement in pediatrics: reference ranges are gender-dependent, validation in medullary thyroid cancer and thyroid diseases., Clin Chem Lab Med, 2019. 57 (8)(8): p. 1242-1250., https://pubmed.ncbi.nlm.nih.gov/30794525/

1076. Castagna, MG, Fugazzola, L, Maino, F, Covelli, D, Memmo, S, Sestini, F, et.al. Reference range of serum calcitonin in pediatric population., J Clin Endocrinol Metab, 2015. 100 (5)(5): p. 1780-4., https://pubmed.ncbi.nlm.nih.gov/25955324/

1077. Kratzsch, J, Petzold, A, Raue, F, Reinhardt, W, Bröcker-Preuss, M, Görges, R, et.al. Basal and stimulated calcitonin and procalcitonin by various assays in patients with and without medullary thyroid cancer., Clin Chem, 2011. 57 (3)(3): p. 467-74., https://pubmed.ncbi.nlm.nih.gov/21159900/

1078. Kahaly, GJ, Algeciras-Schimnich, A, Davis, TE, Diana, T, Feldkamp, J, Karger, S, et.al. United States and European Multicenter Prospective Study for the Analytical Performance and Clinical Validation of a Novel Sensitive Fully Automated Immunoassay for Calcitonin., Clin Chem, 2017. 63 (9)(9): p. 1489-1496., https://pubmed.ncbi.nlm.nih.gov/28687633/

1079. Mian, C, Perrino, M, Colombo, C, Cavedon, E, Pennelli, G, Ferrero, S, et.al. Refining calcium test for the diagnosis of medullary thyroid cancer: cutoffs, procedures, and safety., J Clin Endocrinol Metab, 2014. 99 (5)(5): p. 1656-64., https://pubmed.ncbi.nlm.nih.gov/24552221/

1080. Costante, G, Durante, C, Francis, Z, Schlumberger, M, Filetti, S, Determination of calcitonin levels in C-cell disease: clinical interest and potential pitfalls., Nat Clin Pract Endocrinol Metab, 2009. 5 (1)(1): p. 35-44., https://pubmed.ncbi.nlm.nih.gov/19079272/

1081. Preissner, CM, Dodge, LA, O'Kane, DJ, Singh, RJ, Grebe, SK, Prevalence of heterophilic antibody interference in eight automated tumor marker immunoassays., Clin Chem, 2005. 51 (1)(1): p. 208-10., https://pubmed.ncbi.nlm.nih.gov/15613712/

1082. Schneider, R, Waldmann, J, Swaid, Z, Ramaswamy, A, Fendrich, V, Bartsch, DK, et.al. Calcitonin-secreting pancreatic endocrine tumors: systematic analysis of a rare tumor entity., Pancreas, 2011. 40 (2)(2): p. 213-21., https://pubmed.ncbi.nlm.nih.gov/21178652/

1083. Ahmed, SR, Ball, DW, Clinical review: Incidentally discovered medullary thyroid cancer: diagnostic strategies and treatment., J Clin Endocrinol Metab, 2011. 96 (5)(5): p. 1237-45., https://pubmed.ncbi.nlm.nih.gov/21346073/

1084. Valle, LA, Kloos, RT, The prevalence of occult medullary thyroid carcinoma at autopsy., J Clin Endocrinol Metab, 2011. 96 (1)(1): p. E109-13., https://pubmed.ncbi.nlm.nih.gov/20943788/

1085. Karges, W, Dralle, H, Raue, F, Mann, K, Reiners, C, Grussendorf, M, et.al. Calcitonin measurement to detect medullary thyroid carcinoma in nodular goiter: German evidence-based consensus recommendation., Exp Clin Endocrinol Diabetes, 2004. 112 (1)(1): p. 52-8., https://pubmed.ncbi.nlm.nih.gov/14758572/

1086. Elisei, R, Romei, C, Calcitonin estimation in patients with nodular goiter and its significance for early detection of MTC: european comments to the guidelines of the American Thyroid Association., Thyroid Res, 2013. 6 Suppl 1 (Suppl 1)(Suppl 1): p. S2., https://pubmed.ncbi.nlm.nih.gov/23514432/

1087. Schlumberger, M, Bastholt, L, Dralle, H, Jarzab, B, Pacini, F, Smit, JW, 2012 European thyroid association guidelines for metastatic medullary thyroid cancer., Eur Thyroid J, 2012. 1 (1)(1): p. 5-14., https://pubmed.ncbi.nlm.nih.gov/24782992/

1088. Pacini, F, Castagna, MG, Brilli, L, Pentheroudakis, G, Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up., Ann Oncol, 2012. 23 Suppl 7 (): p. vii110-9., https://pubmed.ncbi.nlm.nih.gov/22997443/

1089. Haugen, BR, 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: What is new and what has changed?, Cancer, 2017. 123 (3)(3): p. 372-381., https://pubmed.ncbi.nlm.nih.gov/27741354/

1090. Verbeek, HH, de Groot, JWB, Sluiter, WJ, Muller Kobold, AC, van den Heuvel, ER, Plukker, JT, et.al. Calcitonin testing for detection of medullary thyroid cancer in people with thyroid nodules., Cochrane Database Syst Rev, 2020. 3 (3)(3): p. CD010159., https://pubmed.ncbi.nlm.nih.gov/32176812/

1091. Niederle, MB, Scheuba, C, Riss, P, Selberherr, A, Koperek, O, Niederle, B, Early Diagnosis of Medullary Thyroid Cancer: Are Calcitonin Stimulation Tests Still Indicated in the Era of Highly Sensitive Calcitonin Immunoassays?, Thyroid, 2020. 30 (7)(7): p. 974-984., https://pubmed.ncbi.nlm.nih.gov/32056502/

1092. Lorenz, K, Elwerr, M, Machens, A, Abuazab, M, Holzhausen, HJ, Dralle, H, Hypercalcitoninemia in thyroid conditions other than medullary thyroid carcinoma: a comparative analysis of calcium and pentagastrin stimulation of serum calcitonin., Langenbecks Arch Surg, 2013. 398 (3)(3): p. 403-9., https://pubmed.ncbi.nlm.nih.gov/23408061/

1093. Russo, M, Scollo, C, Padova, G, Vigneri, R, Pellegriti, G, Cardiac arrest after intravenous calcium administration for calcitonin stimulation test., Thyroid, 2014. 24 (3)(3): p. 606-7., https://pubmed.ncbi.nlm.nih.gov/24015826/

1094. Rosario, PW, Calsolari, MR, Usefulness of Serum Calcitonin in Patients Without a Suspicious History of Medullary Thyroid Carcinoma and with Thyroid Nodules Without an Indication for Fine-Needle Aspiration or with Benign Cytology., Horm Metab Res, 2016. 48 (6)(6): p. 372-276., https://pubmed.ncbi.nlm.nih.gov/27203410/

1095. Allelein, S, Ehlers, M, Morneau, C, Schwartz, K, Goretzki, PE, Seppel, T, et.al. Measurement of Basal Serum Calcitonin for the Diagnosis of Medullary Thyroid Cancer., Horm Metab Res, 2018. 50 (1)(1): p. 23-28., https://pubmed.ncbi.nlm.nih.gov/29169190/

1096. Colombo, C, Verga, U, Mian, C, Ferrero, S, Perrino, M, Vicentini, L, et.al. Comparison of calcium and pentagastrin tests for the diagnosis and follow-up of medullary thyroid cancer., J Clin Endocrinol Metab, 2012. 97 (3)(3): p. 905-13., https://pubmed.ncbi.nlm.nih.gov/22170709/

1097. Barbosa, SL, Rodien, P, Leboulleux, S, Niccoli-Sire, P, Kraimps, JL, Caron, P, et.al. Ectopic adrenocorticotropic hormone-syndrome in medullary carcinoma of the thyroid: a retrospective analysis and review of the literature., Thyroid, 2005. 15 (6)(6): p. 618-23., https://pubmed.ncbi.nlm.nih.gov/16029131/

1098. Choi, N, Moon, WJ, Lee, JH, Baek, JH, Kim, DW, Park, SW, Ultrasonographic findings of medullary thyroid cancer: differences according to tumor size and correlation with fine needle aspiration results., Acta Radiol, 2011. 52 (3)(3): p. 312-6., https://pubmed.ncbi.nlm.nih.gov/21498368/

1099. Trimboli, P, Nasrollah, N, Amendola, S, Rossi, F, Ramacciato, G, Romanelli, F, et.al. Should we use ultrasound features associated with papillary thyroid cancer in diagnosing medullary thyroid cancer?, Endocr J, 2012. 59 (6)(6): p. 503-8., https://pubmed.ncbi.nlm.nih.gov/22447142/

1100. Woliński, K, Rewaj-Łosyk, M, Ruchała, M, Sonographic features of medullary thyroid carcinomas--a systematic review and meta-analysis., Endokrynol Pol, 2014. 65 (4)(4): p. 314-8., https://pubmed.ncbi.nlm.nih.gov/25185855/

1101. Kim, SH, Kim, BS, Jung, SL, Lee, JW, Yang, PS, Kang, BJ, et.al. Ultrasonographic findings of medullary thyroid carcinoma: a comparison with papillary thyroid carcinoma., Korean J Radiol, 2009. 10 (2)(2): p. 101-5., https://pubmed.ncbi.nlm.nih.gov/19270854/

1102. Lee, S, Shin, JH, Han, BK, Ko, EY, Medullary thyroid carcinoma: comparison with papillary thyroid carcinoma and application of current sonographic criteria., AJR Am J Roentgenol, 2010. 194 (4)(4): p. 1090-4., https://pubmed.ncbi.nlm.nih.gov/20308516/

1103. Liu, MJ, Liu, ZF, Hou, YY, Men, YM, Zhang, YX, Gao, LY, et.al. Ultrasonographic characteristics of medullary thyroid carcinoma: a comparison with papillary thyroid carcinoma., Oncotarget, 2017. 8 (16)(16): p. 27520-27528., https://pubmed.ncbi.nlm.nih.gov/28460476/

1104. Cho, KE, Gweon, HM, Park, AY, Yoo, MR, Kim, J, Youk, JH, et.al. Ultrasonographic Features of Medullary Thyroid Carcinoma: Do they Correlate with Pre and PostOperative Calcitonin Levels?, Asian Pac J Cancer Prev, 2016. 17 (7)(7): p. 3357-62., https://pubmed.ncbi.nlm.nih.gov/27509975/

1105. Oh, HS, Kwon, H, Song, E, Jeon, MJ, Song, DE, Kim, TY, et.al. Preoperative Clinical and Sonographic Predictors for Lateral Cervical Lymph Node Metastases in Sporadic Medullary Thyroid Carcinoma., Thyroid, 2018. 28 (3)(3): p. 362-368., https://pubmed.ncbi.nlm.nih.gov/29350102/

1106. Trimboli, P, Giovanella, L, Valabrega, S, Andrioli, M, Baldelli, R, Cremonini, N, et.al. Ultrasound features of medullary thyroid carcinoma correlate with cancer aggressiveness: a retrospective multicenter study., J Exp Clin Cancer Res, 2014. 33 (1)(1): p. 87., https://pubmed.ncbi.nlm.nih.gov/25344474/

1107. Valderrabano, P, Klippenstein, DL, Tourtelot, JB, Ma, Z, Thompson, ZJ, Lilienfeld, HS, et.al. New American Thyroid Association Sonographic Patterns for Thyroid Nodules Perform Well in Medullary

Thyroid Carcinoma: Institutional Experience, Systematic Review, and Meta-Analysis., Thyroid, 2016. 26 (8)(8): p. 1093-100., https://pubmed.ncbi.nlm.nih.gov/27267210/

1108. Yun, G, Kim, YK, Choi, SI, Kim, JH, Medullary thyroid carcinoma: Application of Thyroid Imaging Reporting and Data System (TI-RADS) Classification., Endocrine, 2018. 61 (2)(2): p. 285-292., https://pubmed.ncbi.nlm.nih.gov/29680915/

1109. Giovanella, L, Treglia, G, Iakovou, I, Mihailovic, J, Verburg, FA, Luster, M, EANM practice guideline for PET/CT imaging in medullary thyroid carcinoma., Eur J Nucl Med Mol Imaging, 2020. 47 (1)(1): p. 61-77., https://pubmed.ncbi.nlm.nih.gov/31482429/

1110. Brammen, L, Niederle, MB, Riss, P, Scheuba, C, Selberherr, A, Karanikas, G, et.al. Medullary Thyroid Carcinoma: Do Ultrasonography and F-DOPA-PET-CT Influence the Initial Surgical Strategy?, Ann Surg Oncol, 2018. 25 (13)(13): p. 3919-3927., https://pubmed.ncbi.nlm.nih.gov/30306375/

1111. Alzumaili, B, Xu, B, Spanheimer, PM, Tuttle, RM, Sherman, E, Katabi, N, et.al. Grading of medullary thyroid carcinoma on the basis of tumor necrosis and high mitotic rate is an independent predictor of poor outcome., Mod Pathol, 2020. 33 (9)(9): p. 1690-1701., https://pubmed.ncbi.nlm.nih.gov/32313184/

1112. Fuchs, TL, Nassour, AJ, Glover, A, Sywak, MS, Sidhu, SB, Delbridge, LW, et.al. A Proposed Grading Scheme for Medullary Thyroid Carcinoma Based on Proliferative Activity (Ki-67 and Mitotic Count) and Coagulative Necrosis., Am J Surg Pathol, 2020. 44 (10)(10): p. 1419-1428., https://pubmed.ncbi.nlm.nih.gov/32452872/

1113. Xu, B, Fuchs, TL, Ahmadi, S, Alghamdi, M, Alzumaili, B, Bani, MA, et.al. International Medullary Thyroid Carcinoma Grading System: A Validated Grading System for Medullary Thyroid Carcinoma., J Clin Oncol, 2022. 40 (1)(1): p. 96-104., https://pubmed.ncbi.nlm.nih.gov/34731032/

1114. Rosai, J, Handling of thyroid follicular patterned lesions., Endocr Pathol, 2005. 16 (4)(4): p. 279-83., https://pubmed.ncbi.nlm.nih.gov/16627915/

1115. Pandit, AA, Phulpagar, MD, Worrisome histologic alterations following fine needle aspiration of the thyroid., Acta Cytol, 2001. 45 (2)(2): p. 173-9., https://pubmed.ncbi.nlm.nih.gov/11284302/

1116. Bolat, F, Kayaselcuk, F, Nursal, TZ, Reyhan, M, Bal, N, Yildirim, S, et.al. Histopathological changes in thyroid tissue after fine needle aspiration biopsy., Pathol Res Pract, 2007. 203 (9)(9): p. 641-5., https://pubmed.ncbi.nlm.nih.gov/17582696/

1117. Kaserer, K, Scheuba, C, Neuhold, N, Weinhäusel, A, Haas, OA, Vierhapper, H, et.al. Sporadic versus familial medullary thyroid microcarcinoma: a histopathologic study of 50 consecutive patients., Am J Surg Pathol, 2001. 25 (10)(10): p. 1245-51., https://pubmed.ncbi.nlm.nih.gov/11688458/

1118. Aubert, S, Berdelou, A, Gnemmi, V, Behal, H, Caiazzo, R, D'herbomez, M, et.al. Large sporadic thyroid medullary carcinomas: predictive factors for lymph node involvement., Virchows Arch, 2018. 472 (3)(3): p. 461-468., https://pubmed.ncbi.nlm.nih.gov/29388012/

1119. Romei, C, Cosci, B, Renzini, G, Bottici, V, Molinaro, E, Agate, L, et.al. RET genetic screening of sporadic medullary thyroid cancer (MTC) allows the preclinical diagnosis of unsuspected gene carriers and the identification of a relevant percentage of hidden familial MTC (FMTC)., Clin Endocrinol (Oxf), 2011. 74 (2)(2): p. 241-7., https://pubmed.ncbi.nlm.nih.gov/21054478/

1120. Machens, A, Dralle, H, Biological relevance of medullary thyroid microcarcinoma., J Clin Endocrinol Metab, 2012. 97 (5)(5): p. 1547-53., https://pubmed.ncbi.nlm.nih.gov/22399508/

1121. Machens, A, Hauptmann, S, Dralle, H, Increased risk of lymph node metastasis in multifocal hereditary and sporadic medullary thyroid cancer., World J Surg, 2007. 31 (10)(10): p. 1960-5., https://pubmed.ncbi.nlm.nih.gov/17665245/

1122. Chandeze, MM, Noullet, S, Faron, M, Trésallet, C, Godiris-Petit, G, Tissier, F, et.al. Can We Predict the Lateral Compartment Lymph Node Involvement in RET-Negative Patients with Medullary Thyroid Carcinoma?, Ann Surg Oncol, 2016. 23 (11)(11): p. 3653-3659., https://pubmed.ncbi.nlm.nih.gov/27271930/

1123. Dralle, H, Lymph node dissection and medullary thyroid carcinoma., Br J Surg, 2002. 89 (9)(9): p. 1073-5., https://pubmed.ncbi.nlm.nih.gov/12190669/

1124. Moley, JF, Fialkowski, EA, Evidence-based approach to the management of sporadic medullary thyroid carcinoma., World J Surg, 2007. 31 (5)(5): p. 946-56., https://pubmed.ncbi.nlm.nih.gov/17426901/

1125. Selberherr, A, Riss, P, Scheuba, C, Niederle, B, Prophylactic "First-Step" Central Neck Dissection (Level 6) Does Not Increase Morbidity After (Total) Thyroidectomy., Ann Surg Oncol, 2016. 23 (12)(12): p. 4016-4022., https://pubmed.ncbi.nlm.nih.gov/27393573/

1126. Miyauchi, A, Matsuzuka, F, Hirai, K, Yokozawa, T, Kobayashi, K, Ito, Y, et.al. Prospective trial of unilateral surgery for nonhereditary medullary thyroid carcinoma in patients without germline RET mutations., World J Surg, 2002. 26 (8)(8): p. 1023-8., https://pubmed.ncbi.nlm.nih.gov/12016484/

1127. Raffel, A, Cupisti, K, Krausch, M, Wolf, A, Schulte, KM, Röher, HD, Incidentally found medullary thyroid cancer: treatment rationale for small tumors., World J Surg, 2004. 28 (4)(4): p. 397-401., https://pubmed.ncbi.nlm.nih.gov/14994142/

1128. Hartung-Knemeyer, V, Müller, S, Nagarajah, J, Lahner, H, Broecker-Preuss, M, Bockisch, A, et.al. [Influence of the calcitonin assay on the definition of biochemical cure in patients with medullary thyroid carcinoma]., Nuklearmedizin, 2012. 51 (4)(4): p. 125-32., https://pubmed.ncbi.nlm.nih.gov/22526413/

1129. Rowland, KJ, Jin, LX, Moley, JF, Biochemical cure after reoperations for medullary thyroid carcinoma: a meta-analysis., Ann Surg Oncol, 2015. 22 (1)(1): p. 96-102., https://pubmed.ncbi.nlm.nih.gov/25234024/

1130. Machens, A, Dralle, H, Benefit-risk balance of reoperation for persistent medullary thyroid cancer., Ann Surg, 2013. 257 (4)(4): p. 751-7., https://pubmed.ncbi.nlm.nih.gov/23023200/

1131. Machens, A, Lorenz, K, Dralle, H, Prediction of biochemical cure in patients with medullary thyroid cancer., Br J Surg, 2020. 107 (6)(6): p. 695-704., https://pubmed.ncbi.nlm.nih.gov/32108330/

1132. Scheuba, C, Kaserer, K, Bieglmayer, C, Asari, R, Riss, P, Drosten, R, et.al. Medullary thyroid microcarcinoma recommendations for treatment - a single-center experience., Surgery, 2007. 142 (6)(6): p. 1003-10; discussion 1010.e1-3., https://pubmed.ncbi.nlm.nih.gov/18063088/

1133. Kim, JH, Pyo, JS, Cho, WJ, Clinicopathological Significance and Prognosis of Medullary Thyroid Microcarcinoma: A Meta-analysis., World J Surg, 2017. 41 (10)(10): p. 2551-2558., https://pubmed.ncbi.nlm.nih.gov/28451761/

1134. Lindsey, SC, Ganly, I, Palmer, F, Tuttle, RM, Response to initial therapy predicts clinical outcomes in medullary thyroid cancer., Thyroid, 2015. 25 (2)(2): p. 242-9., https://pubmed.ncbi.nlm.nih.gov/25338223/

1135. Tuttle, RM, Ganly, I, Risk stratification in medullary thyroid cancer: moving beyond static anatomic staging., Oral Oncol, 2013. 49 (7)(7): p. 695-701., https://pubmed.ncbi.nlm.nih.gov/23601563/

1136. Kwon, H, Kim, WG, Jeon, MJ, Song, DE, Lee, YM, Sung, TY, et.al. Dynamic risk stratification for medullary thyroid cancer according to the response to initial therapy., Endocrine, 2016. 53 (1)(1): p. 174-81., https://pubmed.ncbi.nlm.nih.gov/26754662/

1137. Choi, JB, Lee, SG, Kim, MJ, Kim, TH, Ban, EJ, Lee, CR, et.al. Dynamic risk stratification in medullary thyroid carcinoma: Single institution experiences., Medicine (Baltimore), 2018. 97 (3)(3): p. e9686., https://pubmed.ncbi.nlm.nih.gov/29505021/

1138. Leidig-Bruckner, G, Bruckner, T, Raue, F, Frank-Raue, K, Long-Term Follow-Up and Treatment of Postoperative Permanent Hypoparathyroidism in Patients with Medullary Thyroid Carcinoma: Differences in Complete and Partial Disease., Horm Metab Res, 2016. 48 (12)(12): p. 806-813., https://pubmed.ncbi.nlm.nih.gov/27813050/

1139. Machens, A, Gimm, O, Ukkat, J, Hinze, R, Schneyer, U, Dralle, H, Improved prediction of calcitonin normalization in medullary thyroid carcinoma patients by quantitative lymph node analysis., Cancer, 2000. 88 (8)(8): p. 1909-15., https://pubmed.ncbi.nlm.nih.gov/10760769/

1140. Fialkowski, E, DeBenedetti, M, Moley, J, Long-term outcome of reoperations for medullary thyroid carcinoma., World J Surg, 2008. 32 (5)(5): p. 754-65., https://pubmed.ncbi.nlm.nih.gov/18188643/

1141. Barbet, J, Campion, L, Kraeber-Bodéré, F, Chatal, JF, Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma., J Clin Endocrinol Metab, 2005. 90 (11)(11): p. 6077-84., https://pubmed.ncbi.nlm.nih.gov/16091497/

1142. Randle, RW, Bates, MF, Schneider, DF, Sippel, RS, Pitt, SC, Survival in patients with medullary thyroid cancer after less than the recommended initial operation., J Surg Oncol, 2018. 117 (6)(6): p. 1211-1216., https://pubmed.ncbi.nlm.nih.gov/29266278/

1143. Machens, A, Lorenz, K, Dralle, H, Time to calcitonin normalization after surgery for node-negative and node-positive medullary thyroid cancer., Br J Surg, 2019. 106 (4)(4): p. 412-418., https://pubmed.ncbi.nlm.nih.gov/30725475/

1144. Kloos, RT, Eng, C, Evans, DB, Francis, GL, Gagel, RF, Gharib, H, et.al. Medullary thyroid cancer: management guidelines of the American Thyroid Association., Thyroid, 2009. 19 (6)(6): p. 565-612., https://pubmed.ncbi.nlm.nih.gov/19469690/

1145. Laure Giraudet, A, Al Ghulzan, A, Aupérin, A, Leboulleux, S, Chehboun, A, Troalen, F, et.al. Progression of medullary thyroid carcinoma: assessment with calcitonin and carcinoembryonic antigen doubling times., Eur J Endocrinol, 2008. 158 (2)(2): p. 239-46., https://pubmed.ncbi.nlm.nih.gov/18230832/

1146. Romei, C, Ciampi, R, Casella, F, Tacito, A, Torregrossa, L, Ugolini, C, et.al. RET mutation heterogeneity in primary advanced medullary thyroid cancers and their metastases., Oncotarget, 2018. 9 (11)(11): p. 9875-9884., https://pubmed.ncbi.nlm.nih.gov/29515777/

1147. Romei, C, Ugolini, C, Cosci, B, Torregrossa, L, Vivaldi, A, Ciampi, R, et.al. Low prevalence of the somatic M918T RET mutation in micro-medullary thyroid cancer., Thyroid, 2012. 22 (5)(5): p. 476-81., https://pubmed.ncbi.nlm.nih.gov/22404432/

1148. Schilling, T, Bürck, J, Sinn, HP, Clemens, A, Otto, HF, Höppner, W, et.al. Prognostic value of codon 918 (ATG-->ACG) RET proto-oncogene mutations in sporadic medullary thyroid carcinoma., Int J Cancer, 2001. 95 (1)(1): p. 62-6., https://pubmed.ncbi.nlm.nih.gov/11241313/

1149. Kushchayev, SV, Kushchayeva, YS, Tella, SH, Glushko, T, Pacak, K, Teytelboym, OM, Medullary Thyroid Carcinoma: An Update on Imaging., J Thyroid Res, 2019. 2019 (): p. 1893047., https://pubmed.ncbi.nlm.nih.gov/31360432/

1150. Raue, F, Frank-Raue, K, Long-Term Follow-up in Medullary Thyroid Carcinoma., Recent Results Cancer Res, 2015. 204 (): p. 207-25., https://pubmed.ncbi.nlm.nih.gov/26494391/

1151. Giraudet, AL, Vanel, D, Leboulleux, S, Aupérin, A, Dromain, C, Chami, L, et.al. Imaging medullary thyroid carcinoma with persistent elevated calcitonin levels., J Clin Endocrinol Metab, 2007. 92 (11)(11): p. 4185-90., https://pubmed.ncbi.nlm.nih.gov/17726071/

1152. Treglia, G, Cocciolillo, F, Di Nardo, F, Poscia, A, de Waure, C, Giordano, A, et.al. Detection rate of recurrent medullary thyroid carcinoma using fluorine-18 dihydroxyphenylalanine positron emission tomography: a meta-analysis., Acad Radiol, 2012. 19 (10)(10): p. 1290-9., https://pubmed.ncbi.nlm.nih.gov/22819076/

1153. Kauhanen, S, Schalin-Jäntti, C, Seppänen, M, Kajander, S, Virtanen, S, Schildt, J, et.al. Complementary roles of 18F-DOPA PET/CT and 18F-FDG PET/CT in medullary thyroid cancer., J Nucl Med, 2011. 52 (12)(12): p. 1855-63., https://pubmed.ncbi.nlm.nih.gov/22052128/

1154. Treglia, G, Castaldi, P, Villani, MF, Perotti, G, de Waure, C, Filice, A, et.al. Comparison of 18F-DOPA, 18F-FDG and 68Ga-somatostatin analogue PET/CT in patients with recurrent medullary thyroid carcinoma., Eur J Nucl Med Mol Imaging, 2012. 39 (4)(4): p. 569-80., https://pubmed.ncbi.nlm.nih.gov/22223169/

1155. Terroir, M, Caramella, C, Borget, I, Bidault, S, Dromain, C, El Farsaoui, K, et.al. F-18-Dopa Positron Emission Tomography/Computed Tomography Is More Sensitive Than Whole-Body Magnetic Resonance Imaging for the Localization of Persistent/Recurrent Disease of Medullary Thyroid Cancer Patients., Thyroid, 2019. 29 (10)(10): p. 1457-1464., https://pubmed.ncbi.nlm.nih.gov/31530235/

1156. Rowell, NP, The role of external beam radiotherapy in the management of medullary carcinoma of the thyroid: A systematic review., Radiother Oncol, 2019. 136 (): p. 113-120., https://pubmed.ncbi.nlm.nih.gov/31015112/

1157. Kukulska, A, Krajewska, J, Kolosza, Z, Paliczka-Cieslik, E, Kropinska, A, Pawlaczek, A, et.al. The role of postoperative adjuvant radiotherapy in the local control in medullary thyroid carcinoma., Endocr Connect, 2019. 9 (1)(1): p. 1-8., https://pubmed.ncbi.nlm.nih.gov/31778360/

1158. Xu, JY, Murphy, WA, Milton, DR, Jimenez, C, Rao, SN, Habra, MA, et.al. Bone Metastases and Skeletal-Related Events in Medullary Thyroid Carcinoma., J Clin Endocrinol Metab, 2016. 101 (12)(12): p. 4871-4877., https://pubmed.ncbi.nlm.nih.gov/27662441/

1159. Vogel, T, Wendler, J, Frank-Raue, K, Kreissl, MC, Spitzweg, C, Fassnacht, M, et.al. Bone Metastases in Medullary Thyroid Carcinoma: High Morbidity and Poor Prognosis Associated With Osteolytic Morphology., J Clin Endocrinol Metab, 2020. 105 (6)(6):, https://pubmed.ncbi.nlm.nih.gov/32072159/

1160. Polascik, TJ, Bisphosphonates in oncology: evidence for the prevention of skeletal events in patients with bone metastases., Drug Des Devel Ther, 2009. 3 (): p. 27-40., https://pubmed.ncbi.nlm.nih.gov/19920919/

1161. Tappenden, P, Carroll, C, Hamilton, J, Kaltenthaler, E, Wong, R, Wadsley, J, et.al. Cabozantinib and vandetanib for unresectable locally advanced or metastatic medullary thyroid cancer: a systematic review and economic model., Health Technol Assess, 2019. 23 (8)(8): p. 1-144., https://pubmed.ncbi.nlm.nih.gov/30821231/

1162. Wells, SA, Robinson, BG, Gagel, RF, Dralle, H, Fagin, JA, Santoro, M, et.al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial., J Clin Oncol, 2012. 30 (2)(2): p. 134-41., https://pubmed.ncbi.nlm.nih.gov/22025146/

1163. Elisei, R, Schlumberger, MJ, Müller, SP, Schöffski, P, Brose, MS, Shah, MH, et.al. Cabozantinib in progressive medullary thyroid cancer., J Clin Oncol, 2013. 31 (29)(29): p. 3639-46., https://pubmed.ncbi.nlm.nih.gov/24002501/

1164. Bible, KC, Suman, VJ, Molina, JR, Smallridge, RC, Maples, WJ, Menefee, ME, et.al. A multicenter phase 2 trial of pazopanib in metastatic and progressive medullary thyroid carcinoma: MC057H., J Clin Endocrinol Metab, 2014. 99 (5)(5): p. 1687-93., https://pubmed.ncbi.nlm.nih.gov/24606083/

1165. Lam, ET, Ringel, MD, Kloos, RT, Prior, TW, Knopp, MV, Liang, J, et.al. Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer., J Clin Oncol, 2010. 28 (14)(14): p. 2323-30., https://pubmed.ncbi.nlm.nih.gov/20368568/

1166. Schlumberger, M, Jarzab, B, Cabanillas, ME, Robinson, B, Pacini, F, Ball, DW, et.al. A Phase II Trial of the Multitargeted Tyrosine Kinase Inhibitor Lenvatinib (E7080) in Advanced Medullary Thyroid Cancer., Clin Cancer Res, 2016. 22 (1)(1): p. 44-53., https://pubmed.ncbi.nlm.nih.gov/26311725/

1167. Capdevila, J, Trigo, JM, Aller, J, Manzano, JL, Adrián, SG, Llopis, CZ, et.al. Axitinib treatment in advanced RAI-resistant differentiated thyroid cancer (DTC) and refractory medullary thyroid cancer (MTC)., Eur J Endocrinol, 2017. 177 (4)(4): p. 309-317., https://pubmed.ncbi.nlm.nih.gov/28687563/

1168. Efstathiadou, ZA, Tsentidis, C, Bargiota, A, Daraki, V, Kotsa, K, Ntali, G, et.al. Benefits and Limitations of TKIs in Patients with Medullary Thyroid Cancer: A Systematic Review and Meta-Analysis., Eur Thyroid J, 2021. 10 (2)(2): p. 125-139., https://pubmed.ncbi.nlm.nih.gov/33981617/

1169. Subbiah, V, Hu, MI, Wirth, LJ, Schuler, M, Mansfield, AS, Curigliano, G, et.al. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study., Lancet Diabetes Endocrinol, 2021. 9 (8)(8): p. 491-501., https://pubmed.ncbi.nlm.nih.gov/34118198/

1170. Hadoux, J, Elisei, R, Brose, MS, Hoff, AO, Robinson, BG, Gao, M, et.al. Phase 3 Trial of Selpercatinib in Advanced , N Engl J Med, 2023. 389 (20)(20): p. 1851-1861., https://pubmed.ncbi.nlm.nih.gov/37870969/

1171. Raue, F, Frank-Raue, K, Update multiple endocrine neoplasia type 2., Fam Cancer, 2010. 9 (3)(3): p. 449-57., https://pubmed.ncbi.nlm.nih.gov/20087666/

1172. Frank-Raue, K, Rybicki, LA, Erlic, Z, Schweizer, H, Winter, A, Milos, I, et.al. Risk profiles and penetrance estimations in multiple endocrine neoplasia type 2A caused by germline RET mutations located in exon 10., Hum Mutat, 2011. 32 (1)(1): p. 51-8., https://pubmed.ncbi.nlm.nih.gov/20979234/

1173. Raue, F, Dralle, H, Machens, A, Bruckner, T, Frank-Raue, K, Long-Term Survivorship in Multiple Endocrine Neoplasia Type 2B Diagnosed Before and in the New Millennium., J Clin Endocrinol Metab, 2018. 103 (1)(1): p. 235-243., https://pubmed.ncbi.nlm.nih.gov/29077903/

1174. Castinetti, F, Moley, J, Mulligan, L, Waguespack, SG, A comprehensive review on MEN2B., Endocr Relat Cancer, 2018. 25 (2)(2): p. T29-T39., https://pubmed.ncbi.nlm.nih.gov/28698189/

1175. Schmid, KW, Histopathology of C Cells and Medullary Thyroid Carcinoma., Recent Results Cancer Res, 2015. 204 (): p. 41-60., https://pubmed.ncbi.nlm.nih.gov/26494383/

1176. Machens, A, Lorenz, K, Dralle, H, Individualization of lymph node dissection in RET (rearranged during transfection) carriers at risk for medullary thyroid cancer: value of pretherapeutic calcitonin levels., Ann Surg, 2009. 250 (2)(2): p. 305-10., https://pubmed.ncbi.nlm.nih.gov/19638924/

1177. Rohmer, V, Vidal-Trecan, G, Bourdelot, A, Niccoli, P, Murat, A, Wemeau, JL, et.al. Prognostic factors of disease-free survival after thyroidectomy in 170 young patients with a RET germline

mutation: a multicenter study of the Groupe Francais d'Etude des Tumeurs Endocrines., J Clin Endocrinol Metab, 2011. 96 (3)(3): p. E509-18., https://pubmed.ncbi.nlm.nih.gov/21190982/

1178. Machens, A, Elwerr, M, Lorenz, K, Weber, F, Dralle, H, Long-term outcome of prophylactic thyroidectomy in children carrying RET germline mutations., Br J Surg, 2018. 105 (2)(2): p. e150-e157., https://pubmed.ncbi.nlm.nih.gov/29341155/

1179. Mucha, L, Leidig-Bruckner, G, Frank-Raue, K, Bruckner, T, Kroiss, M, Raue, F, Phaeochromocytoma in multiple endocrine neoplasia type 2: RET codon-specific penetrance and changes in management during the last four decades., Clin Endocrinol (Oxf), 2017. 87 (4)(4): p. 320-326., https://pubmed.ncbi.nlm.nih.gov/28605116/

1180. Därr, R, Pamporaki, C, Peitzsch, M, Miehle, K, Prejbisz, A, Peczkowska, M, et.al. Biochemical diagnosis of phaeochromocytoma using plasma-free normetanephrine, metanephrine and methoxytyramine: importance of supine sampling under fasting conditions., Clin Endocrinol (Oxf), 2014. 80 (4)(4): p. 478-86., https://pubmed.ncbi.nlm.nih.gov/24102244/

1181. Castinetti, F, Qi, XP, Walz, MK, Maia, AL, Sansó, G, Peczkowska, M, et.al. Outcomes of adrenal-sparing surgery or total adrenalectomy in phaeochromocytoma associated with multiple endocrine neoplasia type 2: an international retrospective population-based study., Lancet Oncol, 2014. 15 (6)(6): p. 648-55., https://pubmed.ncbi.nlm.nih.gov/24745698/

1182. Asari, R, Scheuba, C, Kaczirek, K, Niederle, B, Estimated risk of pheochromocytoma recurrence after adrenal-sparing surgery in patients with multiple endocrine neoplasia type 2A., Arch Surg, 2006. 141 (12)(12): p. 1199-205; discussion 1205., https://pubmed.ncbi.nlm.nih.gov/17178962/

1183. Machens, A, Lorenz, K, Dralle, H, Peak incidence of pheochromocytoma and primary hyperparathyroidism in multiple endocrine neoplasia 2: need for age-adjusted biochemical screening., J Clin Endocrinol Metab, 2013. 98 (2)(2): p. E336-45., https://pubmed.ncbi.nlm.nih.gov/23284010/

1184. Raue, F, Kraimps, JL, Dralle, H, Cougard, P, Proye, C, Frilling, A, et.al. Primary hyperparathyroidism in multiple endocrine neoplasia type 2A., J Intern Med, 1995. 238 (4)(4): p. 369-73., https://pubmed.ncbi.nlm.nih.gov/7595174/

1185. Scholten, A, Schreinemakers, JM, Pieterman, CR, Valk, GD, Vriens, MR, Borel Rinkes, IH, Evolution of surgical treatment of primary hyperparathyroidism in patients with multiple endocrine neoplasia type 2A., Endocr Pract, 2011. 17 (1)(1): p. 7-15., https://pubmed.ncbi.nlm.nih.gov/20570815/

1186. Moley, JF, Skinner, M, Gillanders, WE, Lairmore, TC, Rowland, KJ, Traugott, AL, et.al. Management of the Parathyroid Glands During Preventive Thyroidectomy in Patients With Multiple Endocrine Neoplasia Type 2., Ann Surg, 2015. 262 (4)(4): p. 641-6., https://pubmed.ncbi.nlm.nih.gov/26366543/

1187. Quak, E, Lasne-Cardon, A, Cavarec, M, Lireux, B, Bastit, V, Roudaut, N, et.al. F18-Choline PET/CT or MIBI SPECT/CT in the Surgical Management of Primary Hyperparathyroidism: A Diagnostic Randomized Clinical Trial., JAMA Otolaryngol Head Neck Surg, 2024. 150 (8)(8): p. 658-665., https://pubmed.ncbi.nlm.nih.gov/38900416/

1188. Chintakuntlawar, AV, Foote, RL, Kasperbauer, JL, Bible, KC, Diagnosis and Management of Anaplastic Thyroid Cancer., Endocrinol Metab Clin North Am, 2019. 48 (1)(1): p. 269-284., https://pubmed.ncbi.nlm.nih.gov/30717908/

1189. Oken, MM, Creech, RH, Tormey, DC, Horton, J, Davis, TE, McFadden, ET, et.al. Toxicity and response criteria of the Eastern Cooperative Oncology Group., Am J Clin Oncol, 1982. 5 (6)(6): p. 649-55., https://pubmed.ncbi.nlm.nih.gov/7165009/

1190. Haymart, MR, Banerjee, M, Yin, H, Worden, F, Griggs, JJ, Marginal treatment benefit in anaplastic thyroid cancer., Cancer, 2013. 119 (17)(17): p. 3133-9., https://pubmed.ncbi.nlm.nih.gov/23839797/

1191. Deeken-Draisey, A, Yang, GY, Gao, J, Alexiev, BA, Anaplastic thyroid carcinoma: an epidemiologic, histologic, immunohistochemical, and molecular single-institution study., Hum Pathol, 2018. 82 (): p. 140-148., https://pubmed.ncbi.nlm.nih.gov/30075157/

1192. Loevner, LA, Kaplan, SL, Cunnane, ME, Moonis, G, Cross-sectional imaging of the thyroid gland., Neuroimaging Clin N Am, 2008. 18 (3)(3): p. 445-61, vii., https://pubmed.ncbi.nlm.nih.gov/18656027/

1193. Salama, JK, Golden, DW, Yom, SS, Garg, MK, Lawson, J, McDonald, MW, et.al. ACR Appropriateness Criteria® thyroid carcinoma., Oral Oncol, 2014. 50 (6)(6): p. 577-86., https://pubmed.ncbi.nlm.nih.gov/24824115/

1194. Rios, A, Torregrosa, B, Rodríguez, JM, Rodríguez, D, Cepero, A, Abellán, MD, et.al. Ultrasonographic risk factors of malignancy in thyroid nodules., Langenbecks Arch Surg, 2016. 401 (6)(6): p. 839-49., https://pubmed.ncbi.nlm.nih.gov/27263038/

1195. Smallridge, RC, Ain, KB, Asa, SL, Bible, KC, Brierley, JD, Burman, KD, et.al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer., Thyroid, 2012. 22 (11)(11): p. 1104-39., https://pubmed.ncbi.nlm.nih.gov/23130564/

1196. Goffredo, P, Thomas, SM, Adam, MA, Sosa, JA, Roman, SA, Impact of Timeliness of Resection and Thyroidectomy Margin Status on Survival for Patients with Anaplastic Thyroid Cancer: An Analysis of 335 Cases., Ann Surg Oncol, 2015. 22 (13)(13): p. 4166-74., https://pubmed.ncbi.nlm.nih.gov/26271394/

1197. Haddad, RI, Nasr, C, Bischoff, L, Busaidy, NL, Byrd, D, Callender, G, et.al. NCCN Guidelines Insights: Thyroid Carcinoma, Version 2.2018., J Natl Compr Canc Netw, 2018. 16 (12)(12): p. 1429-1440., https://pubmed.ncbi.nlm.nih.gov/30545990/

1198. Nguyen, BD, Ram, PC, PET/CT staging and posttherapeutic monitoring of anaplastic thyroid carcinoma., Clin Nucl Med, 2007. 32 (2)(2): p. 145-9., https://pubmed.ncbi.nlm.nih.gov/17242574/

1199. Bogsrud, TV, Karantanis, D, Nathan, MA, Mullan, BP, Wiseman, GA, Kasperbauer, JL, et.al. 18F-FDG PET in the management of patients with anaplastic thyroid carcinoma., Thyroid, 2008. 18 (7)(7): p. 713-9., https://pubmed.ncbi.nlm.nih.gov/18630999/

1200. Poisson, T, Deandreis, D, Leboulleux, S, Bidault, F, Bonniaud, G, Baillot, S, et.al. 18F-fluorodeoxyglucose positron emission tomography and computed tomography in anaplastic thyroid cancer., Eur J Nucl Med Mol Imaging, 2010. 37 (12)(12): p. 2277-85., https://pubmed.ncbi.nlm.nih.gov/20694463/

1201. Akaishi, J, Sugino, K, Kitagawa, W, Nagahama, M, Kameyama, K, Shimizu, K, et.al. Prognostic factors and treatment outcomes of 100 cases of anaplastic thyroid carcinoma., Thyroid, 2011. 21 (11)(11): p. 1183-9., https://pubmed.ncbi.nlm.nih.gov/21936674/

1202. Sugitani, I, Miyauchi, A, Sugino, K, Okamoto, T, Yoshida, A, Suzuki, S, Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC Research Consortium of Japan cohort study of 677 patients., World J Surg, 2012. 36 (6)(6): p. 1247-54., https://pubmed.ncbi.nlm.nih.gov/22311136/

1203. Samih, N, Hovsepian, S, Notel, F, Prorok, M, Zattara-Cannoni, H, Mathieu, S, et.al. The impact of N- and O-glycosylation on the functions of Glut-1 transporter in human thyroid anaplastic cells., Biochim Biophys Acta, 2003. 1621 (1)(1): p. 92-101., https://pubmed.ncbi.nlm.nih.gov/12667615/

1204. Chiu, AC, Delpassand, ES, Sherman, SI, Prognosis and treatment of brain metastases in thyroid carcinoma., J Clin Endocrinol Metab, 1997. 82 (11)(11): p. 3637-42., https://pubmed.ncbi.nlm.nih.gov/9360519/

1205. Salvati, M, Frati, A, Rocchi, G, Masciangelo, R, Antonaci, A, Gagliardi, FM, et.al. Single brain metastasis from thyroid cancer: report of twelve cases and review of the literature., J Neurooncol, 2001. 51 (1)(1): p. 33-40., https://pubmed.ncbi.nlm.nih.gov/11349878/

1206. Antoch, G, Vogt, FM, Freudenberg, LS, Nazaradeh, F, Goehde, SC, Barkhausen, J, et.al. Whole-body dual-modality PET/CT and whole-body MRI for tumor staging in oncology., JAMA, 2003. 290 (24)(24): p. 3199-206., https://pubmed.ncbi.nlm.nih.gov/14693872/

1207. Chiacchio, S, Lorenzoni, A, Boni, G, Rubello, D, Elisei, R, Mariani, G, Anaplastic thyroid cancer: prevalence, diagnosis and treatment., Minerva Endocrinol, 2008. 33 (4)(4): p. 341-57., https://pubmed.ncbi.nlm.nih.gov/18923370/

1208. Ribechini, A, Bottici, V, Chella, A, Elisei, R, Vitti, P, Pinchera, A, et.al. Interventional bronchoscopy in the treatment of tracheal obstruction secondary to advanced thyroid cancer., J Endocrinol Invest, 2006. 29 (2)(2): p. 131-5., https://pubmed.ncbi.nlm.nih.gov/16610238/

1209. Yuasa, R, Hata, Y, Otsuka, H, Makino, T, Koezuka, S, Sato, F, et.al. Placement of self-expandable metallic stents for tracheal stenosis secondary to thyroid cancer., Mol Clin Oncol, 2014. 2 (6)(6): p. 1003-1008., https://pubmed.ncbi.nlm.nih.gov/25279189/

1210. Pozdeyev, N, Gay, LM, Sokol, ES, Hartmaier, R, Deaver, KE, Davis, S, et.al. Genetic Analysis of 779 Advanced Differentiated and Anaplastic Thyroid Cancers., Clin Cancer Res, 2018. 24 (13)(13): p. 3059-3068., https://pubmed.ncbi.nlm.nih.gov/29615459/

1211. Godbert, Y, Henriques de Figueiredo, B, Bonichon, F, Chibon, F, Hostein, I, Pérot, G, et.al. Remarkable Response to Crizotinib in Woman With Anaplastic Lymphoma Kinase-Rearranged Anaplastic Thyroid Carcinoma., J Clin Oncol, 2015. 33 (20)(20): p. e84-7., https://pubmed.ncbi.nlm.nih.gov/24687827/

1212. Liu, SV, Macke, LA, Colton, BS, Imran, SS, Christiansen, J, Chow-Maneval, E, et.al. Response to Entrectinib in Differentiated Thyroid Cancer With a , JCO Precis Oncol, 2017. 1 ():, https://pubmed.ncbi.nlm.nih.gov/32913977/

1213. Wagle, N, Grabiner, BC, Van Allen, EM, Amin-Mansour, A, Taylor-Weiner, A, Rosenberg, M, et.al. Response and acquired resistance to everolimus in anaplastic thyroid cancer., N Engl J Med, 2014. 371 (15)(15): p. 1426-33., https://pubmed.ncbi.nlm.nih.gov/25295501/

1214. Sugitani, I, Hasegawa, Y, Sugasawa, M, Tori, M, Higashiyama, T, Miyazaki, M, et.al. Super-radical surgery for anaplastic thyroid carcinoma: a large cohort study using the Anaplastic Thyroid Carcinoma Research Consortium of Japan database., Head Neck, 2014. 36 (3)(3): p. 328-33., https://pubmed.ncbi.nlm.nih.gov/23729360/

1215. Molinaro, E, Romei, C, Biagini, A, Sabini, E, Agate, L, Mazzeo, S, et.al. Anaplastic thyroid carcinoma: from clinicopathology to genetics and advanced therapies., Nat Rev Endocrinol, 2017. 13 (11)(11): p. 644-660., https://pubmed.ncbi.nlm.nih.gov/28707679/

1216. Mitchell, G, Huddart, R, Harmer, C, Phase II evaluation of high dose accelerated radiotherapy for anaplastic thyroid carcinoma., Radiother Oncol, 1999. 50 (1)(1): p. 33-8., https://pubmed.ncbi.nlm.nih.gov/10225555/

1217. Tennvall, J, Lundell, G, Wahlberg, P, Bergenfelz, A, Grimelius, L, Akerman, M, et.al. Anaplastic thyroid carcinoma: three protocols combining doxorubicin, hyperfractionated radiotherapy and surgery., Br J Cancer, 2002. 86 (12)(12): p. 1848-53., https://pubmed.ncbi.nlm.nih.gov/12085174/

1218. Wang, Y, Tsang, R, Asa, S, Dickson, B, Arenovich, T, Brierley, J, Clinical outcome of anaplastic thyroid carcinoma treated with radiotherapy of once- and twice-daily fractionation regimens., Cancer, 2006. 107 (8)(8): p. 1786-92., https://pubmed.ncbi.nlm.nih.gov/16967442/

1219. Kebebew, E, Greenspan, FS, Clark, OH, Woeber, KA, McMillan, A, Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors., Cancer, 2005. 103 (7)(7): p. 1330-5., https://pubmed.ncbi.nlm.nih.gov/15739211/

1220. Levendag, PC, De Porre, PM, van Putten, WL, Anaplastic carcinoma of the thyroid gland treated by radiation therapy., Int J Radiat Oncol Biol Phys, 1993. 26 (1)(1): p. 125-8., https://pubmed.ncbi.nlm.nih.gov/8482618/

1221. Besic, N, Auersperg, M, Us-Krasovec, M, Golouh, R, Frkovic-Grazio, S, Vodnik, A, Effect of primary treatment on survival in anaplastic thyroid carcinoma., Eur J Surg Oncol, 2001. 27 (3)(3): p. 260-4., https://pubmed.ncbi.nlm.nih.gov/11373102/

1222. Haigh, PI, Ituarte, PH, Wu, HS, Treseler, PA, Posner, MD, Quivey, JM, et.al. Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival., Cancer, 2001. 91 (12)(12): p. 2335-42., https://pubmed.ncbi.nlm.nih.gov/11413523/

1223. De Crevoisier, R, Baudin, E, Bachelot, A, Leboulleux, S, Travagli, JP, Caillou, B, et.al. Combined treatment of anaplastic thyroid carcinoma with surgery, chemotherapy, and hyperfractionated accelerated external radiotherapy., Int J Radiat Oncol Biol Phys, 2004. 60 (4)(4): p. 1137-43., https://pubmed.ncbi.nlm.nih.gov/15519785/

1224. Fan, D, Ma, J, Bell, AC, Groen, AH, Olsen, KS, Lok, BH, et.al. Outcomes of multimodal therapy in a large series of patients with anaplastic thyroid cancer., Cancer, 2020. 126 (2)(2): p. 444-452., https://pubmed.ncbi.nlm.nih.gov/31593317/

1225. Kwon, J, Kim, BH, Jung, HW, Besic, N, Sugitani, I, Wu, HG, The prognostic impacts of postoperative radiotherapy in the patients with resected anaplastic thyroid carcinoma: A systematic review and meta-analysis., Eur J Cancer, 2016. 59 (): p. 34-45., https://pubmed.ncbi.nlm.nih.gov/27014798/

1226. Xia, Q, Wang, W, Xu, J, Chen, X, Zhong, Z, Sun, C, Evidence from an updated meta-analysis of the prognostic impacts of postoperative radiotherapy and chemotherapy in patients with anaplastic thyroid carcinoma., Onco Targets Ther, 2018. 11 (): p. 2251-2257., https://pubmed.ncbi.nlm.nih.gov/29719407/

1227. Pezzi, TA, Mohamed, ASR, Sheu, T, Blanchard, P, Sandulache, VC, Lai, SY, et.al. Radiation therapy dose is associated with improved survival for unresected anaplastic thyroid carcinoma: Outcomes from the National Cancer Data Base., Cancer, 2017. 123 (9)(9): p. 1653-1661., https://pubmed.ncbi.nlm.nih.gov/28026871/

1228. Park, JW, Choi, SH, Yoon, HI, Lee, J, Kim, TH, Kim, JW, et.al. Treatment outcomes of radiotherapy for anaplastic thyroid cancer., Radiat Oncol J, 2018. 36 (2)(2): p. 103-113., https://pubmed.ncbi.nlm.nih.gov/29983030/

1229. Wendler, J, Kroiss, M, Gast, K, Kreissl, MC, Allelein, S, Lichtenauer, U, et.al. Clinical presentation, treatment and outcome of anaplastic thyroid carcinoma: results of a multicenter study in Germany., Eur J Endocrinol, 2016. 175 (6)(6): p. 521-529., https://pubmed.ncbi.nlm.nih.gov/27926471/

1230. Prasongsook, N, Kumar, A, Chintakuntlawar, AV, Foote, RL, Kasperbauer, J, Molina, J, et.al. Survival in Response to Multimodal Therapy in Anaplastic Thyroid Cancer., J Clin Endocrinol Metab, 2017. 102 (12)(12): p. 4506-4514., https://pubmed.ncbi.nlm.nih.gov/29029287/

1231. Derbel, O, Limem, S, Ségura-Ferlay, C, Lifante, JC, Carrie, C, Peix, JL, et.al. Results of combined treatment of anaplastic thyroid carcinoma (ATC)., BMC Cancer, 2011. 11 (): p. 469., https://pubmed.ncbi.nlm.nih.gov/22044775/

1232. Seto, A, Sugitani, I, Toda, K, Kawabata, K, Takahashi, S, Saotome, T, Chemotherapy for anaplastic thyroid cancer using docetaxel and cisplatin: report of eight cases., Surg Today, 2015. 45 (2)(2): p. 221-6., https://pubmed.ncbi.nlm.nih.gov/25734195/

1233. Zhao, X, Wang, JR, Dadu, R, Busaidy, NL, Xu, L, Learned, KO, et.al. Surgery After BRAF-Directed Therapy Is Associated with Improved Survival in BRAF, Thyroid, 2023. 33 (4)(4): p. 484-491., https://pubmed.ncbi.nlm.nih.gov/36762947/

1234. Lorimer, C, Cheng, L, Chandler, R, Garcez, K, Gill, V, Graham, K, et.al. Dabrafenib and Trametinib Therapy for Advanced Anaplastic Thyroid Cancer - Real-World Outcomes From UK Centres., Clin Oncol (R Coll Radiol), 2023. 35 (1)(1): p. e60-e66., https://pubmed.ncbi.nlm.nih.gov/36379836/

1235. Higashiyama, T, Ito, Y, Hirokawa, M, Fukushima, M, Uruno, T, Miya, A, et.al. Induction chemotherapy with weekly paclitaxel administration for anaplastic thyroid carcinoma., Thyroid, 2010. 20 (1)(1): p. 7-14., https://pubmed.ncbi.nlm.nih.gov/20025538/

1236. Wang, JR, Zafereo, ME, Dadu, R, Ferrarotto, R, Busaidy, NL, Lu, C, et.al. Complete Surgical Resection Following Neoadjuvant Dabrafenib Plus Trametinib in , Thyroid, 2019. 29 (8)(8): p. 1036-1043., https://pubmed.ncbi.nlm.nih.gov/31319771/

1237. Brown, RF, Ducic, Y, Aggressive surgical resection of anaplastic thyroid carcinoma may provide long-term survival in selected patients., Otolaryngol Head Neck Surg, 2013. 148 (4)(4): p. 564-71., https://pubmed.ncbi.nlm.nih.gov/23396588/

1238. Keutgen, XM, Sadowski, SM, Kebebew, E, Management of anaplastic thyroid cancer., Gland Surg, 2015. 4 (1)(1): p. 44-51., https://pubmed.ncbi.nlm.nih.gov/25713779/

1239. Sosa, JA, Elisei, R, Jarzab, B, Balkissoon, J, Lu, SP, Bal, C, et.al. Randomized safety and efficacy study of fosbretabulin with paclitaxel/carboplatin against anaplastic thyroid carcinoma., Thyroid, 2014. 24 (2)(2): p. 232-40., https://pubmed.ncbi.nlm.nih.gov/23721245/

1240. Nachalon, Y, Stern-Shavit, S, Bachar, G, Shvero, J, Limon, D, Popovtzer, A, Aggressive Palliation and Survival in Anaplastic Thyroid Carcinoma., JAMA Otolaryngol Head Neck Surg, 2015. 141 (12)(12): p. 1128-32., https://pubmed.ncbi.nlm.nih.gov/26512447/

1241. Cabanillas, ME, Zafereo, M, Gunn, GB, Ferrarotto, R, Anaplastic Thyroid Carcinoma: Treatment in the Age of Molecular Targeted Therapy., J Oncol Pract, 2016. 12 (6)(6): p. 511-8., https://pubmed.ncbi.nlm.nih.gov/27288464/

1242. Subbiah, V, Kreitman, RJ, Wainberg, ZA, Cho, JY, Schellens, JHM, Soria, JC, et.al. Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer., J Clin Oncol, 2018. 36 (1)(1): p. 7-13., https://pubmed.ncbi.nlm.nih.gov/29072975/

1243. Dias-Santagata, D, Lennerz, JK, Sadow, PM, Frazier, RP, Govinda Raju, S, Henry, D, et.al. Response to RET-Specific Therapy in , Thyroid, 2020. 30 (9)(9): p. 1384-1389., https://pubmed.ncbi.nlm.nih.gov/32292131/

1244. Drilon, A, Laetsch, TW, Kummar, S, DuBois, SG, Lassen, UN, Demetri, GD, et.al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children., N Engl J Med, 2018. 378 (8)(8): p. 731-739., https://pubmed.ncbi.nlm.nih.gov/29466156/

1245. Cabanillas, M.E., Drilon, A., Farago, A.F., Brose, M.S., McDermott, R., Sohal, D., et.al. 1916P Larotrectinib treatment of advanced TRK fusion thyroid cancerElsevier, Annals of Oncology, 2020. 31: p. S1086., https://doi.org/10.1016/j.annonc.2020.08.1404

1246. Cabanillas, ME, Ryder, M, Jimenez, C, Targeted Therapy for Advanced Thyroid Cancer: Kinase Inhibitors and Beyond., Endocr Rev, 2019. 40 (6)(6): p. 1573-1604., https://pubmed.ncbi.nlm.nih.gov/31322645/

1247. Tahara, M, Kiyota, N, Yamazaki, T, Chayahara, N, Nakano, K, Inagaki, L, et.al. Lenvatinib for Anaplastic Thyroid Cancer., Front Oncol, 2017. 7 (): p. 25., https://pubmed.ncbi.nlm.nih.gov/28299283/

1248. Wirth, LJ, Brose, MS, Sherman, EJ, Licitra, L, Schlumberger, M, Sherman, SI, et.al. Open-Label, Single-Arm, Multicenter, Phase II Trial of Lenvatinib for the Treatment of Patients With Anaplastic Thyroid Cancer., J Clin Oncol, 2021. 39 (21)(21): p. 2359-2366., https://pubmed.ncbi.nlm.nih.gov/33961488/

1249. Iyer, PC, Dadu, R, Ferrarotto, R, Busaidy, NL, Habra, MA, Zafereo, M, et.al. Real-World Experience with Targeted Therapy for the Treatment of Anaplastic Thyroid Carcinoma., Thyroid, 2018. 28 (1)(1): p. 79-87., https://pubmed.ncbi.nlm.nih.gov/29161986/

1250. Iyer, PC, Dadu, R, Gule-Monroe, M, Busaidy, NL, Ferrarotto, R, Habra, MA, et.al. Salvage pembrolizumab added to kinase inhibitor therapy for the treatment of anaplastic thyroid carcinoma., J Immunother Cancer, 2018. 6 (1)(1): p. 68., https://pubmed.ncbi.nlm.nih.gov/29996921/

1251. Besic, N, Gazic, B, Sites of metastases of anaplastic thyroid carcinoma: autopsy findings in 45 cases from a single institution., Thyroid, 2013. 23 (6)(6): p. 709-13., https://pubmed.ncbi.nlm.nih.gov/23148580/

1252. Baek, SK, Lee, MC, Hah, JH, Ahn, SH, Son, YI, Rho, YS, et.al. Role of surgery in the management of anaplastic thyroid carcinoma: Korean nationwide multicenter study of 329 patients with anaplastic thyroid carcinoma, 2000 to 2012., Head Neck, 2017. 39 (1)(1): p. 133-139., https://pubmed.ncbi.nlm.nih.gov/27534388/

1253. Hugen, N, Sloot, YJE, Netea-Maier, RT, van de Water, C, Smit, JWA, Nagtegaal, ID, et.al. Divergent Metastatic Patterns Between Subtypes of Thyroid Carcinoma Results From the Nationwide Dutch Pathology Registry., J Clin Endocrinol Metab, 2020. 105 (3)(3): p. e299-306., https://pubmed.ncbi.nlm.nih.gov/31641763/

1254. Rades, D, Janssen, S, Käsmann, L, Bolm, L, Schild, SE, Outcomes After Irradiation of Epidural Spinal Cord Compression Due to Metastatic Thyroid Cancer., Anticancer Res, 2016. 36 (4)(4): p. 2035-9., https://pubmed.ncbi.nlm.nih.gov/27069199/

1255. Tickoo, SK, Pittas, AG, Adler, M, Fazzari, M, Larson, SM, Robbins, RJ, et.al. Bone metastases from thyroid carcinoma: a histopathologic study with clinical correlates., Arch Pathol Lab Med, 2000. 124 (10)(10): p. 1440-7., https://pubmed.ncbi.nlm.nih.gov/11035572/

1256. Kim, JH, Leeper, RD, Treatment of locally advanced thyroid carcinoma with combination doxorubicin and radiation therapy., Cancer, 1987. 60 (10)(10): p. 2372-5., https://pubmed.ncbi.nlm.nih.gov/3664425/

1257. Venkatesh, YS, Ordonez, NG, Schultz, PN, Hickey, RC, Goepfert, H, Samaan, NA, Anaplastic carcinoma of the thyroid. A clinicopathologic study of 121 cases., Cancer, 1990. 66 (2)(2): p. 321-30., https://pubmed.ncbi.nlm.nih.gov/1695118/

1258. Demeter, JG, De Jong, SA, Lawrence, AM, Paloyan, E, Anaplastic thyroid carcinoma: risk factors and outcome., Surgery, 1991. 110 (6)(6): p. 956-61; discussion 961-3., https://pubmed.ncbi.nlm.nih.gov/1745983/

1259. Schlumberger, M, Parmentier, C, Delisle, MJ, Couette, JE, Droz, JP, Sarrazin, D, Combination therapy for anaplastic giant cell thyroid carcinoma., Cancer, 1991. 67 (3)(3): p. 564-6., https://pubmed.ncbi.nlm.nih.gov/1985750/

1260. Wong, CS, Van Dyk, J, Simpson, WJ, Myelopathy following hyperfractionated accelerated radiotherapy for anaplastic thyroid carcinoma., Radiother Oncol, 1991. 20 (1)(1): p. 3-9., https://pubmed.ncbi.nlm.nih.gov/1902319/

1261. Hadar, T, Mor, C, Shvero, J, Levy, R, Segal, K, Anaplastic carcinoma of the thyroid., Eur J Surg Oncol, 1993. 19 (6)(6): p. 511-6., https://pubmed.ncbi.nlm.nih.gov/8270035/

1262. Tan, RK, Finley, RK, Driscoll, D, Bakamjian, V, Hicks, WL, Shedd, DP, Anaplastic carcinoma of the thyroid: a 24-year experience., Head Neck, 1995. 17 (1)(1): p. 41-7; discussion 47-8., https://pubmed.ncbi.nlm.nih.gov/7883548/

1263. Kitamura, Y, Shimizu, K, Nagahama, M, Sugino, K, Ozaki, O, Mimura, T, et.al. Immediate causes of death in thyroid carcinoma: clinicopathological analysis of 161 fatal cases., J Clin Endocrinol Metab, 1999. 84 (11)(11): p. 4043-9., https://pubmed.ncbi.nlm.nih.gov/10566647/

1264. Busnardo, B, Daniele, O, Pelizzo, MR, Mazzarotto, R, Nacamulli, D, Devido, D, et.al. A multimodality therapeutic approach in anaplastic thyroid carcinoma: study on 39 patients., J Endocrinol Invest, 2000. 23 (11)(11): p. 755-61., https://pubmed.ncbi.nlm.nih.gov/11194710/

1265. Rodriguez, JM, Piñero, A, Ortiz, S, Moreno, A, Sola, J, Soria, T, et.al. Clinical and histological differences in anaplastic thyroid carcinoma., Eur J Surg, 2000. 166 (1)(1): p. 34-8., https://pubmed.ncbi.nlm.nih.gov/10688214/

1266. McIver, B, Hay, ID, Giuffrida, DF, Dvorak, CE, Grant, CS, Thompson, GB, et.al. Anaplastic thyroid carcinoma: a 50-year experience at a single institution., Surgery, 2001. 130 (6)(6): p. 1028-34., https://pubmed.ncbi.nlm.nih.gov/11742333/

1267. Swaak-Kragten, AT, de Wilt, JH, Schmitz, PI, Bontenbal, M, Levendag, PC, Multimodality treatment for anaplastic thyroid carcinoma--treatment outcome in 75 patients., Radiother Oncol, 2009. 92 (1)(1): p. 100-4., https://pubmed.ncbi.nlm.nih.gov/19328572/

1268. Levy, A, Leboulleux, S, Lepoutre-Lussey, C, Baudin, E, Ghuzlan, AA, Hartl, D, et.al. (18)F-fluorodeoxyglucose positron emission tomography to assess response after radiation therapy in anaplastic thyroid cancer., Oral Oncol, 2015. 51 (4)(4): p. 370-5., https://pubmed.ncbi.nlm.nih.gov/25595614/

1269. Lee, EK, Kim, SM, Kim, BH, Kim, MJ, Lim, DJ, Kim, MH, et.al. Lesion-Based Evaluation Predicts Treatment Response to Lenvatinib for Radioactive Iodine-Refractory Differentiated Thyroid Cancer: A Korean Multicenter Retrospective Study., Thyroid, 2019. 29 (12)(12): p. 1811-1819., https://pubmed.ncbi.nlm.nih.gov/31482759/

1270. Iwasaki, H, Yamazaki, H, Takasaki, H, Suganuma, N, Nakayama, H, Toda, S, et.al. Lenvatinib as a novel treatment for anaplastic thyroid cancer: A retrospective study., Oncol Lett, 2018. 16 (6)(6): p. 7271-7277., https://pubmed.ncbi.nlm.nih.gov/30546466/

1271. Wahl, RL, Jacene, H, Kasamon, Y, Lodge, MA, From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors., J Nucl Med, 2009. 50 Suppl 1 (Suppl 1)(Suppl 1): p. 122S-50S., https://pubmed.ncbi.nlm.nih.gov/19403881/

1272. Giannetta, E, Isidori, AM, Durante, C, Di Gioia, C, Longo, F, Tombolini, V, et.al. Anaplastic thyroid carcinoma and foscarnet use in a multitarget treatment documented by 18F-FDG PET/CT: A case report., Medicine (Baltimore), 2017. 96 (6)(6): p. e5621., https://pubmed.ncbi.nlm.nih.gov/28178124/

1273. Spitzweg, C, Harrington, KJ, Pinke, LA, Vile, RG, Morris, JC, Clinical review 132: The sodium iodide symporter and its potential role in cancer therapy., J Clin Endocrinol Metab, 2001. 86 (7)(7): p. 3327-35., https://pubmed.ncbi.nlm.nih.gov/11443208/

1274. Graff-Baker, A, Roman, SA, Thomas, DC, Udelsman, R, Sosa, JA, Prognosis of primary thyroid lymphoma: demographic, clinical, and pathologic predictors of survival in 1,408 cases., Surgery, 2009. 146 (6)(6): p. 1105-15., https://pubmed.ncbi.nlm.nih.gov/19958938/

1275. Ohye, H, Fukata, S, Hirokawa, M, [Malignant lymphoma of the thyroid]., Nihon Rinsho, 2007. 65 (11)(11): p. 2092-8., https://pubmed.ncbi.nlm.nih.gov/18018576/

1276. Pedersen, RK, Pedersen, NT, Primary non-Hodgkin's lymphoma of the thyroid gland: a population based study., Histopathology, 1996. 28 (1)(1): p. 25-32., https://pubmed.ncbi.nlm.nih.gov/8838117/

1277. Skacel, M, Ross, CW, Hsi, ED, A reassessment of primary thyroid lymphoma: high-grade MALT-type lymphoma as a distinct subtype of diffuse large B-cell lymphoma., Histopathology, 2000. 37 (1)(1): p. 10-8., https://pubmed.ncbi.nlm.nih.gov/10931213/

1278. Compagno, J, Oertel, JE, Malignant lymphoma and other lymphoproliferative disorders of the thyroid gland. A clinicopathologic study of 245 cases., Am J Clin Pathol, 1980. 74 (1)(1): p. 1-11., https://pubmed.ncbi.nlm.nih.gov/7395811/

1279. Matsuzuka, F, Miyauchi, A, Katayama, S, Narabayashi, I, Ikeda, H, Kuma, K, et.al. Clinical aspects of primary thyroid lymphoma: diagnosis and treatment based on our experience of 119 cases., Thyroid, 1993. 3 (2)(2): p. 93-9., https://pubmed.ncbi.nlm.nih.gov/8369658/

1280. Walsh, S, Lowery, AJ, Evoy, D, McDermott, EW, Prichard, RS, Thyroid lymphoma: recent advances in diagnosis and optimal management strategies., Oncologist, 2013. 18 (9)(9): p. 994-1003., https://pubmed.ncbi.nlm.nih.gov/23881987/

1281. Luo, J, Huang, F, Zhou, P, Chen, J, Sun, Y, Xu, F, et.al. Is ultrasound combined with computed tomography useful for distinguishing between primary thyroid lymphoma and Hashimoto's thyroiditis?, Endokrynol Pol, 2019. 70 (6)(6): p. 463-468., https://pubmed.ncbi.nlm.nih.gov/31529457/

1282. Aiken, AH, Imaging of thyroid cancer., Semin Ultrasound CT MR, 2012. 33 (2)(2): p. 138-49., https://pubmed.ncbi.nlm.nih.gov/22410362/

1283. Sakorafas, GH, Kokkoris, P, Farley, DR, Primary thyroid lymphoma (correction of lympoma): diagnostic and therapeutic dilemmas., Surg Oncol, 2010. 19 (4)(4): p. e124-9., https://pubmed.ncbi.nlm.nih.gov/20620043/

1284. Onal, C, Li, YX, Miller, RC, Poortmans, P, Constantinou, N, Weber, DC, et.al. Treatment results and prognostic factors in primary thyroid lymphoma patients: a rare cancer network study., Ann Oncol, 2011. 22 (1)(1): p. 156-164., https://pubmed.ncbi.nlm.nih.gov/20587509/

1285. Watanabe, N, Noh, JY, Narimatsu, H, Takeuchi, K, Yamaguchi, T, Kameyama, K, et.al. Clinicopathological features of 171 cases of primary thyroid lymphoma: a long-term study involving 24553 patients with Hashimoto's disease., Br J Haematol, 2011. 153 (2)(2): p. 236-43., https://pubmed.ncbi.nlm.nih.gov/21371004/

1286. Wang, X, Huang, Y, Zheng, Z, Cao, W, Chen, B, Wang, X, Metastases to the thyroid gland: A retrospective analysis of 21 patients., J Cancer Res Ther, 2018. 14 (7)(7): p. 1515-1518., https://pubmed.ncbi.nlm.nih.gov/30589032/

1287. Straccia, P, Mosseri, C, Brunelli, C, Rossi, ED, Lombardi, CP, Pontecorvi, A, et.al. Diagnosis and Treatment of Metastases to the Thyroid Gland: a Meta-Analysis., Endocr Pathol, 2017. 28 (2)(2): p. 112-120., https://pubmed.ncbi.nlm.nih.gov/28332062/

1288. Chung, AY, Tran, TB, Brumund, KT, Weisman, RA, Bouvet, M, Metastases to the thyroid: a review of the literature from the last decade., Thyroid, 2012. 22 (3)(3): p. 258-68., https://pubmed.ncbi.nlm.nih.gov/22313412/

1289. Mistelou, A, Papadatos, SS, Kousi, C, Lampri, E, Mitsis, M, Vougiouklakis, T, et.al. Thyroid Gland as a Target of Secondary Malignancies - an Autopsy Study and Review Data., Folia Med (Plovdiv), 2019. 61 (2)(2): p. 277-288., https://pubmed.ncbi.nlm.nih.gov/31301659/

1290. Heffess, CS, Wenig, BM, Thompson, LD, Metastatic renal cell carcinoma to the thyroid gland: a clinicopathologic study of 36 cases., Cancer, 2002. 95 (9)(9): p. 1869-78., https://pubmed.ncbi.nlm.nih.gov/12404280/

1291. Hegerova, L, Griebeler, ML, Reynolds, JP, Henry, MR, Gharib, H, Metastasis to the thyroid gland: report of a large series from the Mayo Clinic., Am J Clin Oncol, 2015. 38 (4)(4): p. 338-42., https://pubmed.ncbi.nlm.nih.gov/23799287/

1292. Cordes, M, Kuwert, T, Metastases of non-thyroidal tumors to the thyroid gland: a regional survey in middle franconia., Exp Clin Endocrinol Diabetes, 2014. 122 (5)(5): p. 273-6., https://pubmed.ncbi.nlm.nih.gov/24839221/

1293. Queipo, FJ, Panizo, A, Yagüe, A, Ruiz-Azua, Y, Rodriguez, I, Gutiérrez-Pecharroman, A, et.al. Metastatic clear cell renal cell carcinoma to the thyroid gland: A clinico-pathological and immunohistochemical study of 8 cases and review of the literature., Rev Esp Patol, 2019. 52 (2)(2): p. 81-86., https://pubmed.ncbi.nlm.nih.gov/30902382/

1294. Nixon, IJ, Coca-Pelaz, A, Kaleva, AI, Triantafyllou, A, Angelos, P, Owen, RP, et.al. Metastasis to the Thyroid Gland: A Critical Review., Ann Surg Oncol, 2017. 24 (6)(6): p. 1533-1539., https://pubmed.ncbi.nlm.nih.gov/27873099/

1295. Surov, A, Machens, A, Holzhausen, HJ, Spielmann, RP, Dralle, H, Radiological features of metastases to the thyroid., Acta Radiol, 2016. 57 (4)(4): p. 444-50., https://pubmed.ncbi.nlm.nih.gov/25907117/

1296. Ishikawa, M, Hirano, S, Tsuji, T, Ito, J, Management of metastasis to the thyroid gland., Auris Nasus Larynx, 2011. 38 (3)(3): p. 426-30., https://pubmed.ncbi.nlm.nih.gov/21239125/

1297. Zhou, L, Chen, L, Xu, D, Shao, Q, Guo, Z, Ge, M, Breast cancer metastasis to thyroid: a retrospective analysis., Afr Health Sci, 2017. 17 (4)(4): p. 1035-1043., https://pubmed.ncbi.nlm.nih.gov/29937874/

1298. Nixon, IJ, Whitcher, M, Glick, J, Palmer, FL, Shaha, AR, Shah, JP, et.al. Surgical management of metastases to the thyroid gland., Ann Surg Oncol, 2011. 18 (3)(3): p. 800-4., https://pubmed.ncbi.nlm.nih.gov/21046263/

1299. Papi, G, Fadda, G, Corsello, SM, Corrado, S, Rossi, ED, Radighieri, E, et.al. Metastases to the thyroid gland: prevalence, clinicopathological aspects and prognosis: a 10-year experience., Clin Endocrinol (Oxf), 2007. 66 (4)(4): p. 565-71., https://pubmed.ncbi.nlm.nih.gov/17371476/

1300. Sozialgesetzbuch (SGB V), Gesetzliche Krankenversicherung, Stand: Zuletzt geändert durch Art. 1b G v. 20.12.2022, 2022. 279:

1301. Sozialgesetzbuch (SGB VI), Gesetzliche Rentenversicherung, Stand: Zuletzt geändert durch Art. 13 G v. 2.3.2023, 2023. 56:

1302. Sozialgesetzbuch (SGB IX), Rehabilitation und Teilhabe von Menschen mit Behinderungen, Stand: Zuletzt geändert durch Art. 4 G v. 20.12.2022, 2022. 2560:

1303. König, V.;, Rehabilitation und sozialmedizinische Leistungsbeurteilung beim SchilddrüsenkarzinomGMS Onkol Rehabil Sozialmed, 2016., https://dx.doi.org/10.3205/ors000030

1304. S3-Leitlinie MüdigkeitDeutsche Gesellschaft fur Allgemeinmedizin und Familienmedizin (DEGAM), AWMF-Register Nr. 053-002, 2022.

1305. Goswami, S, Mongelli, M, Peipert, BJ, Helenowski, I, Yount, SE, Sturgeon, C, Benchmarking health-related quality of life in thyroid cancer versus other cancers and United States normative data., Surgery, 2018. 164 (5)(5): p. 986-992., https://pubmed.ncbi.nlm.nih.gov/30149935/

1306. Altuntaş, SÇ, Hocaoğlu, Ç, Effects of Chronic Suppression or Oversuppression of Thyroid-Stimulating Hormone on Psychological Symptoms and Sleep Quality in Patients with Differentiated Thyroid Cancer., Horm Metab Res, 2021. 53 (10)(10): p. 683-691., https://pubmed.ncbi.nlm.nih.gov/34607367/

1307. Gülsoy Kirnap, N, Turhan Iyidir, Ö, Bozkuş, Y, Işildak, ŞM, Anil, C, Firat, SN, et.al. The effect of iatrogenic subclinical hyperthyroidism on anxiety, depression and quality of life in differentiated thyroid carcinoma., Turk J Med Sci, 2020. 50 (4)(4): p. 870-876., https://pubmed.ncbi.nlm.nih.gov/32490648/

1308. Sawka, AM, Ghai, S, Tomlinson, G, Rotstein, L, Gilbert, R, Gullane, P, et.al. A protocol for a Canadian prospective observational study of decision-making on active surveillance or surgery for low-risk papillary thyroid cancer., BMJ Open, 2018. 8 (4)(4): p. e020298., https://pubmed.ncbi.nlm.nih.gov/29654030/

1309. Sawka, AM, Straus, S, Gafni, A, Meiyappan, S, David, D, Rodin, G, et.al. Thyroid cancer patients' involvement in adjuvant radioactive iodine treatment decision-making and decision regret: an exploratory study., Support Care Cancer, 2012. 20 (3)(3): p. 641-5., https://pubmed.ncbi.nlm.nih.gov/22072050/

1310. Sutton, W, Genberg, B, Prescott, JD, Segev, DL, Zeiger, MA, Bandeen-Roche, K, et.al. Understanding surgical decision-making in older adults with differentiated thyroid cancer: A discrete choice experiment., Surgery, 2021. 169 (1)(1): p. 14-21., https://pubmed.ncbi.nlm.nih.gov/32475718/

1311. Urken, ML, Milas, M, Randolph, GW, Tufano, R, Bergman, D, Bernet, V, et.al. Management of recurrent and persistent metastatic lymph nodes in well-differentiated thyroid cancer: a multifactorial decision-making guide for the Thyroid Cancer Care Collaborative., Head Neck, 2015. 37 (4)(4): p. 605-14., https://pubmed.ncbi.nlm.nih.gov/24436291/

1312. Banach, R, Bartès, B, Farnell, K, Rimmele, H, Shey, J, Singer, S, et.al. Results of the Thyroid Cancer Alliance international patient/survivor survey: Psychosocial/informational support needs, treatment side effects and international differences in care., Hormones (Athens), 2013. 12 (3)(3): p. 428-38., https://pubmed.ncbi.nlm.nih.gov/24121384/

1313. Büttner, M, Rimmele, H, Bartès, B, Singer, S, Luster, M, Management of thyroid cancer: results from a German and French patient survey., Hormones (Athens), 2021. 20 (2)(2): p. 323-332., https://pubmed.ncbi.nlm.nih.gov/33184762/

1314. Husson, O, Mols, F, Oranje, WA, Haak, HR, Nieuwlaat, WA, Netea-Maier, RT, et.al. Unmet information needs and impact of cancer in (long-term) thyroid cancer survivors: results of the PROFILES registry., Psychooncology, 2014. 23 (8)(8): p. 946-52., https://pubmed.ncbi.nlm.nih.gov/24619907/

1315. Pitt, SC, Saucke, MC, Roman, BR, Alexander, SC, Voils, CI, The Influence of Emotions on Treatment Decisions About Low-Risk Thyroid Cancer: A Qualitative Study., Thyroid, 2021. 31 (12)(12): p. 1800-1807., https://pubmed.ncbi.nlm.nih.gov/34641715/

1316. Pitt, SC, Saucke, MC, Wendt, EM, Schneider, DF, Orne, J, Macdonald, CL, et.al. Patients' Reaction to Diagnosis with Thyroid Cancer or an Indeterminate Thyroid Nodule., Thyroid, 2021. 31 (4)(4): p. 580-588., https://pubmed.ncbi.nlm.nih.gov/33012267/

1317. Smith, S, Eatough, V, Smith, J, Mihai, R, Weaver, A, Sadler, GP, 'I know I'm not invincible': An interpretative phenomenological analysis of thyroid cancer in young people., Br J Health Psychol, 2018. 23 (2)(2): p. 352-370., https://pubmed.ncbi.nlm.nih.gov/29356226/

1318. Husson, O, Haak, HR, Oranje, WA, Mols, F, Reemst, PH, van de Poll-Franse, LV, Health-related quality of life among thyroid cancer survivors: a systematic review., Clin Endocrinol (Oxf), 2011. 75 (4)(4): p. 544-54., https://pubmed.ncbi.nlm.nih.gov/21615448/

1319. Hyun, YG, Alhashemi, A, Fazelzad, R, Goldberg, AS, Goldstein, DP, Sawka, AM, A Systematic Review of Unmet Information and Psychosocial Support Needs of Adults Diagnosed with Thyroid Cancer., Thyroid, 2016. 26 (9)(9): p. 1239-50., https://pubmed.ncbi.nlm.nih.gov/27350421/

1320. Adeyemi, OJ, Gill, TL, Paul, R, Huber, LB, Evaluating the association of self-reported psychological distress and self-rated health on survival times among women with breast cancer in the U.S., PLoS One, 2021. 16 (12)(12): p. e0260481., https://pubmed.ncbi.nlm.nih.gov/34852013/

1321. Chen, J, Hua, Y, Su, L, Wang, C, Zhang, H, Ye, J, et.al. The effect of psychological condition before radiotherapy on prognosis in 390 patients initially treated for nasopharyngeal carcinoma., Support Care Cancer, 2021. 29 (10)(10): p. 5967-5972., https://pubmed.ncbi.nlm.nih.gov/33765206/

1322. Kim, GM, Kim, SJ, Song, SK, Kim, HR, Kang, BD, Noh, SH, et.al. Prevalence and prognostic implications of psychological distress in patients with gastric cancer., BMC Cancer, 2017. 17 (1)(1): p. 283., https://pubmed.ncbi.nlm.nih.gov/28427439/

1323. Loth, FL, Meraner, V, Holzner, B, Singer, S, Virgolini, I, Gamper, EM, Following patient pathways to psycho-oncological treatment: Identification of treatment needs by clinical staff and electronic screening., Psychooncology, 2018. 27 (4)(4): p. 1312-1319., https://pubmed.ncbi.nlm.nih.gov/29462499/

1324. Singer, S, Lincke, T, Gamper, E, Bhaskaran, K, Schreiber, S, Hinz, A, et.al. Quality of life in patients with thyroid cancer compared with the general population., Thyroid, 2012. 22 (2)(2): p. 117-24., https://pubmed.ncbi.nlm.nih.gov/22191388/

1325. Goldfarb, M, Casillas, J, Thyroid Cancer-Specific Quality of Life and Health-Related Quality of Life in Young Adult Thyroid Cancer Survivors., Thyroid, 2016. 26 (7)(7): p. 923-32., https://pubmed.ncbi.nlm.nih.gov/27161396/

1326. Hedman, C, Djärv, T, Strang, P, Lundgren, CI, Determinants of long-term quality of life in patients with differentiated thyroid carcinoma - a population-based cohort study in Sweden., Acta Oncol, 2016. 55 (3)(3): p. 365-9., https://pubmed.ncbi.nlm.nih.gov/26541091/

1327. Singer, S, Husson, O, Tomaszewska, IM, Locati, LD, Kiyota, N, Scheidemann-Wesp, U, et.al. Quality-of-Life Priorities in Patients with Thyroid Cancer: A Multinational European Organisation for Research and Treatment of Cancer Phase I Study., Thyroid, 2016. 26 (11)(11): p. 1605-1613., https://pubmed.ncbi.nlm.nih.gov/27605136/

1328. Singer, S, Jordan, S, Locati, LD, Pinto, M, Tomaszewska, IM, Araújo, C, et.al. The EORTC module for quality of life in patients with thyroid cancer: phase III., Endocr Relat Cancer, 2017. 24 (4)(4): p. 197-207., https://pubmed.ncbi.nlm.nih.gov/28223365/

1329. Applewhite, MK, James, BC, Kaplan, SP, Angelos, P, Kaplan, EL, Grogan, RH, et.al. Quality of Life in Thyroid Cancer is Similar to That of Other Cancers with Worse Survival., World J Surg, 2016. 40 (3)(3): p. 551-61., https://pubmed.ncbi.nlm.nih.gov/26546191/

1330. Dionisi-Vici, M, Fantoni, M, Botto, R, Nervo, A, Felicetti, F, Rossetto, R, et.al. Distress, anxiety, depression and unmet needs in thyroid cancer survivors: a longitudinal study., Endocrine, 2021. 74 (3)(3): p. 603-610., https://pubmed.ncbi.nlm.nih.gov/34143334/

1331. Choi, HG, Park, B, Ji, YB, Tae, K, Song, CM, Depressive Disorder in Thyroid Cancer Patients after Thyroidectomy: A Longitudinal Follow-up Study Using a National Cohort., Otolaryngol Head Neck Surg, 2019. 160 (2)(2): p. 239-245., https://pubmed.ncbi.nlm.nih.gov/30274554/

1332. Hedman, C, Strang, P, Djärv, T, Widberg, I, Lundgren, CI, Anxiety and Fear of Recurrence Despite a Good Prognosis: An Interview Study with Differentiated Thyroid Cancer Patients., Thyroid, 2017. 27 (11)(11): p. 1417-1423., https://pubmed.ncbi.nlm.nih.gov/28874092/

1333. Noto, B, Asmus, I, Schäfers, M, Görlich, D, Riemann, B, Predictors of Anxiety and Depression in Differentiated Thyroid Cancer Survivors: Results of a Cross-Sectional Study., Thyroid, 2022. 32 (9)(9): p. 1077-1085., https://pubmed.ncbi.nlm.nih.gov/35734910/

1334. Henry, M, Frenkiel, S, Chartier, G, MacDonald, C, Payne, RJ, Black, MJ, et.al. Thyroid cancer patients receiving an interdisciplinary team-based care approach (ITCA-ThyCa) appear to display better outcomes: Program evaluation results indicating a need for further integrated care and support., Psychooncology, 2018. 27 (3)(3): p. 937-945., https://pubmed.ncbi.nlm.nih.gov/29178318/

1335. Javaloyes, N, Crespo, A, Redal, MC, Brugarolas, A, Botella, L, Escudero-Ortiz, V, et.al. Psycho-Oncological Intervention Through Counseling in Patients With Differentiated Thyroid Cancer in Treatment With Radioiodine (COUNTHY, NCT05054634): A Non-randomized Controlled Study., Front Psychol, 2022. 13 (): p. 767093., https://pubmed.ncbi.nlm.nih.gov/35282223/

1336. Pei, J, Meng, J, Xue, Y, Zhang, L, Disease Experience of Patients With Differentiated Thyroid Cancer at Different Phases Based on Timing It Right Framework: A Qualitative Longitudinal Study., Cancer Nurs, 2023. ():, https://pubmed.ncbi.nlm.nih.gov/36907952/

1337. Wang, S, Huang, H, Wang, L, Wang, X, A Psychological Nursing Intervention for Patients With Thyroid Cancer on Psychological Distress and Quality of Life: A Randomized Clinical Trial., J Nerv Ment Dis, 2020. 208 (7)(7): p. 533-539., https://pubmed.ncbi.nlm.nih.gov/32187128/

1338. Husson, O, Poort, H, Sansom-Daly, UM, Netea-Maier, R, Links, T, Mols, F, Psychological Distress and Illness Perceptions in Thyroid Cancer Survivors: Does Age Matter?, J Adolesc Young Adult Oncol, 2020. 9 (3)(3): p. 375-383., https://pubmed.ncbi.nlm.nih.gov/31990604/

1339. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), Entwicklung von leitlinienbasierten Qualitätsindikatoren. Methodenpapier für das Leitlinienprogramm Onkologie, Version 3.0, 2021., https://www.leitlinienprogramm-onkologie.de/methodik/grundlegende-informationen-zur-methodik