Leitlinienprogramm Onkologie

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Evidenzbericht

S3-Leitlinie Schilddrüsenkarzinom

Stand Dezember 2024
AWMF-Registernummer: 031-056OL

Evidenzbericht

DKG KREBSGESELLSCHAFT Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN. AWMF

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1. Informationen zum Evidenzbericht

1.1. Autor*innen des Evidenzberichts

Prof. Dr. Nicole Skoetz, Uniklinik Köln, Klinik I für Innere Medizin, AG Evidenzbasierte Medizin, ab 11.2023 Universität zu Köln, Institut für Öffentliches Gesundheitswesen,

1.1.1. Weitere Beteiligte der Evidenzaufbereitung

Dr. Angela Aldin, Mandy Baumann, Marius Goldkuhle, Nina Kreuzberger, Ina Monsef, Dr. Vanessa Piechotta, Uniklinik Köln, Klinik I für Innere Medizin, AG Evidenzbasierte Medizin.

2. Methodisches Vorgehen bei der Evidenzaufarbeitung

2.1. Unterstützung bei der Erstellung von Schlüsselfragen

Zunächst wurden Telefonkonferenztermine für die Arbeitsgruppen der Leitlinie angeboten, um diese darin zu unterstützen, die abgestimmten Fragen des Kick-Off Meetings in beantwortbare und recherchierbare Fragen zu überführen. Mit den Arbeitsgruppen, die das Angebot annahmen, wurden Schlüsselfragen in dem PICO Format definiert, wobei „P“ die Population, „I“ die Intervention, „C“ die Vergleichintervention und „O“ die patientenrelevanten Outcomes bezeichnet.

2.1.1. Allgemeines Vorgehen

Die Evidenzrecherchen und Datenextraktionen erfolgten in einem abgestuften Vorgehen für die mit den Arbeitsgruppen abgestimmten PICO Fragen. Zur Erstellung der Suchstrategien wurden die Arbeitsgruppen um bereits bekannte passende Referenzen von Studien oder Übersichtsarbeiten gebeten, zudem um relevante Suchbegriffe zu dem jeweiligen Krankheitsbild, Intervention und Vergleichsinterventino. Zunächst wurde nach evidenzbasierten Leitlinien, systematischen Übersichtsarbeiten und schließlich nach Primärstudien recherchiert. Die Ergebnisse der Recherchen wurden den Arbeitsgruppen präsentiert und abgestimmt, ob die PICO-Frage exakt in die Recherche translatiert wurde und ggf. relevante Referenzen nicht enthalten sind. Sofern das vorkam wurde die PICO-Frage erneut genau besprochen und die Suchstrategie um weitere relevante Suchbegriffe ergänzt.

2.2. Leitlinienadaptation

Die Bewertung der identifizierten Leitlinien erfolgte nach einem formalisierten Verfahren zunächst durch die methodisch ausgewiesenen Mitarbeiter der Klinik I für Innere Medizin des Universitätsklinikums Köln (Arbeitsgruppe Evidence-based Oncology).

2.2.1. Recherche

Im Januar 2019 wurde in der Datenbank des Guideline International Networks (GIN) (www.g-i-n.net) und MEDLINE (www.pubmed.org) mit dem Suchbegriff „Thyroid“ nach relevanten Leitlinien gesucht.

2.2.2. Auswahl der Leitlinien

Die Einschlusskriterien für die detaillierte Betrachtung einer Leitlinie waren, dass sie evidenzbasierte Empfehlungen für die Diagnose oder Therapie von Patienten mit einem Schilddrüsenkarzinom geben sollten.

Ausgeschlossen wurden Leitlinien, die nicht das Schilddrüsenkarzinom thematisierten, nicht evidenzbasiert waren oder keinen Leitlinienreport mit der Methodik der Evidenzbaiserung veröffentlicht hatten.

Von den 45 Suchtreffern zu den teilweise noch in Erstellung befindlichen Leitlinien rschienen Leitlinien der drei folgenden Fachgesellschaften potentiell relevant.

- American Thyroid Association
    - *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 (1)*
    - *Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma (2015) (2)*
    - *American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer (2012) (3)*
- British Thyroid Association
    - *British Thyroid Association Guidelines for the Management of Thyroid Cancer* (2014) (4)
- European Thyroid Association
- *2012 European Thyroid Association Guidelines for Metastatic Medullary Thyroid Cancer* (5)

2.2.3. Leitlinienbewertung

Da es sich um internationale Leitlinien handelt, die auf Versorgungsgegebenheiten zielen, die auf die deutsche Versorgungssituation gegebenenfalls nicht direkt übertragbar sind (z.B. Abweichungen in der Jodversorgung der Patienten, der Inzidenz des Schilddrüsenkarzinoms, der Inzidenz von knotigen Veränderungen des Schilddrüsengewebes, sowie der strukturellen Ausstattung), kein Methodenreport verfügbar war oder die Leitlinien veraltet waren, wurde, wie auf dem Kick Off Meeting festgelegt, keine der Leitlinien zur Evidenzbasierung von Schlüsselfragen herangezogen. Entsprechend wurde keine Leitlinienadaption vorgenommen. Zudem liegen für diese Leitlinien keine Leitlinienreports vor, so dass sie auch methodisch nicht die Kriterien für einen Einschluss erfüllen.

2.3. Systematische Recherche, Auswahl und Bewertung der Literatur: Systematische Reviews, Primärstudien und HTA-Berichte

Die systematische Literatursuche basiert auf dem Prinzip der besten verfügbaren Evidenz. Im Rahmen von Telefonkonferenzen mit den drei Leitern jeder der betreffenden Arbeitsgruppen und gegebenenfalls weiteren, durch die Arbeitsgruppenleiter bestimmten Experten, wurden die evidenzbasierten Fragestellungen, für die eine de novo Suche festgelegt worden ist, systematisiert. Aufbauend auf den Konferenzen wurden die methodischen und inhaltlichen Ein- und Ausschlusskriterien für die systematischen Suchen prospektiv definiert. Anschließend wurden die systematischen Suchen von einer in der medizinischen Terminologie erfahrenen Bibliothekarin in sensitiven und hochkomplexen Suchstrategien für die jeweils zu durchsuchende

Datenbanken MEDLINE und CENTRAL (Register klinischer Studien der Cochrane Library) umgesetzt. Für alle Suchstrategien wurden neben dem Datum der Suche auch die Anzahl der erzielten Treffer dokumentiert. Bei der de novo Recherche wurde nach Volltextpublikationen von systematischen Übersichtsarbeiten mit Meta-Analyse und randomisierten kontrollierten Studien (RCTs) bzw. bei speziellen Fragestellungen, in Absprache mit den Leitern der betreffenden Arbeitsgruppen, auch nach nicht-randomisierten-kontrollierten Studien und Fallserien gesucht.

Alle Referenzen, die durch die Suchstrategien identifiziert wurden, wurden in einem Literaturverwaltungsprogramm erfasst. Sie wurden durch eine wissenschaftliche Mitarbeiterin der Arbeitsgruppe für Evidenzbasierte Mediziin auf die potentielle Relevanz für die Leitlinie ausgewählt und von einem weiteren Mitarbeiter überprüft. Unstimmigkeiten in der Vorauswahl der Referenzen wurden gelöst und die so ermittelten Publikationen in einer Literaturdatenbank als PDF-Volltexte abgelegt. Im nächsten Schritt wurden die Studien, die als Volltext publiziert wurden und zur Beantwortung einer der Schlüsselfragen beitragen, in Evidenztabellen extrahiert.

Die Ergebnisse der Suchen wurden den jeweiligen Arbeitsgruppen-Leitungen zur Überprüfung der Treffer und zur potenziellen Ergänzung der Suchen zur Verfügung gestellt.

2.4. Schema der Evidenzklassifikation und Biasbewertung

Die Bewertung der Evidenz erfolgte nach einem formalisierten Verfahren durch die Mitarbeitenden der Arbeitsgruppe für Evidenzbasierte Medizin entsprechend den Kriterien der evidenzbasierten Medizin. Die in den systematischen Suchrecherchen identifizierte Literatur wurde in Evidenztabellen extrahiert. Dabei wurden Unstimmigkeiten unter Hinzuziehung einer weiteren Expertin geklärt.

Die Qualität der Evidenz wurde anhand der Bewertungsinstrumente AMSTAR-2 für systematische Reviews (6), dem Cochrane Risk of Bias tool für RCTs (7) und dem QUADAS-2 Tool für diagnostische Studien [5] beurteilt. Die Resultate der Bewertung wurden zusammen mit den Ergebnissen der Studien in Evidenztabellen zusammenfassend dargestellt und dienten als Diskussionsgrundlage zur Prüfung der internen Validität der Studienergebnisse im Hinblick auf die zu beantwortende Frage.

Die Evidenzlevel wurden gemäß dem Oxford-Schema präsentiert. Das Oxford Schema ist in der folgenden Tabelle dargestellt.

Tabelle 1: Oxford Schema (Version März 2009)

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity) of RCTs	SR (with homogeneity) inception cohort studies; CDR validated in different populations	SR (with homogeneity) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centers	SR (with homogeneity) of prospective cohort studies	SR (with homogeneity) of Level 1economic studies

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 centre	Prospective cohort study with good follow-up	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
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	SR (with homogeneity) of Level 2b and better studies	SR (with homogeneity) of Level >2 economic 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	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity) of case-control studies		SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study; or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations

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	Case-series or superseded reference standards	Analysis with no sensitivity analysis
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"	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"

2.4.1. Bewertung des Vertrauens in die Evidenz gemäß GRADE

Die Bewertung der den Empfehlungen zugrundeliegenden Evidenz erfolgte für 2 vor ausgewählte PICO Fragen zur Radioiotherapie gemäß dem GRADE-Schema (8), um die jeweils gesamte Evidenz, die einer spezifischen Empfehlung zugrunde liegt, standardisiert und formalisiert zu bewerten.

Hierbei handelt es sich um ein System mit speziell entwickelter, online verfügbarer Software, mittels derer die Qualität der Evidenz formalisiert bewertet, und die Güte der aus der Evidenz abgeleiteten Empfehlungen eingeschätzt und übersichtlich dargestellt wurde (https://gradepro.org/). In dieser Leitlinie erfolgte die Bewertung des Vertrauens in die Evidenz durch GRADE (siehe unten), nicht jedoch die formalisierte Ableitung der Empfehlungen. GRADE kann sowohl für diagnostische als auch therapeutische Empfehlungen verwendet werden.

Für den Fall aggregierter Evidenz aus systematischen Reviews bezieht sich die Beurteilung innerhalb der GRADE-Bewertung für die Domäne „Verzerrungsrisiko" auf die Bewertung der eingeschlossenen Primärstudien. Dementsprechend wurde die Risk-of-Bias-Bewertung der jeweiligen Review bei der Beurteilung berücksichtigt. Falls das Review keine Bewertung des Verzerrungsrisikos durchgeführt hat, wurde die Qualität dieser Studien mit dem entsprechend geeigneten Tool für das Studiendesign überprüft.

Im Rahmen der Ersterstellung der Leitlinie wurden dazu zunächst die Endpunkte für die jeweilige Fragestellung priorisiert. In die Qualitätsbewertung der Evidenz gingen die als wichtig und patient*innen-relevant erachteten Endpunkte (sogenannte kritische Endpunkte) ein, für die jeweils das Vertrauen in die zugrundeliegende Evidenz mittels des GRADE-Systems ermittelt wurde. Für therapeutische Fragestellungen waren diese Endpunkte die folgenden: das Gesamtüberleben (overall survival, OS), das progressionsfreie Überleben (progression-free survival, PFS), die Lebensqualität (quality of life, QoL), akute oder Langzeitnebenwirkungen (adverse events, serious adverse events) und die behandlungsbedingte Mortalität. Die priorisierten Endpunkte wurden für

diese Leitlinienaktualisierung übernommen. Bei den unerwünschten Ereignissen erfolgte die Selektion spezifisch nach Fragestellung in enger Abstimmung mit den Autor*innen und AG-Leitungen der jeweiligen Kapitel. Bei der Lebensqualität wurde grundsätzlich die globale krankheitsbezogene Lebensqualität extrahiert; je nach PICO wurden diese um weitere Lebensqualitätsdomänen ergänzt.

Zur Abwertung des Vertrauensgrades führten folgende Studien- oder Qualitätscharakteristika (9):

- Ein nicht-randomisiertes Studiendesign (10)
- Ein potentiell hohes Verzerrungsrisiko des zugrundeliegenden Evidenzkörpers (10)
- Heterogenität oder Inkonsistenz eines Ergebnisparameters in den betrachteten Einzelstudien (11)
- Ein unpräzise geschätzter Effekt mit einem breiten Konfidenzintervall (12)
- Ein Ergebniswert der indirekt auf die Zielpopulation oder den untersuchten Ergebnisparameter zu übertragen ist (13)
- Ein Hinweis auf Publikationsbias (14)

Folgende Charakteristika führten zur Aufwertung der Qualität eines zugrundeliegenden Evidenzkörpers (15):

- Eine Dosis-Wirkungsbeziehung
- Ein sehr ausgeprägter Effekt
- Residuelles Confounding

Bedeutung der Evidenzgraduierung gemäß der GRADE Working Group (www.gradepro.org):

Tabelle 2: Vertrauen in den Evidenzkörper gemäß GRADE

Vertrauen in die Evidenz	Beschreibung	Symbol
Hohes Vertrauen	Wir sind sehr sicher, dass der wahre Effekt nahe bei dem Effektschätzer liegt.	⊕⊕⊕⊕
Moderates Vertrauen	Wir haben mäßig viel Vertrauen in den Effektschätzer: der wahre Effekt ist wahrscheinlich nahe bei dem Effektschätzer, aber es besteht die Möglichkeit, dass er relevant verschieden ist.	⊕⊕⊕⊖
Geringes Vertrauen	Unser Vertrauen in den Effektschätzer ist begrenzt: Der wahre Effekt kann durchaus relevant verschieden vom Effektschätzer sein.	⊕⊕⊖⊖
Sehr geringes Vertrauen	Wir haben nur sehr wenig Vertrauen in den Effektschätzer: Der wahre Effekt ist wahrscheinlich relevant verschieden vom Effektschätzer.	⊕⊖⊖⊖

Die Studien wurden den Expert*innen der Arbeitsgruppen, zusammen mit den formal standardisierten Evidenztabellen als Evidenzgrundlage für die Empfehlungen, zur Verfügung gestellt. Während der Konsensuskonferenzen wurden die Evidenztabellen auch zur Verfügung gestellt und bei Bedarf präsentiert.

3. Suchstrategien und Evidenztabellen je Schlüsselfrage

3.1. Verwendung von standardisierten Risikostratifizierungssystemen in der Schilddrüsensonographie (TIRADS) – Kapitel 3.4.2 der Langversion

3.1.1. Schlüsselfrage

Diagnostische Wertigkeit von TIRADS-Klassifikationen

3.1.2. Schlüsselfrage im PICO-Format

Patient	Alle Patienten mit operativ entfernten Schilddrüsenknoten
Intervention	TIRADS-Klassifikation
Comparison	Histologischer Befund
Outcome	Positiv bzw. negativ prädiktiver Wert bezüglich Malignität in Abhängigkeit von der TIRADS Klasse

3.1.3. Suchstrategie vom 27.09.2019

3.1.3.1. MEDLINE (via OVID)

#	Searches
1	exp THYROID NEOPLASMS/
2	(thyroid* or thyreoid*).tw,kf.
3	(DTC or RR-DTC or PDTC).tw,kf.
4	or/1-3
5	"thyroid imaging reporting and data system*".tw,kf.
6	(tirads or ti-rads).tw,kf.
7	Thyroid Image Reporting.tw.
8	*ULTRASONOGRAPHY/
9	(ultrasonographical adj3 feature*).tw,kf.
10	"ultrasound (US) feature*".tw,kf.

#	Searches
11	Ultrasound Classification Systems.tw,kf.
12	Ultrasound Risk Assessment.tw,kf.
13	Thyroid Imaging Reporting.tw,kf.
14	thyroid ultrasonograph*.tw,kf.
15	thyroid ultrasound.tw,kf.
16	Single ultrasound parameter*.tw,kf.
17	*Ultrasonography/.kw.]
18	Gray-Scale Ultrasound.tw.
19	*Ultrasonography, Interventional/
20	high-resolution ultrasound.tw.
21	thyroid nodules ultrasound.tw.
22	or/5-21
23	4 and 22

3.1.3.2. Cochrane Central Register of Controlled Trials **(via Cochrane Library)**

ID	Search
#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	thyroid* or thyreoid*
#3	DTC or RR-DTC or PDTC
#4	#1 or #2 #3
#5	thyroid imaging reporting and data system*
#6	(tirads or ti-rads)
#7	Thyroid Image Reporting
#8	MeSH descriptor: [Ultrasonography] this term only
#9	(ultrasonographical near/3 feature*)
#10	ultrasound (US) feature*

ID	Search
#11	Ultrasound Classification Systems
#12	Ultrasound Risk Assessment
#13	Thyroid Imaging Reporting
#14	thyroid ultrasonograph*
#15	thyroid ultrasound
#16	Single ultrasound parameter*
#17	Gray-Scale Ultrasound
#18	MeSH descriptor: [Ultrasonography, Interventional] this term only
#19	high-resolution ultrasound
#20	thyroid nodules ultrasound
#21	#5 or #6 or #7 or #8 or #9 or 10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22	#4 and #21

3.1.3.3. Ergebnis der Recherche

Fundstellen	3.622
Volltextscreening	52
Ausgeschlossen mit Gründen	40 keine Bewertung der TIRADS Kriterien 9 keine systematischen Übersichtsarbeiten
Eingeschlossen	3 Systematische Übersichtsarbeiten

3.1.4. Evidenztabellen

3.1.4.1. Einzelstudien

Keine.

3.1.4.2. Systematische Übersichten/Meta-Analysen

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Methodische Bemerkungen	Evidenzlevel
Migda, B 2019 (16) A systematic review and meta-analysis of the Kwak TIRADS for the diagnostic assessment of indeterminate thyroid nodules Clinical Radiology Volume 74, Pages 123-130	Inclusion criteria: (1) adults with indeterminate nodules (belonging to category III, IV, or V according to Bethesda); (2) using the K-TIRADS classification as a tool for differentiating thyroid nodules; (3) final diagnosis based on histological or cytological examination, but only in cases of definitive diagnosis or for non-suspicious nodule ultrasound follow-up after at least 12 months with no sign of progression; (4) data in the publication had to allow for calculations based on 22 pivot tables; (5) studies published in English or German.	Kwak TIRADS classification with 3/4a cut-off for indeterminate lesions has high sensitivity but low specificity to exclude benign lesions	Pooled sensitivity, specificity, negative and positive likelihood ratios (LR), diagnostic odds ratio (DOR), and area under the curve (AUC) from summarised receiver operating characteristic (SROC) curves.	Six publications describing 1,096 nodules were analysed. The overall pooled sensitivity and specificity for the TIRADS classification were 0.913 (95% confidence interval [CI]: 0.884 - 0.936) and 0.347 (95% CI: 0.311 - 0.386), respectively The overall pooled values of the positive likelihood ratio and negative likelihood ratio were 1.396 (95% CI: 1.155 - 1.686) and 0.341 (95% CI: 0.179 - 0.649), respectively The overall pooled DOR was 5.832 (95% CI: 2.517e13.515) The AUC was 0.7180 (Q*¼0.6673)	Use of TIRADS to put nodules into categories High degree of statisitical heterogeneity for sensitivity (I^2 = 95%), specificity (96.4%), positive LR (87.4%), negative LR (74.4%) and DOR (62.8%) QUADAS2 tool used for study quality assessment: Results not reported No use of GRADE Level of evidence of review (Systematic review of prospective and retrospective studies; variable reference standards (surgery, FNAB)): 3- (substantial inconsistency between studies for core outcomes)	2a
Wei, X., Li, Y., Zhang, S., Gao, M. 2016 Meta-analysis of thyroid imaging reporting and data system in the	Selection criteria: (1) the language limited in English or Chinese; (2) methodological quality of included studies were included in this review and quality assessment of diagnostic accuracy studies was used as a quality assessment tool to assess the quality of articles; (3) TI-RADS	(…) to perform meta-analyses to evaluate the diagnostic accuracy of TI-RADS in patients with thyroid nodules	Combined sensitivity, specificity, likelihood ratio (LR), and diagnostic odds ratio (DOR)	12 studies involving 10437 thyroid nodules included The pooled sensitivity and specificity of TI-RADS were 0.79 (95% CI = 0.77–0.81) and 0.71 (95% CI = 0.70–0.72), respectively.	QUADAS tool used for study quality assessment: Results not reported High degree of statisitical heterogeneity for sensitivity (I^2 = 95.1%), specificity (99.2%), positive LR	2a

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Methodische Bemerkungen	Evidenzlevel
ultrasonographic diagnosis of 10,437 thyroid nodules Head & Neck Volume 38 Pages 309-315	system was performed in the differentiated diagnosis of thyroid nodules; (4) histological and/or cytological analyses were used as the reference standard; (5) sufficient patients in studies were presented to calculate the true-positive, false-negative, false-positive, and true-negative values for data statistics; and (6) the duplicated articles were chosen to keep the most details or the most recent studies			The summary positive and negative likelihood ratio were 6.6 (95% CI = 4.4–9.9) and 0.20 (95% CI = 0.14–0.29) The pooled DOR was 35.2 (95% CI = 19.5–63.4) The overall AUC was 0.9177 and the Q* index was 0.8507, indicating very good diagnostic accuracy.	(98.7%), negative LR (92.0%) and DOR (90.8%) No use of GRADE Level of evidence of review (Systematic review of prospective and retrospective studies; consistent reference standard): 2- (substantial inconsistency between studies for core outcomes)	
Wei, X 2014 (17) Thyroid imaging reporting and data system (TI-RADS) in the diagnostic value of thyroid nodules: a systematic review Tumor Biology Volume 35 Pages 6769-6779	Selection critera: (a) Language is limited in English; (b) Quality assessment of diagnostic accuracy studies (QUADAS) was used as a quality assessment tool to assess the quality of article (…) (c) The TI-RADS system was performed in the differentiated diagnosis of thyroid nodules. Those studies which were not seen as a diagnostic tool in thyroid nodules were excluded; (d) Histological and/or cytological analyses were used as the reference standard; (e) Sufficient patients in studies were presented to calculate the true-positive (TP), false-negative (FN), false-positive (FP), and true negative (TN) values for data statistics; (f) The data or subsets of data were not published more than once.	(…) to assess the overall diagnostic value of TI-RADS in the thyroid imaging strategy.	Combined sensitivity, specificity, likelihood ratio, and diagnostic odds ratio (DOR)	5 studies involving 7753 thyroid nodules included TI-RADS had a pooled sensitivity of 0.75 (95 % confidence interval 0.72–0.78) and a pooled specificity of 0.69 (95 % confidence interval 0.68–0.70). The pooled diagnostic odds ratio was 24.28 (95 % confidence interval 14.25–41.38). The overall area under the curve was 0.9177, and the Q* index was 0.8304.	QUADAS tool used for study quality assessment: Results not reported High degree of statisitical heterogeneity for sensitivity (I^2 = 97.8%), specificity (99.6%), positive LR (99.4%), negative LR (95.9%) and DOR (70.2%) No use of GRADE Level of evidence of review (Systematic review of prospective and retrospective studies; consistent reference standard): 2- (substantial inconsistency between studies for core outcomes)	2a

3.2. Kontrastmittelverstärkte Sonographie (CEUS) der Schilddrüse - Kapitel 3.4.5 der Langversion

3.2.1. Schlüsselfrage

Diagnostische Wertigkeit der kontrastmittelverstärkten Sonographie der Schilddrüse

3.2.2. Schlüsselfrage im PICO-Format

Patient	Alle Patienten mit Schilddrüsenknoten
Intervention	Kontrastmittelverstärkte Sonographie
Comparison	Sonographie
Outcome	Positiv bzw. negativ prädiktiver Wert bezüglich Malignität

3.2.3. Suchstrategie vom 27.09.2019

3.2.3.1. MEDLINE (via OVID)

#	Searches
1	exp THYROID NEOPLASMS/
2	(thyroid* or thyreoid*).tw,kf.
3	(DTC or RR-DTC or PDTC).tw,kf.
4	or/1-3
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12	Ultrasound Risk Assessment.tw,kf.
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14	thyroid ultrasonograph*.tw,kf.

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15	thyroid ultrasound.tw,kf.
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18	Gray-Scale Ultrasound.tw.
19	*Ultrasonography, Interventional/
20	high-resolution ultrasound.tw.
21	thyroid nodules ultrasound.tw.
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#12	Ultrasound Risk Assessment
#13	Thyroid Imaging Reporting
#14	thyroid ultrasonograph*

ID	Search
#15	thyroid ultrasound
#16	Single ultrasound parameter*
#17	Gray-Scale Ultrasound
#18	MeSH descriptor: [Ultrasonography, Interventional] this term only
#19	high-resolution ultrasound
#20	thyroid nodules ultrasound
#21	#5 or #6 or #7 or #8 or #9 or 10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22	#4 and #21

3.2.3.3. Ergebnis der Recherche

Fundstellen	3.622
Volltextscreening	52
Ausgeschlossen mit Gründen	51 keine Bewertung der kontrastmittelverstärkten Sonographie
Eingeschlossen	1 Systematische Übersichtsarbeit

3.2.4. Evidenztabellen

3.2.4.1. Einzelstudien

Keine.

3.2.4.2. Systematische Übersichten/Meta-Analysen

Referenz/ Studientyp	Untersuchte Population	Suchstrategie, Einschlusskriterien	Eingeschlossene Studien	Ergebnisse	methodische Bemerkungen / Evidenzklasse (AMSTAR2)	Evidenz-level
Liu, Q 2018 (18) The diagnostic accuracy of contrast-enhanced ultrasound for the differentiation of benign and malignant thyroid nodules: A PRISMA compliant meta-analysis Medicine 97 49(e13325)	Selection criteria: 1. The studies that assessed the diagnostic accuracy of CEUS for the distinction between benign and malignant thyroid nodules, that is, the studies using CEUS to evaluate the nature of thyroid nodules to be benign or malignant, elucidating the diagnostic accuracy of CEUS with reference methods such as FNA or pathological results; 2. The studies that adopted the appropriate reference diagnostic standard, the pathology diagnosis, defined as the histology and cytology of biopsy specimens or histology	Analyzed the diagnostic accuracy of CEUS on thyroid nodules	33 diagnostic studies The performance of Contrast-enhanced ultrasound (CEUS) Pooled estimates of sensitivity, specificity, diagnostic odds ratio (DOR), positive and negative likelihood ratio (NLR)	Mean age of patients included ranged from 39.9 to 55.9 years, with 3 studies conducted in Singapore, 4 studies in Italy, 1 in the USA, 1 in Australia and 24 studies performed in China. The contrast agent used of the included studies were all Sonovue, with different doses, ranging from 1.2 to 4.8mL Pooled estimates of sensitivity were 0.88 (95% CI 0.85, 0.91) Pooled estimates of specificity were 0.88 (95% CI 0.83, 0.91), respectively Pooled estimates of DOR 54% (95% CI 33, 89) Pooled estimates of positive LR 7.1% (95% CI 5.2%, 9.8%) Pooled estimates of negative LR 0.13% (95% CI 0.10%, 0.18%)	No significant publication bias was observed. High degree of statisitical heterogeneity for sensitivity (I^2 = 78.78%) and specificity (85.14%) QUADAS tool used for study quality assessment: It showed that the overall quality of the included studies was high" No use of GRADE Level of evidence of review (Systematic review of prospective and retrospective studies; variable reference standards (surgery, FNAB)): 3- (substantial inconsistency between studies for core outcomes)	2

Referenz/ Studientyp	Untersuchte Population	Suchstrategie, Einschlusskriterien	Eingeschlossene Studien	Ergebnisse	methodische Bemerkungen / Evidenzklasse (AMSTAR2)	Evidenz-level
	of the surgical specimens; 3. The studies that provided the diagnostic data that were sufficient for us to calculate the values of true-positive (TP), false-positive (FP), true-negative (TN) and false-negative (FN) results for the 2×2 contingency table.					

3.3. Elastographie der Schilddrüse - Kapitel 3.4.3 der Langversion

3.3.1. Schlüsselfrage

Diagnostische Wertigkeit der Elastographie

3.3.2. Schlüsselfrage im PICO-Format

Patient	Alle Patienten mit operativ entfernten Schilddrüsenknoten*
Intervention	Elastographie
Comparison	Histologischer Befund
Outcome	Positiv bzw. negativ prädiktiver Wert bezüglich Malignität

* Alle Formen der Schilddrüsenoperation

3.3.3. Suchstrategie vom 26.09.2019

3.3.3.1. MEDLINE (via OVID)

#	Searches
1	exp Thyroid Neoplasms/
2	(thyroid* or thyreoid*).tw,kf,ot.
3	Thyroid Diseases/pa
4	(DTC or RR-DTC).tw.
5	PDTC.tw.
6	or/1-5
7	Elasticity Imaging Techniques/
8	(elastograph* or sonoelastograph* or elastosonograph* or elastogram*).tw,kf.
9	(elasticity imaging adj3 (technique* or tissue*)).tw,kf.
10	acoustic radiation force impulse imaging.tw,kf.
11	(vibro acoustograph* or vibroacoustograph*).tw,kf.
12	or/7-11
13	6 and 12
14	Thyroid Diseases/pa [Pathology]
15	Ultrasonography/
16	14 and 15

#	Searches
17	13 or 16

3.3.3.2. Cochrane Central Register of Controlled Trials (via Cochrane Library)

ID	Search
#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	thyroid* or thyreoid*
#3	MeSH descriptor: [Thyroid Diseases] this term only
#4	DTC or RR-DTC or PDTC
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Elasticity Imaging Techniques] explode all trees
#7	elastograph* or sonoelastograph* or elastosonograph* or elastogram*
#8	elasticity imaging near/3 (technique* or tissue*)
#9	acoustic radiation force impulse imaging
#10	vibro acoustograph* or vibroacoustograph*
#11	#6 or #7 or #8 or #9 or #10
#12	#5 and #11
#13	MeSH descriptor: [Ultrasonography] explode all trees
#14	#3 and #13
#15	#12 or #14

3.3.3.3. Ergebnis der Recherche

Fundstellen	771
Volltextscreening	24
Ausgeschlossen mit Gründen	20 keine Bewertung der Elastographie 2 keine systematischen Übersichtsarbeiten
Eingeschlossen	2 systematische Übersichtsarbeiten

3.3.4. Evidenztabellen

3.3.4.1. Einzelstudien

Keine

3.3.4.2. Systematische Übersichten/Meta-Analysen

Referenz/ Studientyp	Untersuchte Population	Suchstrategie, Einschlusskriterien	Eingeschlossene Studien	Ergebnisse	methodische Bemerkungen / Evidenzklasse (AMSTAR2)	Evidenz-level
Nattabi, 2022 (19)	Patients with thyroid nodules Quantitative 2D-SWE (Shear Wave Elastography) for malignancy risk stratification in the thyroid gland	Databases: Pubmed Web of Science Scopus Search period December 12, 2016 Key words: Thyroid thyroid nodule thyroid cancer elastography shear wave US	14 studies Sebag, 2010 Bhatia, 2012 Veyrieres, 2012 Kim, 2013 Szczepanek-Parulska, 2013 Liu, 2014a Liu, 2015b Park, 2015 Samir, 2015 Liu, 2015c Wang, 2016 Duan, 2016 Dobruch-Sobczak, 2016 He, 2016	**2D-SWE (Shear Wave Elastography compared with fine needle aspiration cytology (FNAC) or histopathology of surgical specimens.** Sensitivity: - Liu et al a: 0.68 (0.43 – 0.87) - Liu et al b: 0.69 (0.58 – 0.78) - Liu et al e: 0.66 (0.56 – 0.75) - Bhatia et al: 0.53 (0.28 – 0.77) - Duan et al: 0.84 (0.74 – 0.90) - Szczepanek et al: 0.95 (0.77 – 1.00) - Dobruch et al: 0.88 (0.76 – 0.95) - Kim et al: 0.67 (0.43 – 0.85) - Park et al: 0.44 (0.38 – 0.49) - He et al (Aiken): 0.64 (0.49 – 0.77) - He et al (Toshiba): 0.83 (0.69 – 0.92) - Samir et al: 0.82 (0.48 – 0.98)	AMSTAR-2 rating 1. PICO elements: no 2. A priori design: yes, 3. Justification for design: no 4. Literature search >= 2 databases, search strategy + other sources: partial yes 5. Selection in duplicate: yes 6. Data extraction in duplicate: yes 7. List of excluded studies: no 8. sufficient detail on studies: partial yes 9. RoB assessed: partial yes 10. Funding of incl. studies: no 11. MA appropriate: yes 12. RoB considered in MA: yes 13. RoB in interpretation: yes	2a

Referenz/ Studientyp	Untersuchte Population	Suchstrategie, Einschlusskriterien	Eingeschlossene Studien	Ergebnisse	methodische Bemerkungen / Evidenzklasse (AMSTAR2)	Evidenz-level
		without language or document type restrictions		- Sebag et al: 0.86 (0.68 – 0.96) - Veyrieres et al: 0.80 (0.63 – 0.92) - Wang et al: 0.86 (0.80 – 0.91) <u>Specificity:</u> - Liu et al a: 0.87 (0.73 – 0.95) - Liu et al b: 0.86 (0.80 – 0.91) - Liu et al c: 0.84 (0.79 – 0.89) - Bhatia et al: 0.78 (0.64 – 0.89) - Duan et al: 0.78 (0.64 – 0.89) - Szczepanek et al: 0.67 (0.62 – 0.72) - Dobruch et al: 0.42 (0.33 – 0.51) - Kim et al: 0.72 (0.60 – 0.81) - Park et al: 0.89 (0.81 – 0.94) - He et al (Aiken): 0.88 (0.80 – 0.94) - He et al (Toshiba): 0.69 (0.58 – 0.78) - Samir et al: 0.88 (0.68 – 0.97) - Sebag et al: 0.94 (0.88 – 0.98) - Veyrieres et al: 0.90 (0.86 – 0.94) - Wang et al: 0.68 (0.51 – 0.82)	14. Heterogeneity explained: no 15. Publication bias investigated: no 16. Sources of CoI: none	
Nell, 2015 (20)	Patients referred for diagnostic evaluation of	<u>Databases:</u> Pubmed	20 studies Guazzaroni,	**qualitative elastography compared with thyroid nodule cytology (fine needle aspiration cytology,**	<u>AMSTAR-2 rating</u>	2a

Referenz/ Studientyp	Untersuchte Population	Suchstrategie, Einschlusskriterien	Eingeschlossene Studien	Ergebnisse	methodische Bemerkungen / Evidenzklasse (AMSTAR2)	Evidenz-level
	thyroid nodules	Embase Cochrane Library Search period December 5th, 2014 Key words: NR English, German, French, or Dutch	2014 Tatar, 2014 Azizi, 2013 Mehrota, 2013 Bojunga, 2012 Ciledag, 2012 Friedrich-Rust, 2012 Mansor, 2012 Moon, 2012 Trimboli, 2012 Unluturk, 2012 Bhatia, 2011 Merino, 2011 Yerli, 2011 Kagoya, 2010 Friedrich-Rust, 2009 Rubaltelli, 2009 Asteria, 2008 Ferrari, 2008 Tranquart, 2008	**FNAC) or histology from surgical specimens.** Pooled sensitivity: 85% (95% CI, 79-90%) Pooled specificity: 80% (95% CI, 73-86%) Only reported in a graph without precise numbers. AUC: NR	1. PICO elements: no 2. A priori design: yes 3. Justification for design: no 4. Literature search >= 2 databases, search strategy + other sources: partial yes 5. Selection in duplicate: yes 6. Data extraction in duplicate: yes 7. List of excluded studies: partial yes 8. sufficient detail on studies: no 9. RoB assessed: partial yes 10. Funding of incl. studies: no 11. MA appropriate: yes 12. RoB considered in MA: yes 13. RoB in interpretation: yes 14. Heterogeneity explained: no 15. Publication bias investigated: yes 16. Sources of CoI: none	

3.4. Szintigraphie mit ^{99m}Tc-MIBI - Kapitel 3.8.1 der Langversion

3.4.1. Schlüsselfrage

Diagnostische Genauigkeit der MIBI-Szintigraphie

3.4.2. Schlüsselfrage im PICO-Format

Patient	Alle Patienten mit operativ entfernten Schilddrüsenknoten
Intervention	^{99m}Tc-MIBI-Szintigraphie
Comparison	Histologischer Befund
Outcome	Positiv bzw. negativ prädiktiver Wert bezüglich Malignität

3.4.3. Suchstrategien von 09.09.2019 (SRs) und 09.10.2019 (Aktualisierungssuche für Einzelstudien)

3.4.3.1. MEDLINE: Systematic Reviews (via OVID)

#	Searches
1	exp THYROID NEOPLASMS/
2	thyr?oid*.tw,kf,nm,ot,fs.
3	(DTC or RR-DTC or PDTC).tw.
4	or/1-3
5	RADIONUCLIDE IMAGING/
6	(scintigra* or radios?intigra* or szintigra*).tw,kf,ot.
7	(gamma scan* or scintiscan* or szintiscan*).tw,kf.
8	or/5-7
9	TECHNETIUM TC 99M SESTAMIBI/
10	(Technetium-99m* or 99m-tetrofosmin or Tc-Tetrofosmin).tw,kf.
11	("(99m)Tc*" or 99mTc*).tw,kf.
12	(Tc-99m* or Tc99m* or 99Tcm* or 99-Tcm*).tw,kf.
13	((methoxyisobutylisonitrile* adj2 scintigraph*) or (methoxyisobutylisonitrile* adj2 technetium*)).tw,kf.
14	"Tc^{99}".ti.

#	Searches
15	or/9-14
16	((MIBI adj2 scan*) or (MIBI adj2 scintigraph*)).tw,kf.
17	(sestaMIBI* or Tc-MIBI).tw,kf.
18	((methoxyisobutylisonitrile* adj2 scintigraph*) or (methoxyisobutylisonitrile adj2 technetium*)).tw,kf.
19	(Methoxy-Isobutyl-Isonitrile or MIBI or methoxyisobutylisonitrile).tw,kf.
20	or/16-19
21	4 and 8 and 15
22	4 and 15 and 20
23	21 or 22
24	(review or review,tutorial or review, academic).pt.
25	(medline or medlars or embase or pubmed or cochrane).tw,sh.
26	(scisearch or psychinfo or psycinfo).tw,sh.
27	(psychlit or psyclit).tw,sh.
28	cinahl.tw,sh.
29	((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
30	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
31	(pooling or pooled or mantel haenszel).tw,sh.
32	(peto or dersimonian or der simonian or fixed effect).tw,sh.
33	(retraction of publication or retracted publication).pt.
34	or/25-33
35	24 and 34
36	meta-analysis.pt.
37	meta-analysis.sh.
38	(meta-analys$ or meta analys$ or metaanalys$).tw,sh.
39	(systematic$ adj5 review$).tw,sh.
40	(systematic$ adj5 overview$).tw,sh.
41	(quantitativ$ adj5 review$).tw,sh.
42	(quantitativ$ adj5 overview$).tw,sh.

#	Searches
43	(quantitativ$ adj5 synthesis$).tw,sh.
44	(methodologic$ adj5 review$).tw,sh.
45	(methodologic$ adj5 overview$).tw,sh.
46	(integrative research review$ or research integration).tw.
47	or/36-46
48	35 or 47
49	23 and 48

3.4.3.2. Cochrane Central Register of Controlled Trials: Systematic Reviews (via Cochrane Library)

ID	Search
#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	thyroid* or thyreoid*
#3	DTC or RR-DTC or PDTC
#4	#1 or #2 or #3
#5	MeSH descriptor: [Radionuclide Imaging] explode all trees
#6	scintigra* or radios?intigra* or szintigra*
#7	gamma scan* or scintiscan* or szintiscan*
#8	#5 or #6 or #7
#9	MeSH descriptor: [Technetium Tc 99m Sestamibi] explode all trees
#10	Technetium-99m* or 99m-tetrofosmin or Tc-Tetrofosmin
#11	"(99m)Tc*" or 99mTc*
#12	"Tc-99m*" OR "Tc99m*" OR "99Tcm*" OR "99-Tcm*"
#13	(methoxyisobutylisonitrile* NEAR/2 scintigraph*) or (methoxyisobutylisonitrile* NEAR/2 technetium*)
#14	"Tc^{99}"
#15	#9 or #10 or #11 or #12 or #13 or #14
#16	(MIBI NEAR/2 scan*) or (MIBI NEAR/2 scintigraph*)
#17	sestaMIBI* or Tc-MIBI

ID	Search
#18	(methoxyisobutylisonitrile* NEAR/2 scintigraph*) or (methoxyisobutylisonitrile NEAR/2 technetium*)
#19	Methoxy-Isobutyl-Isonitrile or MIBI or methoxyisobutylisonitrile
#20	#16 or #17 or #18 or #19
#21	#4 and #8 and #15
#22	#4 and #15 and #20
#23	#21 or #22

3.4.3.3. MEDLINE: Studien (via OVID)

#	Searches
1	exp Thyroid Neoplasms/
2	thyr?oid*.tw,kf,nm,ot,fs.
3	(DTC or RR-DTC or PDTC).tw.
4	or/1-3
5	Radionuclide Imaging/
6	(scintigra* or radios?intigra* or szintigra*).tw,kf,ot.
7	(gamma scan* or scintiscan* or szintiscan*).tw,kf.
8	or/5-7
9	Technetium Tc 99m Sestamibi/
10	(Technetium-99m* or 99m-tetrofosmin or Tc-Trtrofosmin).tw,kf.
11	("(99m)Tc*" or 99mTc*).tw,kf.
12	(Tc-99m* or Tc99m* or 99Tcm* or 99-Tcm*).tw,kf.
13	((methoxyisobutylisonitrile* adj2 scintigraph*) or (methoxyisobutylisonitrile* adj2 technetium*)).tw,kf.
14	"Tc^{99}".ti.
15	or/9
16	((MIBI adj2 scan*) or (MIBI adj2 scintigraph*)).tw,kf.
17	(sestaMIBI* or Tc-MIBI).tw,kf.
18	((methoxyisobutylisonitrile* adj2 scintigraph*) or (methoxyisobutylisonitrile adj2 technetium*)).tw,kf.
19	(Methoxy-Isobutyl-Isonitrile or MIBI or methoxyisobutylisonitrile).tw,kf.

#	Searches
20	or/16-19
21	4 and 8 and 15
22	4 and 15 and 20
23	21 or 22

3.4.3.4. Ergebnis der Recherche

Fundstellen SR	90
Volltextscreening	40
Ausgeschlossen mit Gründen	28 nicht MIBI untersucht 9 keine systematischen Übersichtsarbeiten
Eingeschlossen	3 systematische Übersichtsarbeiten

3.4.4. Evidenztabellen

3.4.4.1. Einzelstudien

Keine.

3.4.4.2. Systematische Übersichten/Meta-Analysen

Referenz/ Studientyp	Untersuchte Population	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Methodische Bemerkungen	Evidenz-level
Kim SJ 2018 (21) Diagnostic Performance of Technetium-99m Methoxy-Isobutyl-Isonitrile for Differentiation of Malignant Thyroid Nodules: A Systematic Review and Meta-Analysis THYROID Volume 28 Number 10	Electronic English language literature search was conducted of MEDLINE/PubMed and the Embase database from the earliest available date of indexing through 2018 Inclusion criteria: Tc-99m MIBI thyroid scan had been used to evaluate the TN; sufficient data to reassess sensitivity and specificity of Tc99m MIBI thyroid scan for differentiating the TN or absolute numbers of true-positive (TP), true-negative (TN), falsepositive (FP), and false-negative (FN) data had been presented; and no data overlap Exclusion criteria: Duplicate publications, as were publications such as review articles, case reports, conference papers, and letters, which do not contain original data	Purpose of the current study was to investigate the diagnostic performance of technetium99m (Tc-99m) methoxy-isobutyl-isonitrile (MIBI) for differentiation of malignant thyroid nodules (TN) through a systematic review and meta-analysis	Each study was analyzed to retrieve the number of TP, TN, FP, and FN findings of Tc-99m MIBI thyroid scans for the characterization of the TN, according to the reference standard (i.e., the final histology)	22 studies (with 2421 patients) included in metaalanysis 20 conducted patient based analysis of Tc-99m MIBI thyroid scan and 2 conducted a lesion based analysis Patients were 16 to 86 years old 312 male and 1217 female patients 15 enrolled pateints retrospectively, 7 prospectively 8 used a singlephase acquisition Tc-99m MIBI thyroid scan, and 14 studies used a dual-phase method In 16 studies a Tc-99m MIBI thyroid scan was performed in	The nonsignificant slope indicates that no significant bias was found. The p-value was 0.93 High degree of statisitical heterogeneity for sensitivity (I^2 = 92.3%) and specificity (96.4%) QUADAS2 tool used for study quality assessment: "(...) the overall quality of included studies was deemed satisfactory" No use of GRADE Level of evidence of review (Systematic review of prospective and retrospective studies; variable reference standards (surgery, FNAB)): 3- (substantial	2a

Referenz/ Studientyp	Untersuchte Population	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Methodische Bemerkungen	Evidenz-level
				patients with cold TN, and in six studies the Tc-99m MIBI thyroid scan was performed in patients with indeterminate FNAC Five studies used a semi-quantitative method for interpretation of the Tc-99m MIBI thyroid scans, and 15 used a visual interpretation method. The semi-quantitative analysis group used the washout index (WOind), retention ratio (RR), retention index (RI) , and tumor to normal ratio (T/N) as semi-quantitative indexes. Pooled sensitivity for Tc-99m MIBI thyroid scan was 0.87 [confidence interval (CI) 0.76-0.93] with heterogeneity (I^2=92.3) Pooled specificity of 0.78 [CI 0.67- 0.86] with heterogeneity (I^2=96.4)	inconsistency between studies for core outcomes)	

Referenz/ Studientyp	Untersuchte Population	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Methodische Bemerkungen	Evidenz-level
				LR syntheses gave an overall LR+ of 4.0 [CI 2.5-6.3] and LR- of 0.17 [CI 0.09-0.32] Pooled diagnostic odds ratio was 24 [CI 63-176]. The hierarchical summary receiver operating characteristic curve indicates that the area under the curve was 0.90 [CI 0.87-0.92]		
Treglia, G 2013 (22) Diagnostic performance of (99m)Tc-MIBI scan in predicting the malignancy of thyroid nodules: a meta-analysis Endocrine Volume 44 Pages 70-8	Inclusion criteria: 1. 99mTc-MIBI scan performed in patients with thyroid nodules suspicious for malignancy 2. A sample size of at least five patients with thyroid nodules who performed 99mTc-MIBI scintigraphy in the course of their diagnostic workup 3. Sufficient data to reassess sensitivity and specificity of 99mTc-MIBI scan in patients with thyroid nodules 4. Available histologic data about thyroid nodules, used as the gold standard reference for the purposes of this meta-analysis 5. No data overlap (when possible duplicate studies were found, only the most complete article was included).	Diagnostic performance of 99mTc-MIBI scan in the evaluation of thyroid nodules		21 studies included Pooled sensitivity and specificity of 99mTc-MIBI scan in detecting malignant thyroid nodules were 85.1 % [95 % confidence interval (95 % CI): 81.1-88.5 %] and 45.7 % (95 % CI: 42.7-48.7 %), respectively, on a per lesion based analysis, irrespective of eventual results of previous technetium pertechnetate (99mTcO4) or iodine-123 (123I) scan The area under the ROC curve was 0.78. Subanalysis restricted to data on hypofunctioning nodules on 99mTcO4 or 123I scans was	QUADAS tool used for study quality assessment: "Overall, the studies included in this meta-analysis have shown moderate methodological quality according to QUADAS" High degree of statisitical heterogeneity for sensitivity (I^2 = 61.6%) and specificity (93.9%) No use of GRADE Level of evidence of review (Systematic review of prospective studies; consistent reference standard): 2-	2a

Referenz/ Studientyp	Untersuchte Population	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Methodische Bemerkungen	Evidenz-level
				performed: pooled sensitivity and specificity of 99mTc-MIBI scan in these nodules were 82.1 % (95 % CI: 77.2–86.3 %) and 62.8 % (95 % CI: 58.9–66.7 %), respectively, on a per lesion-based analysis The area under the ROC curve was 0.81	(substantial inconsistency between studies for core outcomes)	
Wale, A 2014 (23) Combined 99mTc-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	The MEDLINE database on PubMed was searched on September 2010 Inclusion criteria: To be included in the review: (1) the study had to have correlated MIBI scintigraphy results with histology from thyroidectomy, (2) the study had to have had a similar MIBI acquisition to our local practice, and (3) the article had to report the raw data required to calculate the prevalence, sensitivity, specificity, PPV and NPV. Exclusion criteria: The following criteria were used to exclude studies from the review: (1) if semiquantification methods were used in the reporting of MIBI scintigraphy, (2) if the histological data were not extractable for each case, (3) if the studywas in animals, (4) if the study was in humans under the age of 18 years, and (5) if the	Combined 99mTc-methoxyisobutylisonitrile scintigraphy and fine-needle aspiration cytology	Prevalence, sensitivity, specificity, PPV and NPV	10 studies included From 712 patients of MIBI scintigraphy for the diagnosis of malignancy Sensitivity 96% Specificity 46% PPV 34% NPV 97 %	QUADAS tool used for study quality assessment: “Overall, the studies included in this meta-analysis have shown moderate methodological quality according to QUADAS” No forest plot nor any information on heterogeneity reported No use of GRADE Level of evidence of review (Systematic review of prospective studies; consistent reference standard): 2 (insufficient information assess	2a

Referenz/ Studientyp	Untersuchte Population	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	Methodische Bemerkungen	Evidenz-level
European Journal of Nuclear Medicine and Molecular Imaging Volume 41 Pages 105-115	article was a conference abstract, editorial, commentary/ letter or review.				consistency among individual study results)	

3.5. Thyreoidektomie - Kapitel 5.3.1.1 der Langversion

3.5.1. Schlüsselfrage

Thyreoidektomie oder Hemithyreoidektomie

3.5.2. Schlüsselfrage im PICO-Format

Patient	PTC pT1b/pT2
Intervention	Totale Thyreoidektomie
Comparison	Hemithyreoidektomie (Tumordurchmesser 1 – 4 cm)
Outcome	Rezidivrate, Morbidität: Hypoparathyreoidismus, Rekurrensparese

3.5.3. Suchstrategie vom 17.09.2019 und Update vom 13.12.2022

3.5.3.1. MEDLINE (via OVID

#	Search
1	exp THYROID NEOPLASMS/
2	((thyroid* or thyreoid*) adj3 (carcinoma or cancer or neoplas* or adenom* or adenocarcinom*)).tw,kf,ot.
3	or/1-2
4	THYROID CANCER, PAPILLARY/
5	Carcinoma, Papillary/ and (thyroid* or thyreoid*).tw,kf.
6	((thyroid* or thyreoid*) adj3 (papillar* or nonmedullar*)).tw,kf,ot.
7	or/4-5
8	exp ADENOCARCINOMA, FOLLICULAR/
9	(follicular* adj6 (adenocarcinoma* or thyroid* or thyreoid*)).tw,kf.
10	or/8-9
11	exp ADENOCARCINOMA, PAPILLARY/

#	Search
12	Carcinoma, Papillary/ and (thyroid* or thyreoid*).tw,kf.
13	(papillar* adj1 (adenocarcinoma* or thyroid* or thyreoid*)).tw,kf.
14	(pseudopapillar* or micropapilla*).tw,kf.
15	or/11-14
16	(differentiated adj3 (thyroid* or thyreoid*)).tw,kf.
17	3 or 7 or 10 or 15 or 16
18	THYROIDECTOMY/
19	hemithyr?oidectom*.tw,kf.
20	thyr?oidectom*.tw,kf.
21	or/18-20
22	17 and 21
23	(review or review,tutorial or review, academic).pt.
24	(medline or medlars or embase or pubmed or cochrane).tw,sh.
25	(scisearch or psychinfo or psycinfo).tw,sh.
26	(psychlit or psyclit).tw,sh.
27	cinahl.tw,sh.
28	((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
29	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
30	(pooling or pooled or mantel haenszel).tw,sh.
31	(peto or dersimonian or der simonian or fixed effect).tw,sh.

#	Search
32	(retraction of publication or retracted publication).pt.
33	or/24-32
34	23 and 33
35	meta-analysis.pt.
36	meta-analysis.sh.
37	(meta-analys$ or meta analys$ or metaanalys$).tw,sh.
38	(systematic$ adj5 review$).tw,sh.
39	(systematic$ adj5 overview$).tw,sh.
40	(quantitativ$ adj5 review$).tw,sh.
41	(quantitativ$ adj5 overview$).tw,sh.
42	(quantitativ$ adj5 synthesis$).tw,sh.
43	(methodologic$ adj5 review$).tw,sh.
44	(methodologic$ adj5 overview$).tw,sh.
45	(integrative research review$ or research integration).tw.
46	or/35-45
47	34 or 46
48	22 and 47

3.5.3.2. Cochrane Central Register of Controlled Trials (via Cochrane Library)

ID	Search
#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees

ID	Search
#2	thyroid* or thyreoid*
#3	#1 or #2
#4	MeSH descriptor: [Thyroid Cancer, Papillary] explode all trees
#5	MeSH descriptor: [Carcinoma, Papillary] this term only
#6	thyroid* or thyreoid*
#7	#5 and #6
#8	(thyroid* NEAR/3 (papillar* or nonmedullar*)) or (thyreoid* NEAR/3 (papillar* or nonmedullar*))
#9	#4 or #7 or #8
#10	MeSH descriptor: [Adenocarcinoma, Follicular] explode all trees
#11	(follicular* NEAR/6 (adenocarcinoma* or thyroid* or thyreoid*))
#12	#10 or #11
#13	MeSH descriptor: [Adenocarcinoma, Papillary] explode all trees
#14	MeSH descriptor: [Carcinoma, Papillary] explode all trees
#15	(thyroid* or thyreoid*)
#16	#14 and #15
#17	(papillar* NEAR/1 (adenocarcinoma* or thyroid* or thyreoid*))
#18	(pseudopapillar* or micropapilla*)
#19	#13 or #16 or #17 or #18
#20	(differentiated NEAR/3 (thyroid* or thyreoid*))
#21	#3 or #9 or #12 or #19 or #20
#22	MeSH descriptor: [Thyroidectomy] explode all trees
#23	(hemithyroidectom* or hemithyreoidectom*)
#24	(thyroidectomy or thyreoidectomy)
#25	#22 or #23 or #24

3.5.3.3. Ergebnis der Recherche

Fundstellen	769
Volltextscreening	35
Ausgeschlossen mit Gründen	28 nicht PTC pT1b/pT2 3 keine systematische Übersichtsarbeit oder aktuelle Studie
Eingeschlossen	2 (1 SR 1 Studie)

3.5.4. Evidenztabellen

3.5.4.1. Einzelstudien

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	Evidenzlevel Methodische Bemerkungen
Song 2019 (24)	**Patients with 1-4 cm Papillary Thyroid Carcinomas (PTC)** **Total N= 2345** **Lobectomy (16.3%) N=383** **TT** **(83.7%) N=1962** **<u>After matching:</u>** **Lobectomy (N=381)** **TT** **(N=381)** **Matching criteria: Age, Sex, Primary tumor size, Extrathyroidal extension (ETE), Multifocality, Cervical LN Metastasis**	Differences in DFS between patients with 1-4 cm DTCs who underwent lobectomy vs. Total Thyroidectomy (TT)	Retrospective cohort study with data from the *Asan medical Center* in Korea	**<u>DFS according to surgical extent</u>**	<u>DFS according to surgical extent</u> TT: N= 18 (4.7%) and Lobectomy: N=24 (6.3%) developed structural persistent/recurrent disease (p = 0.427) **Total 1cm ≤ size < 4cm** TT (N=381) Lobectomy (N=381) HR= 1.35 [CI 0.40-1.36], p = 0.33 **Subgroup 1: ≥1 to <2cm** TT (N= 326) Lobectomy (N=326) HR= 1.57 [CI 0.75-3.25], p = 0.228 **Subgroup 2: ≥2 to <4cm** TT (N=55) Lobectomy (N=55) HR= 0.93 [CI 0.30-2.89], p = 0.902	2b 1.1 clearly focused question: yes 1.2 Population comparable: yes 1.3 Indication how many people got asked to take part: yes 1.4 Knowledge of exposure status possible to influence the outcome: n.a. 1.5 Drop outs reported: n.a. 1.6 Comparison between between full participants and lost to follow-up: n.a 1.7 Outcomes are clearly defined: yes 1.8 Assessment of outcome is made blind to exposure: n.a 1.9 If Blinding was not possible there is recognition

Referenz/ Studientyp	Untersuchte Population	Intervention	Kontrolle	untersuchte Endpunkte	Hauptergebnisse	Evidenzlevel Methodische Bemerkungen
					Impact of surgical extent on recurrent disease **Lobectomy (Matched-Pair N=762)** HR= 1.43 [0.72-2.83] p = 0.306	that it might influenced the outcome: no 1.10 Method is reliable: yes 1.11 Evidence to demonstrate that the used method is valid and reliable: no 1.12 Exposure level is assessed more than once: no 1.13 Main confounders are taken into account in design and analysis 1.14 Confidence intervals been provided: yes

3.5.4.2. Systematische Übersichten/Meta-Analysen

Referenz/ Studientyp	Untersuchte Population	(verglichene) Interventionen/ (ggf. Dosierung)	Eingeschlossene Studien	Ergebnisse	Evidenzlevel Methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Vargas-Pinto, 2019 (25)	TL vs. TT (TL) Thyroid lobectomy for low-risk PTC 1-4 cm (PTC) Papillary thyroid cancers with no clinical evidence of metastasis or extrathyroidal extension Age >= 18	Databases: Pubmed Embase Scopus Cochrane Database Search period 1. January 2012 - 31. December 2017 Key words: papillary thyroid carcinoma, lobectomy, completion thyroidectomy, and guidelines English language	8 nicht-randomisierte kontrollierte studies	**Studies including PTC 1-4 cm only:** **Adam, 2014** TT: 6849 TL: 61775 Median FU 82 months (range, 60-179 months) 5-year OS: TT: 97.2% TL: 96.9%) 10-year OS: TT: 92.9% TL: 91.4% 14-year OS TT: 86.6% TL: 84.4% HR 0.96; 95% CI, 0.84-1.09; P = 0.54	2a AMSTAR-2 rating 1. PICO elements: yes 2. A priori design: yes, PROSPERO ID 91505 3. Justification for design: yes 4. Literature search >= 2 databases, search strategy + other sources: yes 5. Selection in duplicate: yes 6. Data extraction in duplicate: yes 7. List of excluded studies: no 8. sufficient detail on studies: partial yes 9. RoB assessed: Newcastle-Ottawa score, but scores not provided 10. Funding of incl. studies: no **11. MA appropriate: no MA AMSTAR-2 score: 9,5/13*** 12. RoB considered in MA: no MA	**Adam, 2015** Dhir, 2017 Kluijfhout, 2016 Kluijfhout, 2017 **Kim, 2017** Kuba, 2016 Kuo, 2017 Lang, 2017

Referenz/ Studientyp	Untersuchte Population	(verglichene) Interventionen/ (ggf. Dosierung)	Eingeschlossene Studien	Ergebnisse	Evidenzlevel Methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
				Subgroups *Tumor size 1–2 cm (59% of patients)* HR = 1.05; 95% CI, 0.88–1.26; P = 0.61 *Tumor size 2.1–4cm (41% of patients)* HR = 0.89; 95% CI, 0.73–1.07; P = 0.21 **<u>Adam 2015 (<45 years)</u>** **NCDB database** <u>Unadjusted OS 14y</u> 96.2% (1–2 cm) 95.2% (2–4cm) (P= 0.57) HR= 1.45 (95%CI = 0.84–2.51), P = 0.19 *Stratified by tumor size:* 1–2cm: 1.12 [95% CI= 0.50–2.51], P = 0.78 2–4cm: 1.93 [95%CI=0.88–4.23], P = 0.10	13. RoB in interpretation: yes 14. Heterogeneity explained: yes 15. Publication bias investigated: no MA 16. Sources of CoI: none **AMSTAR-2 score: 9,5/13*** * Although formal assessment with AMSTAR showed a high score, there were errors in the content of the review. For some results reported here, primary studies were consulted.	

Referenz/ Studientyp	Untersuchte Population	(verglichene) Interventionen/ (ggf. Dosierung)	Eingeschlossene Studien	Ergebnisse	Evidenzlevel Methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
				SEER database Unadjusted OS 14y 97.9% (1–2 cm) 98.4% (2–4cm) (P= 0.81) HR= 0.95 (95%CI 0.70–1.29), P = 0.75 *Stratified by tumor size:* 1–2cm: 0.95 [95% CI= 0.56–1.62], P = 0.86 2–4cm: 0.94 [95%CI= 0.60–1.49], P = 0.80 **Kim, 2017 (TL vs. TT), (PMS-matched cohort study)** Follow-up: Hemithyroidectomy: 5.9±2.8 years Thyroidectomy: 7.1±2.3 Overall Recurrence Rate: Hemithyroidectomy: 6.1 % Thyroidectomy: 5.7%, P= 0.80		

Referenz/ Studientyp	Untersuchte Population	(verglichene) Interventionen/ (ggf. Dosierung)	Eingeschlossene Studien	Ergebnisse	Evidenzlevel Methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
				Subgroups Recurrence-free survival (HR < 1 favours hemithyroidectomy) *Tumor size 1-2 cm* HR= 1.314 (95% CI= 0.55-3.136) *Tumor size 2-4 cm* HR= 0.887 (95% CI= 0.092-8.532)		

3.6. Zentrale Lymphknotendissektion - Kapitel 5.3.1.2 der Langversion

3.6.1. Schlüsselfrage

Ausmaß der Lymphadenektomie

3.6.2. Schlüsselfrage im PICO-Format

Patient	DTC, PTC / FTC / PDTC
Intervention	Prophylaktische uni- oder bilaterale zentrale Lymphknotendissektion
Comparison	Keine Lymphknotendissektion
Outcome	rezidivfreies (z.B. locoregional recurrence) und Gesamtüberleben

3.6.3. Suchstrategie vom 20.12.2022

3.6.3.1. Medline (via OVID)

ID	Search
#	Searches
1	exp Thyroid Neoplasms/
2	((thyroid* or thyreoid*) adj3 (carcinoma or cancer or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant* or metasta*)).tw,kf,ot.
3	or/1-2
4	Thyroid Cancer, Papillary/
5	Carcinoma, Papillary/ and (thyroid* or thyreoid*).tw,kf.
6	((thyroid* or thyreoid*) adj3 (papillar* or nonmedullar*)).tw,kf,ot.
7	or/4-5
8	exp Adenocarcinoma, Follicular/
9	(follicular* adj6 (adenocarcinoma* or thyroid* or thyreoid*)).tw,kf.
10	or/8-9
11	exp Adenocarcinoma, Papillary/
12	Carcinoma, Papillary/ and (thyroid* or thyreoid*).tw,kf.
13	(papillar* adj1 (adenocarcinoma* or thyroid* or thyreoid*)).tw,kf.
14	or/11-13

ID	Search
15	(differentiated adj3 (thyroid* or thyreoid*)).tw,kf.
16	3 or 7 or 10 or 14 or 15
17	*Lymph Node Excision/
18	*neck dissection/
19	((lymph node* or lymphnode*) adj2 (dissection* or excision*)).tw,kf.
20	lymphadenectom*.tw,kf.
21	Lymph Nodes/su
22	exp Dissection/ and lymph nodes/
23	or/17-22
24	(central* or lateral* or mediastinal* or unilateral* or bilateral*).tw,kf.
25	23 and 24
26	16 and 25
27	randomized controlled trial.pt.
28	controlled clinical trial.pt.
29	randomi?ed.ab.
30	placebo.ab.
31	drug therapy.fs.
32	randomly.ab.
33	trial.ab.
34	groups.ab.
35	or/27-34
36	exp animals/ not humans/
37	35 not 36
38	26 and 37
39	exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/
40	((control and (study or group*)) or (time and factors) or cohort or program or comparative stud* or evaluation studies or survey* or follow-up* or ci).mp.
41	or/39-40
42	26 and 41

ID	Search
43	cochrane database of systematic reviews.jn. or search*.tw. or meta analysis.pt. or medline.tw. or systematic review.tw. or systematic review.pt.
44	26 and 43
45	38 or 42 or 44

3.6.3.2. Cochrane Central Register of Controlled Trials (via Cochrane Library)

ID	Search
#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	thyroid* or thyreoid*:TI,AB,KW
#3	#1 or #2
#4	MeSH descriptor: [Thyroid Cancer, Papillary] explode all trees
#5	MeSH descriptor: [Carcinoma, Papillary] this term only
#6	thyroid* or thyreoid*:TI,AB,KW
#7	#5 and #6
#8	(thyroid* NEAR/3 (papillar* or nonmedullar*)):TI,AB,KW or (thyreoid* NEAR/3 (papillar* or nonmedullar*)):TI,AB,KW
#9	#4 or #7 or #8
#10	MeSH descriptor: [Adenocarcinoma, Follicular] explode all trees
#11	(follicular* NEAR/6 (adenocarcinoma* or thyroid* or thyreoid*)):TI,AB,KW
#12	#10 or #11
#13	MeSH descriptor: [Adenocarcinoma, Papillary] explode all trees
#14	MeSH descriptor: [Carcinoma, Papillary] explode all trees
#15	(thyroid* or thyreoid*):TI,AB,KW
#16	#14 and #15
#17	(papillar* NEAR/1 (adenocarcinoma* or thyroid* or thyreoid*)):TI,AB,KW
#18	#13 or #16 or #17
#19	(differentiated NEAR/3 (thyroid* or thyreoid*)):TI,AB,KW
#20	#3 or #9 or #12 or #18 or #19
#21	MeSH descriptor: [Lymph Node Excision] this term only
#22	MeSH descriptor: [Neck Dissection] this term only

ID	Search
#23	(lymph node* NEAR/2 (dissection* or excision*)):TI,AB,KW or (lymphnode* NEAR/2 (dissection* or excision*)):TI,AB,KW
#24	lymphadenectom*:TI,AB,KW
#25	MeSH descriptor: [Lymph Nodes] this term only
#26	MeSH descriptor: [Dissection] explode all trees
#27	#25 and #26
#28	#21 or #22 or #23 or #24 or #27
#29	(central* or lateral* or unilateral* or bilateral*):TI,AB,KW
#30	#28 and #29
#31	#20 and #30

3.6.3.3. Epistemonikos

Suche I

(title:(((thyroid* OR thyreoid*) AND (carcinoma OR cancer OR tumor* OR tumour* OR neoplas* OR adenom* OR adenocarcinom* OR sarcoma OR lymphom* OR malignant* OR metasta* OR papillar* OR nonmedullar* OR differentiated*))) OR abstract:(((thyroid* OR thyreoid*) AND (carcinoma OR cancer OR tumor* OR tumour* OR neoplas* OR adenom* OR adenocarcinom* OR sarcoma OR lymphom* OR malignant* OR metasta* OR papillar* OR nonmedullar* OR differentiated*)))) AND (title:(((lymph node* OR lymphnode*) AND (dissection* OR excision*) AND (central* OR lateral* OR mediastinal* OR unilateral* OR bilateral*))) OR abstract:(((lymph node* OR lymphnode*) AND (dissection* OR excision*) AND (central* OR lateral* OR mediastinal* OR unilateral* OR bilateral*))))

Suche II

(title:(((follicular* OR papillar*) AND (adenocarcinoma* OR thyroid* OR thyreoid*))) OR abstract:(((follicular* OR papillar*) AND (adenocarcinoma* OR thyroid* OR thyreoid*)))) AND (title:(((lymph node* OR lymphnode*) AND (dissection* OR excision*) AND (central* OR lateral* OR mediastinal* OR unilateral* OR bilateral*))) OR abstract:(((lymph node* OR lymphnode*) AND (dissection* OR excision*) AND (central* OR lateral* OR mediastinal* OR unilateral* OR bilateral*))))

3.6.3.4. Ergebnis der Recherche

Fundstellen	1417
Volltextscreening	43
Ausgeschlossen mit Gründen	34 nicht prophylaktische mit therapeutischer Dissektion untersucht 8 keine systematischen Übersichtsarbeiten
Eingeschlossen	1

3.6.4. Evidenztabellen

3.6.4.1. Einzelstudien

Keine.

3.6.4.2. Systematische Übersichten/Meta-Analysen

Referenz/ Studientyp	Untersuchte Studien	Suchstrategie	Eingeschlossene Studien	Ergebnisse	Evidenzlevel Methodische Bemerkungen(	Literaturbelege/ eingeschlossene Publikationen
Sanabria, 2022 (26)	Low-Risk PTC Total (N= 763) TT = Lee; Viola; Sippel; Ahn Lobectomy = Kim Tumor size <2cm = Lee; Viola; Kim; Ahn Tumor size >2cm = Sippel	Search strategy -Cochrane Central Register of Controlled Trials - Medline - Embase - Latin American and Caribbean Health Sciences Literature - Google Scholar Search period - January 1980 - August 2021 inclusion criteria - adults with PTC - absence of central or	5 RCTS	**Recurrence** structural recurrence between TT + PCND vs. TT N = 763 (Lee; Viola; Kim; Sippel; Ahn) RD= 0.00 (95% CI -0.02, 0.02) p= 0.98 biochemical recurrence between TT + PCND vs. TT N= 342 (Viola; Sippel; Ahn) RD= -0.00 (95% CI -0.05, 0.04) p= 0.95 **Complications** Temporary vocal cord paralysis TT+ PCND vs. TT N= 582 (Lee; Kim; Sippel; Ahn RD= 0.01 (95% CI -0.03, 0.04) p= 0.73	1a AMSTAR-2 rating 1. PICO elements: yes 2. A priori design: yes 3. Justification for design: No 4. Literature search >= 2 databases, search strategy + other sources: yes 5. Selection in duplicate: No 6. Data extraction in duplicate: yes 7. List of excluded studies: No 8. sufficient detail on studies: partial yes	Lee, 2015 Viola, 2015 Kim, 2020 Sippel, 2020 Ahn, 2021

Referenz/ Studientyp	Untersuchte Studien	Suchstrategie	Eingeschlossene Studien	Ergebnisse	Evidenzlevel Methodische Bemerkungen(	Literaturbelege/ eingeschlossene Publikationen
		lateral lymph node metastases (cN0) - interventions assessed were TT or lobectomy versus TT + PCND - only RCTs		Definitive vocal cord paralysis TT+ PCND vs. TT N= 703 (Lee; Viola; Kim; Ahn) RD -0.00 (95% CI -0.03, 0.02) p= 0.66 Temporary hypoparathyroidism TT+ PCND vs. TT N= 582 (Lee; Kim; Sippel; Ahn) RD= 0.04 (95% CI -0.02, 0.10) p=0.20 **Permanent hypoparathyroidism TT+ PCND vs. TT** **N= 703 (Viola; Lee; Kim; Ahn)** **RD= 0.03 (95% CI 0.00, 0.06) p=0.02** Hematoma TT+ PCND vs. TT N= 438 (Lee; Viola) RD= 0.00 (95% CI -0.02, 0.03) p= 0.87	9. RoB assessed: yes 10. Funding of incl. studies: No 11. MA appropriate: yes 12. RoB considered in MA: yes 13. RoB in interpretation: yes 14. Heterogeneity explained: yes 15. Publication bias investigated: yes 16. Sources of Conflict: none AMSTAR-2 score: 12/16	

PCND: prophylactic central neck lymph node dissection
RD: Risk Difference

3.7. Volume Outcome - Kapitel 5.7.1 der Langversion

3.7.1. Schlüsselfrage

Komplikationen in Abhängigkeit von der operativen Fallzahl

3.7.2. Schlüsselfrage im PICO-Format

Patient	Patienten mit Schilddrüsenkarzinom
Intervention	Thyreoidektomie im Zentrum mit hoher Fallzahl bzw. durch Operateur mit häufigem derartigem Eingriff
Comparison	Thyreoidektomie im Zentrum mit geringer Fallzahl bzw. durch Operateur mit seltenem derartigem Eingriff
Outcome	Häufigkeit von Hypoparathyreoidismus und/oder Recurrensparesen

3.7.3. Suchstrategien

3.7.3.1. MEDLINE (via OVID) Suchzeitraum bis 31.12.2020

#	Searches
1	THYROIDECTOMY/
2	hemithyr?oidectom*.tw.
3	thyr?oidectom*.tw.
4	or/1-3
5	((thyroid* or thyreoid*) adj3 (carcinoma or cancer or neoplas* or adenom* or adenocarcinom*)).tw.
6	4 and 5
7	*HOSPITALS, HIGH-VOLUME/sn
8	(high volume adj1 (center* or hospital*)).tw,kf.
9	*HOSPITALS, LOW-VOLUME/sn
10	(low volume adj1 (center* or hospital*)).tw,kf.
11	((volume* adj1 (hospital* or outcome*)) or volume-related or volume-based).tw,kf.
12	or/7-11
13	*SURGEONS/sn

#	Searches
14	((surgical* or surger* or surgeon*) adj1 volume*).tw,kf.
15	or/13-14
16	(number* adj1 case*).tw,kf.
17	*CLINICAL COMPETENCE/sn
18	(clinical adj1 (competenc* or skill*)).tw,kf.
19	or/17-18
20	*"OUTCOME ASSESSMENT (HEALTH CARE)"/sn
21	(outcome adj1 (assessment* or measure* or stud* or research* or volume*)).tw,kf.
22	or/20-21
23	*QUALITY ASSURANCE, HEALTH CARE/sn
24	(healthcare quality adj1 (assurance* or assessment*)).tw,kf.
25	or/23-24
26	*DIAGNOSIS-RELATED GROUPS/sn
27	(casemix or case mix*).tw,kf.
28	or/7-11
29	*"QUALITY OF HEALTH CARE"/sn
30	*QUALITY INDICATORS, HEALTH CARE/sn
31	or/28-29
32	*TREATMENT OUTCOME/
33	(clinical adj1 (effectiveness or efficac*)).tw,kf.
34	(treatment* adj1 (effectiveness or efficac*)).tw,kf.
35	(outcome adj1 (patient-relevant or rehabilitation* or treatment)).tw,kf.
36	or/32-35
37	12 or 15 or 19 or 22 or 25 or 28 or 31 or 36
38	6 and 37

#	Searches
39	cochrane database of systematic reviews.jn. or search*.tw. or meta analysis.pt. or medline.tw. or systematic review.tw. or systematic review.pt.*
40	40 and 39

3.7.3.2. Cochrane Database of Systematic Reviews (via Cochrane Library) Suchzeitraum bis 31.12.2020

ID	Searches
#1	[mh Thyroidectomy]
#2	(hemithyreoidectom* OR hemithyroidectom* OR thyreoidectom OR thyroidectom*):TI,AB,KW
#3	#1 OR #2
#4	((thyroid* or thyreoid*) NEAR/3 (carcinoma or cancer or neoplas* or adenom* or adenocarcinom*)):TI,AB,KW
#5	#3 AND #4
#6	MeSH descriptor: [Hospitals, High-Volume] explode all trees and with qualifier(s): [statistics & numerical data - SN]
#7	(high volume NEAR/1 (center* or hospital*)):TI,AB,KW
#8	MeSH descriptor: [Hospitals, Low-Volume] explode all trees and with qualifier(s): [statistics & numerical data - SN]
#9	(low volume NEAR/1 (center* or hospital*)):TI,AB,KW
#10	((volume* adj1 (hospital* or outcome*)) or volume-related or volume-based):TI,AB,KW
#11	MeSH descriptor: [Surgeons] explode all trees and with qualifier(s): [statistics & numerical data - SN]
#12	((surgical* or surger* or surgeon*) NEAR/1 volume*):TI,AB,KW
#13	(number* NEAR/1 case*):TI,AB,KW
#14	MeSH descriptor: [Clinical Competence] explode all trees and with qualifier(s): [statistics & numerical data - SN]
#15	(clinical NEAR/1 (competenc* or skill*)):TI,AB,KW
#16	MeSH descriptor: [Outcome Assessment, Health Care] explode all trees and with qualifier(s): [statistics & numerical data - SN]
#17	(outcome NEAR/1 (assessment* or measure* or stud* or research* or volume*)):TI,AB,KW

ID	Searches
#18	MeSH descriptor: [Quality Assurance, Health Care] explode all trees and with qualifier(s): [statistics & numerical data - SN]
#19	(healthcare quality NEAR/1 (assurance* or assessment*)):TI,AB,KW
#20	MeSH descriptor: [Diagnosis-Related Groups] explode all trees and with qualifier(s): [statistics & numerical data - SN]
#21	(casemix or case mix*):TI,AB,KW
#22	MeSH descriptor: [Quality of Health Care] explode all trees and with qualifier(s): [statistics & numerical data - SN]
#23	MeSH descriptor: [Quality Indicators, Health Care] explode all trees and with qualifier(s): [statistics & numerical data - SN]
#24	MeSH descriptor: [Treatment Outcome] explode all trees
#25	(clinical NEAR/1 (effectiveness or efficac*)):TI,AB,KW
#26	(treatment* NEAR/1 (effectiveness or efficac*)):TI,AB,KW
#27	(outcome NEAR/1 (patient-relevant or rehabilitation* or treatment)):TI,AB,KW
#28	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
#29	#5 AND #28 in Cochrane Reviews

3.7.4. Ergebnis der Recherche

Fundstellen	15
Volltextscreening	1
Ausgeschlossen mit Gründen	0
Eingeschlossen	1

3.7.5. Evidenztabellen

3.7.5.1. Einzelstudien

keine

3.7.5.2. Systematische Übersichten/Meta-Analysen

Referenz/ Studientyp	Untersuchte Studien	Suchstrategie	Eingeschlossene Studien	Ergebnisse	Evidenzlevel Methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Lorenz 2020 Volume, outcomes, and quality standards in thyroid surgery: an evidence-based analysis—European Society of Endocrine	Published observational and interventional studies that re- ported on volume and outcome relationship in thyroid surgery in humans	Databases: PubMed Search period: 1 January 1990 – 31 December 2018. Key words: •thyroid surgery volume and outcome relationship •benign thyroid surgery	11 studies, Non-randomized prospective studies (cohort studies, single- and multicenter studies) and retrospective studies (cross-sectional analyses) Outcomes: •Recurrent laryngeal nerve injury (transient and permanent)	**Narratively summarized results for outcomes defined in PICO** Recurrent laryngeal nerve injury and volume – “Surgeon volume and outcome relationship exists in thyroid surgery with respect to prevalence of RLN injury. A cut-off value of > 50 thyroidectomies for a single surgeon per year appears reasonable for identifying a high-volume surgeon.” – “Hospital volume and outcome relationship is less clear than surgeon volume in thyroid surgery with respect to prevalence of RLN injury. However, a cut-off value of 100 thyroidectomies for a single center	2a AMSTAR-2 rating 1. PICO elements: no 2. A priori design: no 3. Justification for design: no 4. Literature search >= 2 databases, search strategy + other sources: no 5. Selection in duplicate: unclear 6. Data extraction in duplicate: unclear 7. List of excluded studies: no 8. sufficient detail on studies: partial	Sosa 1998 Thomusch 2000 Gourin 2010 Loyo 2013 Gonzalez-Sanchez 2013 Kandil 2013 Al-Quraysi 2016 Adam 2017 Liang 2016 Nouraei 2017

Referenz/ Studientyp	Untersuchte Studien	Suchstrategie	Eingeschlossene Studien	Ergebnisse	Evidenzlevel Methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Surgeons (ESES) positional statement Systematic Review without meta-analysis, narrative presentation of results		•recurrent laryngeal nerve injury •thyroid cancer surgery •recurrent laryngeal nerve injury • hypocalcemia •hypoparathyroidism •postoperative hemorrhage •thyroid cancer surgery •infection •volume and outcome relationship thyroid cancer surgery.	•Hypopara-thyroidism (transient and permanent) •Bleeding •Infection •Completion thyroidectomy •Local disease control •Recurrence rate	per year appears reasonable for identifying an adequate high-volume unit." <u>Hypoparathyroidism and volume</u> – "Surgeon volume and outcome relationship exists in thyroid surgery with respect to prevalence of hypocalcemia/ hypoparathyroidism. A cut-off value of 50 thyroidectomies for a single surgeon per year appears reasonable for identifying a high-volume surgeon." – "Hospital volume and outcome relationship is less clear than surgeon volume in thyroid surgery with respect to the prevalence of hypocalcemia/hypoparathyroidism. However, a cut-off value of 100 thyroidectomies for a single center per year appears reasonable for identifying an adequate high-volume unit." – "Thyroid surgery for thyroid malignancy performed by low-volume surgeons is associated with an increased risk of recurrence. Reoperative surgery is associated with an increased risk of hypocalcemia/hypoparathyroidism."	yes 9. RoB assessed: no 10. Funding of incl. studies: no 11. MA appropriate: no 12. RoB considered in MA: n.a 13. RoB in interpretation: no 14. Heterogeneity explained: no 15. Publication bias investigated: yes 16. Sources of CoI: yes	Duclos 2012 Mitchell 2008

3.8. Neuromonitoring - Kapitel 5.7.2 der Langversion

3.8.1. Schlüsselfrage

Klinischer Wert des intraoperativen Neuromonitorings

Patient	Alle Patienten mit Schilddrüsenoperation und der ED differenziertes Schilddrüsenkarzinom oder medulläres Schilddrüsenkarzinom
Intervention	Intraoperatives Neuromonitoring
Comparison	Entsprechende Operation ohne Neuromonitoring
Outcome	Zahl der postoperativ geschädigten Nervi recurrentes

3.8.2. Suchstrategien

3.8.2.1. MEDLINE (via OVID) Suchzeitraum bis 31.12.2020

#	Searches
1	THYROIDECTOMY/
2	hemithyr?oidectom*.tw,kf.
3	thyr?oidectom*.tw,kf.
4	or/1-3
5	INTRAOPERATIVE NEUROPHYSIOLOGICAL MONITORING/
6	(intraoperative* adj1 (neuromonitoring* or monitoring*)).tw,kf.
7	or/5-6
8	cochrane database of systematic reviews.jn. or search*.tw. or meta analysis.pt. or medline.tw. or systematic review.tw. or systematic review.pt.
9	4 and 7 and 8

3.8.2.2. **Cochrane Database of Systematic Reviews** (via Cochrane Library) Suchzeitraum bis 31.12.2020

ID	Search
#1	(MeSH descriptor: [Thyroidectomy] explode all trees
#2	hemithyroidectom* or hemithyreoidectom*
#3	thyroidectom* or thyreoidectom*
#4	#1 or #2 or #3

ID	Search
#5	MeSH descriptor: [Intraoperative Neurophysiological Monitoring] explode all trees
#6	(intraoperative* NEAR/1 (neuromonitoring* or monitoring*))
#7	#5 or #6
#8	#4 and #6 in Cochrane Reviews

3.8.2.3. Ergebnis der Recherche

Fundstellen	24
Volltextscreening	1
Ausgeschlossen mit Gründen	0
Eingeschlossen	1

3.8.3. Evidenztabellen

3.8.3.1. Einzelstudien

keine

3.8.3.2. Systematische Übersichten/Meta-Analysen

Referenz/ Studientyp	Untersuchte Studien	Suchstrategie	Eingeschlossene Studien	Ergebnisse	Evidenzlevel Methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Cirocchi, 2019 (27)	Adults undergoing thyroid surgery	Databases: CENTRAL MEDLINE Embase ICTRP Search Portal ClinicalTrials.gov Search period 21st August 2018 Key words: NR	5 studies, RCTs	**Recurrent Laryngeal Nerve (RLN) Palsy**: -No significant difference in permanent RLN palsy rates between IONM (0.7%) and non-IONM groups (0.9%). -Trend towards lower transient RLN palsy rate with IONM (2.1%) vs. without (3.6%), not significant. **Hypoparathyroidism**: -No significant difference in adverse events between IONM (13.6%) and non-IONM groups (12.2%). **Operative Time**: -Mean operative time similar between IONM and non-IONM groups.	1a AMSTAR-2 rating 1. PICO elements: yes 2. A priori design: yes 3. Justification for design: no 4. Literature search >= 2 databases, search strategy + other sources: yes 5. Selection in duplicate: yes 6. Data extraction in duplicate: yes 7. List of excluded studies: partial yes 8. sufficient detail on studies: yes 9. RoB assessed: yes 10. Funding of incl. studies: yes	Barczynski, 2009 Barczynski, 2012 Hei, 2016a Lee 2015 Sari 2010

Referenz/ Studientyp	Untersuchte Studien	Suchstrategie	Eingeschlossene Studien	Ergebnisse	Evidenzlevel Methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
		No language restrictions			11. MA appropriate: yes 12. RoB considered in MA: yes 13. RoB in interpretation: yes 14. Heterogeneity explained: yes 15. Publication bias investigated: yes 16. Sources of CoI: yes	

3.9. Indikationen zu einer Radioiodtherapie (RIT) - Kapitel 5.8.2 und 5.8.10 der Langversion

3.9.1. Schlüsselfrage

Klinischer Wert der Radioiodtherapie in Abhängigkeit des Tumorstadiums

3.9.2. Schlüsselfrage im PICO-Format

Patient	PTC-Patienten – T-Stadienabhängig
Intervention	Radiojodtherapie
Comparison	Keine Radiojodtherapie
Outcome	Rezidivrate, Gesamtüberleben

3.9.3. Suchstrategie vom 19.03.2020 und 05.10.2022

3.9.3.1. MEDLINE (via OVID)

#	Searches
1	exp Thyroid Neoplasms/
2	((thyroid* or thyreoid*) adj3 (carcinoma or cancer or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant*) adj5 (papillar* or differentiat* or follicular*)).tw,kf,ot.
3	(DTC or RR-DTC).tw.
4	or/1-3
5	Iodine Radioisotopes/
6	(radioiodine* or radioiodide* or radio-iodine* or radio-iodide*).tw,kf,nm.
7	((iodine* or iodide*) adj3 (radioactive* or radio-isotope* or radioisotope*)).tw,kf,nm.
8	(iodine-131 or iodine131 or Iodine I 131).tw,kf.
9	(RAIT or RRA or RAIR or RAI).tw,kf.
10	("I-131" or "I131" or "131I" or "131-I").tw,kf.
11	or/5-10
12	4 and 11
13	exp ANIMALS/ not HUMANS/
14	12 not 13

#	Searches
1	exp THYROID NEOPLASMS/
2	((thyroid* or thyreoid*) adj3 (carcinoma or cancer* or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant*) adj5 (papillar* or differentiat* or follicular*)).tw,kf,ot.
3	(DTC or RR-DTC).tw.
4	or/1-3
5	IODINE RADIOISOTOPES/
6	(radioiodine* or radioiodide* or radio-iodine* or radio-iodide*).tw,kf,nm.
7	((iodine* or iodide*) adj3 (radioactive* or radio-isotope* or radioisotope*)).tw,kf,nm.
8	(iodine-131 or iodine131 or Iodine I 131).tw,kf.
9	(RAIT or RRA or RAIR or RAI).tw,kf.
10	("I-131" or "I131" or "131I" or "131-I").tw,kf.
11	or/5-10
12	4 and 11
13	exp ANIMALs/ not HUMANS/
14	12 not 13
15	limit 14 to dt=20171231-20200310
16	14 not 15

#	Searches
1	exp Thyroid Neoplasms/
2	((thyroid* or thyreoid*) adj3 (carcinoma or cancer or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant*) adj5 (papillar* or differentiat* or follicular*)).tw,kf,ot.
3	(DTC or RR-DTC).tw.
4	or/1-3
5	Iodine Radioisotopes/
6	(radioiodine* or radioiodide* or radio-iodine* or radio-iodide*).tw,kf,nm.

#	Searches
7	((iodine* or iodide*) adj3 (radioactive* or radio-isotope* or radioisotope*)).tw,kf,nm.
8	(iodine-131 or iodine131 or Iodine I 131).tw,kf.
9	(RAIT or RRA or RAIR or RAI).tw,kf.
10	("I-131" or "I131" or "131I" or "131-I").tw,kf.
11	or/5-10
12	4 and 11
13	exp ANIMALS/ not HUMANS/
14	12 not 13
15	limit 14 to dt=20171201-20191216
16	limit 14 to dt=20191216-20200310
17	limit 14 to dt=20200310-20221005

3.9.3.2. Cochrane Central Register of Controlled Trials (via Cochrane Library)

#	Searches
#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	((thyroid* or thyreoid*) near/3 (carcinoma or cancer* or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant*) near/5 (papillar* or differentiat* or follicular*)):ti,ab,kw
#3	DTC or RR-DTC:ti,ab
#4	#1 or #2 or #3
#5	MeSH descriptor: [Iodine Radioisotopes] explode all trees
#6	(radioiodine* or radioiodide* or radio-iodine* or radio-iodide*)
#7	((iodine* or iodide*) near/3 (radioactive* or radio-isotope* or radioisotope*))
#8	(iodine-131 or iodine131 or Iodine I 131):ti,ab,kw
#9	(RAIT or RRA or RAIR or RAI):ti,ab,kw
#10	("I-131" or "I131" or "131I" or "131-I"):ti,ab,kw
#11	#5 or #6 or #7 or #8 or #9 or #10
#12	#4 and #11

#	Searches
#13	#12 with Cochrane Library publication date Between Dec 2017 and Dec 2019
#14	#12 with Cochrane Library publication date Between Dec 2019 and Mar 2020
#15	#13 or #14
#16	#12 not #15

#	Searches
#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	((thyroid* or thyreoid*) near/3 (carcinoma or cancer* or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant*) near/5 (papillar* or differentiat* or follicular*)):ti,ab,kw
#3	DTC or RR-DTC:ti,ab
#4	#1 or #2 or #3
#5	MeSH descriptor: [Iodine Radioisotopes] explode all trees
#6	(radioiodine* or radioiodide* or radio-iodine* or radio-iodide*)
#7	((iodine* or iodide*) near/3 (radioactive* or radio-isotope* or radioisotope*))
#8	(iodine-131 or iodine131 or Iodine I 131):ti,ab,kw
#9	(RAIT or RRA or RAIR or RAI):ti,ab,kw
#10	("I-131" or "I131" or "131I" or "131-I"):ti,ab,kw
#11	#5 or #6 or #7 or #8 or #9 or #10
#12	#4 and #11
#13	#12 with Cochrane Library publication date Between Dec 2017 and Dec 2019
#14	#12 with Cochrane Library publication date Between Dec 2019 and Mar 2020

3.9.3.3. Ergebnis der Recherche

Fundstellen	12.260
Volltexte	253
Ausgeschlossen mit Gründen	65 keine Studie oder SR 162 keine Angaben zu Radioiod versus kein Radioiod
Eingeschlossen	12 Systematische Übersichtsarbeiten, 24 Primärstudien

3.9.4. Evidenztabellen

3.9.4.1. Einzelstudien

Tabelle 2: Übersicht der eingeschlossenen Primärstudien Studien zu RAIT (chronologisch)

Referenz	Studie	Gesamt N	+RAI	Endpunkte	Datenquelle	Patientenkohorte
(28)	Leboulleux 2022	776	50.1%	EFS (3y); Excellent response rate	RCT in 35 centres in France, 2013-2017	Papillary: 95.9% Follicular: 3.1% Hürthle: 1%
(29)	Kim 2022	5,374 PSM	50% (PSM)	Secondary malignancy	OHDSI, 4 hospitals in South Korea 2001-2020	thyroidectomy + RAI therapy, any age
(30)	Holoubek 2022	160,458	44%	OS	NCDB, 2004 to 2016	cPTC, TC or DS; ≥ 18 years, Tumor size 1-40mm
(31)	Hay 2022	2,668	31.2%	CSM, TRR	MRPD, 1966 to 2015	PTC patients with TNM stage 1
(32)	Pasqual 2022	36,311	41%	Solid & hematologic malignancies	nine SEER registries, 1975 to 2017	Primary DTC in < 45 years old, no distant metastases
(33)	Xu 2022	882	66.0%	OS, CSS	SEER, 2004 to 2015	Poorly differentiated thyroid carcinoma
(34)	Zhao 2022	15,179, PMS: 3,385 p.g.	77.7%	OS, CSS	SEER, 2004 to 2018	PTC with cervical lymph node metastasis (N1a, N1b, N1NOS)
(35)	Lee 2021	1,580	64.3%	Occurrence of new treatment event	NHID, South Korea, 2004 to 2016	TC <20 years old
(36)	Seo 2021	18,617	51.2%	Secondary cancers, top 10 secondary cancers	HIRA claims database of South Korea, 2008 to 2018	Underwent thyroidectomy for TC 0-29 years old
(37)	Kim 2020	4,845	52.3%	CD, IS, IHD, HS, CD, HF	NHIS-HEALS (Korea), 2002-2015	TC of all types (ICD-10 C73)
(38)	Liu 2020	89,204	45.7%	OS (10y) CSS (10y)	SEER database, 2006 to 2015	PTC with FU ≥ 2 months
(39)	Sutton 2020	117,098	45.6%	Overall mortality	SEER-18 database, 2004 - 2015	≥ 18 years old Thyroid cancer
(40)	Orosco 2019	199,371 NCDB 77,187 SEER	51.8% NCDB 46.6% SEER	All-cause mortality, CSM	NCDB 2004-2012 & SEER 1992-2009	DTC

Referenz	Studie	Gesamt N	+RAI	Endpunkte	Datenquelle	Patientenkohorte
(41)	Kwon 2017	1,932	85%	RFS	Seoul registry (1998-2009)	100% microcarcinoma
(42)	Yang 2017	11,832	65-93%	OS (5y, 10y)	NCDB database (2002-2012)	100% stage IV
(43)	Zhang 2017	8,601	68%	OS; CSS (5y, 10y)	SEER database (2004-2013)	100% intermed. risk
(44)	Al-Qahtani 2015	326	56%	DFS (5y, 10y)	Riyadh registry (2000-2012)	100% microcarcinoma
(45)	Carhill 2015	4,941	74%	OS; DFS	NTCTCSG registry (1987-2012)	43% stage I, 27% II, 24% III (5% IV)
(46)	Kiernan 2015	32,119	24%	OS (5y, 10y)	NCDB database (1998-2011)	78% stage I (14% II, 7% III, 1% IV)
(47)	Ruel 2015	21,870	71%	OS	NCDB database (1998-2006)	100% intermed. risk
(48)	Nixon 2013	1,129	61%	CSS; RFS (5y)	MSKCC registry (1986-2005)	41% low risk, 45% intermed. (14% high)
(49)	Kim 2013	704	82%	RFS	Korean registry (1994-2004)	100% microcarcinoma
(50)	Schvartz 2012	1,298	70%	OS; DFS (10y)	French registry (1975-2004)	100% low risk
(51)	Lin 2009	7,818	22%	OS; CSS	SEER database (1988-2005)	100% microcarcinoma

CD: cardiovascular disease; CSM: cancer-specific mortality; CSS: cancer-specific survival; DFS: disease-free survival; EFS: event-free survival; OS: overall survival; RCT: randomised controlled trial; RFS: recurrence-free survival. TRR: tumor recurrence rates

Database abbreviations:

- HIRA: Health Insurance Review and Assessment claims database (South Korea)
- MSKCC: Memorial Sloan-Kettering Cancer Center registry (USA)
- MRPD: Mayo Rochester PTC (papillary thyroid carcinoma) Database
- NCDB: National Cancer Database (USA)
- NTCTCSG: National Thyroid Cancer Treatment Cooperative Study Group (USA)
- NHID: National Health Information Database (South Korea)
- NHIS-HEALS: National Health Insurance Service - National Health Screening Cohort (Korea)
- OHDSI: Observational Health Data Science and Informatics (South Korea)
- SEER: Surveillance, Epidemiology, and End Results (USA)

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
Studies on differentiated thyroid carcinoma (all stages / risk groups)						
Leboulleux et al. (28) *Thyroidectomy without radioiodine in patients with low-risk thyroid cancer*	Patients with • differentiated TC • with a multifocal pT1a tumor (a diameter of each lesion of ≤1 cm and a sum of the longest diameters of the lesions of ≤2 cm) or a pT1b tumor (>1 cm and ≤2 cm) • all N0 or Nx • complete tumor resection n = 776 randomised <u>RAI, ctrl</u> PTC: 95.6%, 96.1% FTC: 3.3%, 2.8% OHC: 1%, 1% <u>RAI, ctrl</u>	Radioiodine (1.1 GBq (30 mCi) administered 24 hours after the second intramuscular injection of recombinant human thyrotropin RAI in 50.1% of patients median follow-up: not reported, 10-month and 3-year FU time points reported	Randomized controlled trial, with stratification according to the trial site and lymph-node status (N0 or Nx) non-inferiority trial tumor staging system: pTNM Staging System Analysis: EFS as per protocol analysis (treatment adhered to and 3-year follow-up), logistic regression Sensitivity analysis ITT as survival analysis, two-sided 90% CI Secondary outcomes reported as point estimates and 95% estimates total n: 750	*Per-protocol* Radioiodine: n = 363 Control: n = 367 No visible differences in baseline characteristics <u>**OS:**</u> not reported <u>**EFS at 3 years:**</u> RAI: 95.9% (95% CI 93.3% to 97.7%) Ctrl: 95.6% (95% CI 93.0 to 97.5%) <u>**Excellent response (according to local Tg and Tg-Ab determination) at 3 years:**</u> RAI: 73.0% Ctrl: 74.1%	Study type: RCT Study population described: yes Randomisation: yes (with the Tenalea program, based on block and by site) Allocation concealment: probably (numbers returned by fax or e-mail) Blinding: no Population well-balanced: yes Outcomes standard, valid and reliable? Drop-out reported and balanced: yes	1b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
	pT1aN0: 6.7%, 5.9% pT1aNx: 14.4%, 10.9% pT1bN0: 36.8%, 38.2% pT1bNx: 42.2%, 45% mean age (years) RAI: 52.2 ± 13.4 Ctrl: 52.6 ± 13.5				ITT: no, but with reasoning (non-inferiority trial, PP and ITT similar outcomes) Results comparable across sites: n.r., but this was a stratification factor statistic methods reported: yes How well was the study done to minimise bias: allocaton concealment unclear, no blinding, minimal missing data; outcome measure standard? As in protocol financial support/conflicts of interest reported: reported, some authors with links to industry Acceptable quality of the study	
Kim 2022 (29) Radioiodine (1.1 GBq (30 mCi) administereddif	Patients with • Malignant tumor of thyroid gland • substerna, subtotal, total substerna, partial	Iodine 131 therapy RAI in 50% of patients	Retrospective propensity-matched cohorts Matching covariates: sex and age groups and condition	Due to matching no considerable group differences RAI: 5,374 Ctrl: 5,374	Study type: Retrospective propensity-matched cohorts Populations comparable: no, RAI group has a longer FU and higher	2b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
ferentiated thyroid carcinoma *Second primary malignancy risk in thyroid cancer and matched* *patients with and without radioiodine therapy analysis* *from the observational health data sciences and informatics*	substernal, total thyroidectomy and total thyroidectomy with cervical lymph node dissection cohort N = 24.318 RAI: 10.845 Ctrl: 13.473; Selection: 5,374 per group, matched **Thyroid cancer stage, RAI vs. Ctrl, n (%)** SNUBH I: 46.4%, 64.3% II: 2.8%, 0.9% III: 36.2%, 25.3% IV: 7.8%, 0.7% Unknown: 4.1%, 5.6% Similarly unbalanced for the other hospitals	after PMS **Median follow-up, IQR, per hospital** SNUBH: RAI: 4.76 (2.76-6.67) Ctrl: 4.23 (2.38-8.80) SNUH RAI: 6.28 (4.22-9.05) Ctrl: 5.78 (3.15-8.80) CMCS RAI: 5.56 (4.50-5.19) Ctrl: 3.97 (2.04-5.63) SSCHMC RAI: 5.33 (3.65-6,87) Ctrl: 4.11 (1.76-5.47)	occurrence (short: 30 days before the index date; medium: 180 days before the index date; long: 365 days before the index date) Analysis: Cox proportional hazard model to calculate the HRs with 95% confidence interval (CIs), then meta-analysis to calculate the HR pooling effect estimates across the databases Total N (matched): 10,748	**Second primary malignancy** RAI: 7.55 per 1,000 person-years Ctrl: 7.07 per 1,000 person-years Pooled HR across 4 hospitals: 1.08 (95% CI: 0.89 to 2.68) Stage I: HR 0.99, 95% CI 0.66-1.46 Stage II: n.r. Stage III: HR 1.02, 95% CI 0.63-1.63 Stage IV: n.r. Haematologic SPM: HR 0.91 (95% CI 0.37 to 2.23) Non-heamatologic SPM: HR 1.07 (95% CI 0.88 to 1.30)	disease stage Drop-outs reported: yes, appendix, but without reasons, comparison between matched and unmatched cohort provided Knowledge of exposure status possible to influence the outcome? Possible as retrospective, but unlikely Outcome measure valid and reliable: yes Main cofounders taken into account: yes, propensity matched cohorts statistic methods reported: yes definition of endpoint parameters/ treatment protocol reported; yes, extracted based on codes from hospital databases	

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
	Mean age (years) RAI: 48.9 Ctrl: 49.2				ITT analysis: N.A. Financial conflicts of interest: reported, none.	
Holoubek 2022 (30) *Radioactive iodine does not improve overall survival for patients with aggressive variants of papillary thyroid carcinoma less than 2 cm*	Patients with • classic papillary TC • tall cell, or diffuse sclerosing 1 mm to 40 mm total cohort n: 160,458 PTC: 155,940 TC: 4,011 DS: 507 Lobectomy: 20,505 Total thyroidectomy: 139,953 mean age (years) 49 ± 15	Adjuvant radioactive iodine RAI in 44% of patients Mean follow up 4.6 (± 3.0) years; median 4.3 years	Retrospective propensity score-matched analysis [based on logistic regression model, adjusting for age, sex, race, insurance, comorbidity, tumor size, multifocality, ETE, nodal status, metastasis, and operation type] Total N matched: not clear	RAI PTC: 67,897 TC: 307 DS: 1,546 No RAI PTC: 85,014 TC: 187 DS: 1,374 **10-year overall survival** T1-2N0M0 cohort TT- RAI vs. TT+RAI • 0.1 – 1.0 cm, 86.5% vs. 97.0%, p =.44 • 1.1 – 2.0 cm, 91.0% vs 92.6%, p = .18 • 2.1 – 4 cm, 82.4% vs. 80.8%, p = .027	Study type: retrospective NCDB analysis, propensity score matched Populations comparable: yes Drop-outs reported: n.a., only completely recorded cases in NCDB database available Knowledge of exposure status possible to influence the outcome: Possible as retrospective, but unlikely Outcome measure valid and reliable: yes Main cofounders taken into account: yes, propensity matched cohorts	2b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				Aggressive variant subtypes only There were no statistical differences in groups after matching TT+RAI: 1,216 TT-RAI: 1,216 Tumors <=2 cm: no differences in 10-year OS between TT without RAI versus TT with RAI • 0.1 - 1.0 cm, 92.2% vs 84.8%; p = .98 (n=358 per group) • 1.1 - 2.0 cm, 72.7% vs 88.1%; p = .82 (n=520 per group) Tumors >2 cm: significant differences in OS between TT without RAI versus TT with RAI • 2.1 - 4.0 cm, 70.0% vs 83.4%; p = .004 (n=338 per group)	statistic methods reported: yes definition of endpoint parameters/ treatment protocol reported; OS ITT analysis: N.A. Financial conflicts of interest: The authors have no disclosures and no conflicts of interest.	

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
Liu 2020 (38) *The impact of radioactive iodine treatment on survival among papillary thyroid cancer patients according to the 7th and 8th editions of the AJCC/TNM staging system: a SEER-based study*	Patients with • PTC (primary tumor site code C73.9 (thyroid) in ICD-O-3 • Includes Classic papillaryTC, follicular variant papillary TC, other vairants: 8052/3, 8130/3, 8342/3, 8344/3, 8350/3 • Subtotal or near total thyroidectomy • In the SEER database • Between 2006 and 2015 With FU >= 2 months <u>Age</u> < 45: 33,979 >45: 55,225	RAI after subtotal or near total thyroidectomy, or total thyroidectomy RAI in 45.7% of patients median FU not reported, 10-year OS and CSS	Retrospective cohort study National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database 2006 to 2015 Adjusted Cox regression models, but unclear which adjustment factors used for main analysis (stage, and more) Total N: 89,204	RAI: 40,781 No RAI: 48,423 **8th T staging system (also presented: 7th staging system, AJCC, N)** <u>**10-year OS (multivariable analysis)**</u> HR: 0.398 (95% CI 0.375-0.423, p<0.01) T1a: 0.585 (0.514-0.666) T1b: 0.396 (0.347-0.452) T2: 0.363 (0.313-0.420) T3a: 0.293 (0.257-0.335) T3b: 0.575 (0.453-0.730) T4a: 0.504 (0.403-0.629) T4b: 0.390 (0.297-0.512) <u>**10-year CSS (multivariable analysis)**</u> HR 0.22 (95% CI 0.193-0.250, p<0.01) T1a: 0.449 (0.291-0.693)	Study type: retrospective cohort study Populations comparable: no, different rates of sex, age groups and ethnic groups, which are all prognostic factors for survival Drop-outs reported: n.a., only completely recorded cases in database available Knowledge of exposure status possible to influence the outcome: Possible as retrospective, but unlikely Outcome measure valid and reliable: probably yes Main cofounders taken into account: probably, not exactly reported (adjusted analysis reported, but confounders adjusted for not reported) statistic methods reported: yes	2b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				T1b: 0.115 (0.070–0.189) T2: 0.132 (0.090–0.194) T3a: 0.145 (0.113–0.187) T3b: 0.434 (0.271–0.695) T4a: 0.443 (0.316–0.621) T4b: 0.373 (0.259–0.537)	definition of endpoint parameters/ treatment protocol reported; ITT analysis: N.A. Financial conflicts of interest: The authors have no conflicts of interest.	
Hay 2022 (31) *Radioiodine remnant ablation in stage I adult papillary thyroid carcinoma: does it improve postoperative outcome?*	• Adults • PTC patients with TNM stage I (8th edition) 2668 TBN stage I APTC patients <u>Complete cohort:</u> BT alone: 1836 BT+RRA within 6 mo: 832 <u>Overall Median age (at diagnosis):</u> 44 years	925 (35%) had postoperative RRA For complete cohort: Ablation within 6 postoperative months: 832 (31%) Mean dose: 51.1 mCi, 1890 MBq median dose: 30 mCi, 1110MBq). RAI in 31.2% of patients	Retrospective cohort study (prospective data collection) Mayo Rochester PTC Database (MRPD), consecutively managed with BT between January 1, 1966, and December 31, 2015 Split into two cohorts: THEN cohort (consecutively managed during 1966–1990) THEN cohort of 809 stage I APTC patients	OS, AE: not reported **THEN-cohort (1966–1990), median FU 27.8 years, n = 809** BT+RRA: n = 291 BT only: n = 518 **<u>20-year CSM</u>** BT+RRA: CSM rate: 1.2% BT only: CSM rate: 0.6% **<u>20-year TRR</u>** BT+RRA: TRR (any site): 11.7%	Study type: retrospective cohort study Populations comparable: only partly, there were differences: ablation performed more frequently when younger, male, iniial NTT or neck nodal resection, gross extrathyroid invasion, larger tumor size, grade 2 histology, multicentricity or path. Confirmed RNM (pN1) Drop-outs reported: n.a., only completely recorded cases in database available	2b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
	(range: 19 – 85)	Median follow-up for the 2668 stage 1 patients was 12.6 years; longest follow-up was 52.8 years; mean follow-up was 15.4 years and accounted for 41,188 patient-years of observation	managed with BT NOW cohort of 1859 stage I APTC patients managed between 1991 and 2015	BT only: TRR (any site): 7.9% **NOW-cohort (1991-2015), median FU 9.3 years, n = 1859** BT+RRA: n = 541 BT only: n = 1318 **15-year CSM rate** BT+RRA: 0% BT only: 0% **15-year TRR (any site):** BT+RRA: 18.5% (pN0/Nx: 6.8%, pN1: 26%) BT only: 6.9% (pN0/Nx: 3.1%, pN1: 17%) **15-year LRR:** BT+RRA: 18.4% (pN0/Nx: 6.8 %, pN1: n.r.) BT only: 6.9% (pN0/Nx: 3.1%, pN1: n.r.) **15-year occurrence rate postoperative**	Knowledge of exposure status possible to influence the outcome: Possible as retrospective, but unlikely Outcome measure valid and reliable: probably yes Main cofounders taken into account: probably not; not reported statistic methods reported: yes definition of endpoint parameters/ treatment protocol reported; ITT analysis: N.A. Financial conflicts of interest: The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported	

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				DM BT+RRA: 1% (pN0/Nx:1.9%, pN1 : n.r.) BT only: 0.1% (pN0/Nx: 0%, pN1: n.r.)		
Lee 2021 (35) *Trends in pediatric thyroid cancer incidence, treatment, and clinical course in Koreaduring 2004–2016: a nationwide population-based study*	Patients in the NHOD database with • thyroid cancer, coded as C73 • <20 years old • Who underwent thyroidectomy (total or subtotal thyroidectomy or lobectomy • FU >= 12 months	radioactive-iodine therapy (RAIT) after total, subtotal thyroidectomy or lobectomy RAI in 64.3% of patients Median follow-up: TT-only: 5.7 years, range 1.0 to 12.9 years) TT+RAIT: 6.2 years (range: 1.0 to 3.0 years)	Retrospective cohort study NHID data from the Ministry for Health, Welfare, and Family Affairs, which cover the entire Korean population between January 2004 and December 2016 Total N: 1580	1464 with FU >12 months RAI: 523 No RAI: 941 OS, CSM, recurrence rate and AE not reported **Occurrence of a new treatment event,** defined as ‘‘reoperation after 6 months of initial treatment’’ and/or ‘‘additional RAIT after 12 months of initial treatment.’’ TT+RAIT: 12.8% (80/941: 20 reoperation, 48 additional RAIT) TT only: 10.7% (56/523; 17 reoperation only, 10 RAIT only, 29 reoperation + RAIT)	Study type: retrospective cohort study Populations comparable: no significant difference in sex or age group; but as expected, the surgery + RAIT group received more extensive thyroidectomy (p < 0.001 for L, ST, L/ST+completion, to TT) and LND (p < 0.001 for none, unilateral, to bilateral LND), leading to more extensive surgery (p < 0.001 for L, L + LND, ST/TT, to ST/TT+LND) Drop-outs reported: n.a., only completely recorded cases in database available Knowledge of exposure status possible to influence the outcome:	2b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
					Possible as retrospective, but unlikely Outcome measure valid and reliable: surrogate outcome, as exact data could not be retrieved from health insurance records Main cofounders taken into account: frequencies only reported, subgroup analyses available. HR not extracted because participants were excluded from that analysis. statistic methods reported: yes definition of endpoint parameters/ treatment protocol reported; ITT analysis: N.A. Financial conflicts of interest: No competing financial interests exist.	

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
Sutton 2020 (39) *Treatment variation in older adults with differentiated thyroid cancer*	Patients with • Thyroid cancer, primary site thyroid, ICD-O-3: C73-9) • Age >=18 years old • Availability of histologic subtype and TNM • 2004-2015 117,098 patients with differentiated thyroid cancer (DTC) T1: 60% Unifocal tumors: 59%, nodal metastases: 21.6% PTC: 57.8% microPTC: 34.5% FTC: 5.2% HCC: 2.5% Age-stratified analysis	No surgery, Thyroid lobectomy, total thyroidectomy, + RAI RAI in 45.6% of patients Median follow-up: not reported	Retrospective cohort study National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER-18) database 2004 - 2015 Total N: 117,098	<u>Overall cohort</u> 5-year overall mortality: 4.9% Five-year disease-specific mortality: 0.9% Total 6,385 deaths, 1,50 attributable to thyroid cancer **<u>5-year overall mortality, radiation vs. no radiation:</u>** Univariable HR: 0.8 (95% CI 0.7-0.9, p<0.001) Multivariable HR: 0.7 (95% CI 0.6-0.8, P<0.001)	Study type: retrospective cohort study Populations comparable: unclear, population plotted per age range Drop-outs reported: n.a., only completely recorded cases in database available Knowledge of exposure status possible to influence the outcome: Possible as retrospective, but unlikely Outcome measure valid and reliable: surrogate outcome, as exact data could not be retrieved from health insurance records Main cofounders taken into account: frequencies only reported, subgroup analyses available. HR not extracted because participants were excluded from that analysis.	2b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
					statistic methods reported: yes definition of endpoint parameters/ treatment protocol reported; ITT analysis: N.A. Financial conflicts of interest: No competing financial interests exist.	
Zhao 2022 (34) *Radioactive iodine in low- to intermediate-risk papillary thyroid cancer*	Patients with • Papillary thyroid carcinoma (PTC) • TT and cervical lymph node dissection • cervical lymph node metastasis (N1a, N1b, N1NOS) patients with relevant missing baseline information excluded	TT+RAI or TT alone RAI in 77.7% of patients median follow-up: not reported	propensity score matching (PSM), retrospective cohort Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2018 adjustment for patient age, year of diagnosis, sex, race, capsular extension, multifocality, T/N stage, cervical lymph node	**Before propensity score matching** **Overall survival (multivariable analysis)** HR: 0.66 (95% CI 0.54–0.80) in favour of RAI KM curve: 1.52 (95% CI 1.23 to 1.88) **Cancer-specific survival (multivariable analysis)** HR: 0.89 (95% CI 0.62–1.27) in favour of RAI **Overall survival, subgroup analyses**	Study type: retrospective cohort study, propensity matching Populations comparable: partly, "PSM analysis was performed between groups to balance the statistical differences of the clinicopathologic features such as year of diagnosis, multifocality, capsular extension, T/N stage, and positive regional lymph nodes between TT and TT+RAI groups.", but "The following characteristics of patients were more likely to present in the TT+RAI group	2b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
	AJCC 8 TT: 3,387 (22.3%) TT+RAI: 11,792 (77.7%) *Age:* TT: 41 (32-52) TT+RAI: 41 (32-52 Stage T1: 46.9% T2: 19.3%, 20.5% T3: 33.8%, 32.6%		examined, and positive cervical lymph nodes in the multivariate Cox regression model Total N: 15,179	Low-risk : HR 0.71 (95% CI 0.51-0.97) Intermediate risk: HR 0.63 (95% CI 0.49-0.80) **After propensity score matching** TT: 3385 TT+RAI: 3385 **Overall survival (HR, 95% CI)** Overall HR 1.47 (95% CI 1.15-1.88) (HR>1 favours RAI) *Here, direction changed, HR<1 favours RAI* N1a: 0.72 (95% CI 0.54-0.95) N1b: 0.59 (95% CI 0.43-0.81) ATA low risk: 0.71 (95% CI 0.51-0.97) ATA intermediate risk: 0.63 (95% CI 0.49-0.80) *T-stage* PTMC: 0.79 (95% CI 0.49-1.25)	compared with the TT group: multifocality, extracapsular extension, T3, N1b, more cervical lymph node examined, and more metastatic cervical lymph nodes" Drop-outs reported: n.a., only completely recorded cases in database available Knowledge of exposure status possible to influence the outcome: Possible as retrospective, but unlikely Outcome measure valid and reliable: yes Main cofounders taken into account: yes, in the analysis before PSM, and PSM made cohorts more equal statistic methods reported: yes	

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				T1: 0.71 (95% CI 0.51–0.99) T2: 0.53 (95% CI 0.32–0.88) T3: 0.67 (95% CI 0.51–0.88) <u>Cancer-specific survival (HR, 95% CI)</u> N1a : 1.47 (95% CI 0.74–2.93) N1b : 0.64 (95% CI 0.39–1.04) ATA low risk: 1.83 (95% CI 0.71–4.78) ATA intermediate risk: 0.75 (95% CI 0.51–1.11) *T-stage* PTMC: 1.44 (95% CI 0.41–5.10) T1: 1.07 (95% CI 0.39–2.92) T2: 0.89 (95% CI 0.32–2.48) T3: 0.82 (95% CI 0.54–1.25) More subgroup analyses available (multifocality, metastatic lymph nodes, extracapsular extension)	definition of endpoint parameters/ treatment protocol reported; ITT analysis: N.A. Financial conflicts of interest: “absence of any commercial or financial relationships that could be construed as a potential conflict of interest.”	
Xu 2022 (33)	Patients with • Poorly differentiated	RAI vs. no RAI	Retrospective cohort study	RAI: 582 No RAI: 300	Study type: retrospective cohort study	2b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
Postoperative radioiodine therapy impact on survival in poorly differentiated thyroid carcinoma: a population-based study	thyroid carcinoma(PDTC) N = 1179 PDTC <u>Age (median, range)</u> RAI: 55.0 (11-97) No RAI: 60.0 (12-94) <u>T-staging (RAI, no RAI)</u> T1: 14.9%, 21.3% T2: 20.1%, 18.3% T3: 49.4%, 42.1% T4: 15.6%, 18.3%	RAI in 66.0% of patients Median follow-up: not reported	Surveillance, Epidemiology and End Results (SEER) 2004 to 2015 Search for independent prognostic factors in univariable Cox regression analysis, of those, age, histology, extension, regional metastasis, distant metastasis and radioiodine therapy were finally included (adjustment) N total analysed: 882 PDTC	<u>**Overall survival**</u> Multivariable analysis HR: 0.57 (95% CI, 0.44-0.75; P < 0.001) Univariable analsis HR : 0.65 (95% CI 0.50 to 0.84, p =0.001) <u>**Cancer-specific survival**</u> Univariable analysis HR: 0.73 (95% CI 0.5 - 0.84; p=0.083)	Populations comparable: no, "A higher proportion of the radioiodine group had aggressive characteristics such as advanced T stage, tumor size >1 cm, extrathyroidal extension and neck lymph nodes metastasis, and more patients underwent total thyroidectomy and neck lymph nodes dissection" Drop-outs reported: n.a., only completely recorded cases in database available Knowledge of exposure status possible to influence the outcome: Possible as retrospective, but unlikely Outcome measure valid and reliable: yes Main cofounders taken into account: for OS only	

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
					statistic methods reported: yes definition of endpoint parameters/ treatment protocol reported; ITT analysis: N.A. Financial conflicts of interest: "absence of any commercial or financial relationships that could be construed as a potential conflict of interest."	
Pasqual 2022 (32) *Association between radioactive iodine treatment for pediatric and young adulthood differentiated thyroid cancer and risk of second primary*	Patients with • primary DTC (papillary or follicular TC) • <45 years old • between 1975 and 2017 • no distant metastases at diagnosis • FU after 2 or 5 years (HM, solid) <u>Papillary:</u>	RAI therapy, defined as receipt of radioisotope therapy after 1988 or "other radiation" (n 5 1,116) or "radiation NOS" (n 520) RAI in 41.0% of patients	Retrospective cohort study nine SEER registries (San Francisco–Oakland, Connecticut, Detroit, Iowa, Hawaii, New Mexico, Seattle, Utah, and Atlanta) between 1975 and 2017 Multivariable Poisson regression models that were adjusted through	N = 36,311 pediatric and young adults with nonmetastatic DTC during 1975–2017 in database RAI: 16,296 (45%) No RAI: 20,015 (55%) <u>**Solid malignancies in 5-year survivors**</u> 1,524/27,050 (median FU 16.6 years) **Cumulative incidence of second solid malignancy**	Study type: retrospective cohort study Populations comparable: RAI use was higher in males, younger than 15 years, and lowest in black patients Drop-outs reported: n.a., only completely recorded cases in database available Knowledge of exposure status	2b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
malignancies	RAI: 14,907 No RaI: 18,266 Follicular: RAI: 1389 No RAI: 1749 Age (years, RAI vs. no RAI) 0–14: 201; 157 15–24: 2,261; 2,569 25–44: 13,834; 17,279	Maximum follow-up was 43 years Median (IQR) follow-up (years) RAI: 10.2 (4.9–17.7) No RAI: 12.7 (4.8–24.5)	stratification for sex, age at DTC diagnosis, and latency (time between DTC and SPM diagnoses) and were indirectly adjusted for attained age and calendar year using the log of the expected number of cases as an offset cumulative incidence of second solid and hematologic malignancies by time since DTC diagnosis, accounting for competing risk of death and other cancers Total N: N = 36,311	at 20 years after DTC diagnosis RAI: 5.6% (95% CI 5.0 to 6.0) No RAI: 5.0% (4.6 to 5.4) At 30 years after DTC diagnosis RAI: 12.5% (95% CI 11.3 to 13.8) No RAI: 10.2% (9.5 to 11.0) RR 1.23 (95% CI, 1.11 to 1.37) – increased risk with RAI Especially elevated cancers: salivary gland: RR 2.15 (95% CI, 0.91 to 5.08) stomach: RR 1.61 (95% CI, 0.70 to 3.69) kidney: RR 1.34; (95% CI, 1.14 to 2.09) uterus: RR 1.55 (95% CI 1.03 to 2.32) female breast, 591 cases: RR 1.18 (95% CI, 0.99 to 1.40) lung: RR 1.42 (95% CI, 0.97 to 2.08) SIR for second solid cancer RAI: 1.15 (95% CI 1.06 to 1.25) No RAI: 0.89 (95% CI 0.83 to 0.94)	possible to influence the outcome: Possible as retrospective, but unlikely Outcome measure valid and reliable: yes Main cofounders taken into account: probably yes statistic methods reported: yes definition of endpoint parameters/ treatment protocol reported; ITT analysis: N.A. Financial conflicts of interest: “No potential conflicts of interest were reported.”	

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				Estimate: 106 (95% CI, 51 to 161) excess solid cancers and 32 (95% CI, -2 to 67) excess breast cancers were attributable to RAI in this cohort, corresponding to 6% (95% CI, 3 to 9) and 5% (95% CI, 0 to 11) of all solid and breast cancers, respectively, in $ 1-year DTC survivors <u>Second Hematologic Malignancies in >= 2-year survivors</u> 146/32,171 (median FU 13 years) **Cumulative incidence of second hematologic malignancies** <u>at 5 years</u> RAI: 0.10% (95% CI 0.06 to 0.17) No RAI: 0.05 (95% CI 0.03 to 0.10) <u>At 20 years</u> RAI: 0.67% (95% CI 0.49 to 0.88) No RAI: 0.37 (0.27 to 0.50) <u>Especially elevated:</u> Leukemia: RR 1.92 (95% CI .04 to 3.56)		

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				Nonly,phocytic leukemia: RR 2.17 (95% CI 1.03 to 4.55) 22 (95% CI, 4 to 41) excess hematologic malignancies were attributable to RAI in this cohort, corresponding to an attributable risk of 14% (3 to 26)		
Seo 2021 (36) Radioactive iodine treatment for children and young adults with thyroid cancer in South Korea: a population-based study	Patients • who underwentthyroidectomy (HIRA codes P4561, P4552, P4554, P4551, and P4553) • to treat a thyroid malignancy (C73) • 0–29 years old • No history of malignancy • death or another malignancy within 1 year of TC diagnosis • between 2008 and 2018 mean age at surgery: 25.2 ± 3.7 years	Thyroidectomy vs. thyroidectomy + RAIT, defined as an RAI dose >0.93 GBq (25 mCi) (claim code 3684) median interval from surgery to RAIT was 85 days (IQR 60–119 days) RAI in 51.2% of patients Observation time: 120 474 person-years; median follow-up period was 79 months (IQR = 46–108 months)	Retrospective cohort study Health Insurance Review and Assessment (HIRA) claims database of South Korea between 2008 and 2018 “The hazard ratio (HR) was calculated using Cox’s proportional hazards regression with adjustment for age, sex, year of surgery, and lymph node dissection status.” Total N = 18 617	TT: 9069 TT+RAIT: 9548 <u>**Secondary cancers**</u> TT+RAIT: 81/9548 (0.8%) TT: 43/9069 (0.5%) adjusted HR 1.52 (95% CI 1.03–2.24, P = 0.035) <u>mean time to secondary cancer development:</u> TT+RAI: 72.6 ± 29.6 months (P = 0.143) TT: 63.8 ± 32.4 months Cumulative incidence during first 4 years:	Study type: retrospective cohort study Populations comparable: relatively comparable, sign. Differences due to the large sample size Drop-outs reported: n.a., only completely recorded cases in database available Knowledge of exposure status possible to influence the outcome: Possible as retrospective, but unlikely Outcome measure valid and reliable: yes	2b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				adjusted HR 1.12 (95% CI 0.54–2.31, P = 0.762) Cumulative incidence after 4 years: adjusted HR 1.68 (95% CI 1.06–2.66, P = 0.028) <u>Top 10 cancers</u> Breast: TT+RAI: 19/9548 TT: 11/9069 Stomach: TT+RAI: 5/9548 TT: 7/9069 Parotid gland: TT+RAI: 8/9548 TT: 0/9069 Endocervical: TT+RAI: 5/9548 TT: 2/9069	Main cofounders taken into account: yes for the HRs statistic methods reported: yes definition of endpoint parameters/ treatment protocol reported; ITT analysis: N.A. Financial conflicts of interest: “No potential conflict of interest relevant to this article was reported”	

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				Kidney: TT+RAI: 4/9548 TT: 3/9069 Brain: TT+RAI: 3/9548 TT: 3/9069 Myeloid: TT+RAI: 4/9548 TT: 2/9069 Rectal: TT+RAI: 5/9548 TT: 0/9069 Ovarian: TT+RAI: 3/9548 TT: 2/9069 Liver: TT+RAI: 3/9548		

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				TT: 0/9069		
Kim 2020 (49) Effects of radioactive iodine treatment on cardiovascular disease in thyroid cancer patients: a nationwide cohort study	Patients with • newly diagnosed TC of all types (ICD-10 C73) • between January 1, 2004 to December 31, 2015 • who underwent thyroidectomy after TC • had no prior other malignancies • had no history of levothyroxine or RAI treatment <u>Age (median, IQR, in years)</u> RAI: 55 (51-61) No RAI: 56 (52-62)	median cumulative RAI dose was 103 mCi (IQR, 40-162 mCi). RAI in 52.3% of patients <u>median follow-up:</u> <u>RAI:</u> 72 months, IQR 45-101 <u>No RAI:</u> 58 months, IQR 34-91	Retrospective cohort study Korean National Health Insurance-Health Screening Cohort (NHIS-HEALS, 2002-2015), of this: TC of all types (ICD-10 C73) between January 1, 2004 to December 31, 2015 Variables adjusted for were age, sex, body mass index, socioeconomical status, smoking, alcohol consumption, levothyroxine dosage, and previous history of hypertension, DM, dyslipidemia, and CVD Total N with TC: 4845	RAI: 2533 No RAI: 2312 <u>Cardiovascular disease</u> (composite of ischemic stroke (IS), ischemic heart disease (IHD), hemorrhagic stroke (HS), or heart failure (HF) (events, N, incidence rate per 1000 person-years) • RAI: 204/2533 (8.1%), 13.96 (12.17 - 16.01) • No RAI: 199/2312 (8.6%), 17.32 (15.07 - 19.90) Adjusted HR: 0.87 (95% CI: 0.71 to 1.07, p = 0.188) <u>Ischemic stroke</u> (events, N, incidence rate per 1000 person-years) • RAI: 36/2533 (1.4%), 2.34 (1.69-3.24) • No RAI: 38/2312 (1.6%), 3.12 (2.27-4.29) Adjusted HR: 0.83 (0.51-1.34), p = 0.448	Study type: retrospective cohort study Populations comparable: in main CVD risk factors yes, follow-up between groups varies Drop-outs reported: n.a., only completely recorded cases in database available Knowledge of exposure status possible to influence the outcome: Possible as retrospective, but unlikely Outcome measure valid and reliable: yes, according to ICD codes, but "real-wold" data Main cofounders taken into account: yes statistic methods reported: yes	2b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				Ischemic heart disease (events, N, incidence rate per 1000 person-years) • RAI: 162/2533 (6.4%), 10.96 (9.4-12.78) • No RAI: 154/2312 (6.7%), 13.21 (11.28-15.47) Adjusted HR: 0.90 (0.71-1.13), p = 0.368 Hemorrhagic stroke (events, N, incidence rate per 1000 person-years) • RAI: 18/2533 (0.7%), 1.16 (0.73-1.84) • No RAI: 14/2312 (0.6%), 1.14 (0.68-1.93) Adjusted HR: 1.01 (0.49-2.09), p = 0.978 Cerebrovascular disease (events, N, incidence rate per 1000 person-years) • RAI: 103/2533 (4.1%), 6.78 (5.59-8.23) • No RAI: 97/2312 (4.2%), 8.08 (6.62-9.86) Adjusted HR: 0.88 (0.66-1.17), p =	definition of endpoint parameters/ treatment protocol reported; ITT analysis: N.A. Financial conflicts of interest: The authors have no conflicts of interest.	

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				0.379 Heart failure (events, N, incidence rate per 1000 person-years) • RAI: 25/2533 (1.0%), 1.62 (1.09-2.40) • No RAI: 22/2312 (1.0%), 1.8 (1.18-2.73) Adjusted HR: 0.89 (0.49-1.63), p = 0.714		
Orosco 2019 (40) *Radioactive iodine in differentiated thyroid cancer: a national database perspective*	Patients with • DTC as their only malignancy • papillary or follicular carcinomas **median age** NCDB: 44 years SEER: 48 years **T stage** NCDB: 1a: 28,108 (15.1%) 1b:87,570 (47.2%)	Radioiodine therapy compared to no RAI NCDB: RAI in 51.8% of patients SEER; RAI in 46.6% of patients **Median follow-up:** Not reported	Retrospective cohort study National Cancer Database (NCDB) from 2004 to 2012 and Surveillance, Epidemiology, and End Results (SEER) database from 1992 to 2009 Cox multivariate analyses were applied to each dataset and covariates included: receipt of RAI, T/N/M stages, age, gender, and race. Charlson Comorbidity Index (CCI) information was not available in SEER, but	**All-cause mortality** NCDB: 3.5% SEER: 5.1% NCDB: HR 0.55 (95% CI 0.52 to 0.59) SEER : HR 0.64 (95% CI 0.58 to 0.70) Subgroups *T1a* NCDB: HR 0.58 (95% CI 0.42 to 0.79; n = 25,736) SEER: HR 0.58 (95% CI 0.46 to 0.73; n = 21,123)	Study type: retrospective cohort study Populations comparable: sex and race yes, however, RAI was given more often at higher disease stage Drop-outs reported: n.a., only completely recorded cases in database available Knowledge of exposure status possible to influence the outcome: Possible as retrospective, but unlikely	2b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
	2: 32,567 (17.5%) 3: 31,677 (17.1%) 4: 5,718 (3.1%) <u>SEER:</u> 1a: 23,960 (33.9%) 1b: 17,726 (25.1%) 2: 14,506 (20.5%) 3: 9,605 (13.6%) 4: 4948 (7.0%)		was added as a covariate in the NCDB analyses (reference group CCI = 0). Total N NCDB: 199,371 Total N SEER: 77,187	*T1b* NCDB: HR 0.60 (95% CI 0.55 to 0.66, n = 79,653) SEER: HR 0.56 (95% CI 0.45 to 0.69; n = 15,476) *T2* NCDB: HR 0.59 (95% CI 0.51 to 0.68; n = 29,482) SEER: HR 0.79 (95% CI 0.65 to 0.96 ; n = 12,481) *T3* NCDB: HR 0.55 (95% CI 0.49 to 0.61 ; n = 28,685) SEER: HR 0.62 (95% CI 0.51 to 0.77 ; n = 8,746) *T4*: NCDB: HR 0.42 (95% CI 0.37 to 0.48 ; n = 4933) SEER: HR 0.64 (95% CI 0.52 to 0.80 ; n = 3718) <u>Thyroid cancer specific mortality (SEER</u>	Outcome measure valid and reliable: yes Main cofounders taken into account: yes statistic methods reported: yes definition of endpoint parameters/ treatment protocol reported; ITT analysis: N.A. Financial conflicts of interest: “there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported”	

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				database only) RAI: 1.6% No RAI: 1.1%, p<0.001 SEER : HR 0.82 (95% CI 0.69 to 0.99) Subgroups *T1a:* RAI: 0.4% (n = 30) No RAI: 0.1% (n = 13), p<0.001 HR 7.89 (95% CI 2.54 to 24.55; n = 21,123) *T1b:* RAI: 0.6 (n=45) No RAI: 0.4% n=36), p=0.03 HR 0.71 (95% CI 0.40 to 1.29; n = 15,476) *T2:* RAI: 1.2% (n=70) No RAI: 1.4% (n=122), p=0.35 HR 1.06 (95% CI 0.72 to 1.56, n = 12,481)		

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				T3: RAI: 2.9% (n=100) No RAI: 2.5% (n=154), p=0.20 HR 1.08 (95% CI 0.58 to 1.08; n = 8,746) *T4:* RAI: 7.3% (n=119) No RAI: 4.9% (n=162), <0.001 HR 0.58 (95% CI 0.44 to 0.77, n=3,718)		
Yang 2017 (42) *Comparison of Survival Outcomes Following Postsurgical Radioactive Iodine Versus External Beam Radiation in Stage IV Differentiated Thyroid Carcinoma.*	differentiated thyroid carcinoma, n=11,832 PTC: 91.24% FTC: 8.76% pat.s with dx of stage IV; thyroidectomy as primary surg.tx mean age 61.6y	adjuvant radiation tx: RAI, EBRT, or no RT - PTC: RAI+/- n=7500 vs 2692 - FTC: RAI+/- n=538 vs 286 median follow-up [unclear - data for 5y and 10y]	National Cancer Database (tx in 2002-2012) stratification by histology (follicular vs papillary) and sub-stage [multivariable models - adjusted for age, sex, race, socioecon. factors; clinical variables: surgical length of stay, tx w/ neck dissection -- *adjusted analyses for sub-stages only*]	**cohort group characteristics:** PTC cohort - significant differences: group +RAI younger than -RAI group (median 58 vs 61y) FTC cohort - significant differences: group +RAI younger than -RAI group (median 66 vs 73y) **all-cause mortality:** PTC cohort - 5y mortality: 22.7% w/o RAI vs 11.0% with adjuvant RAI - 10y mortality: 25.5% w/0 RAI vs 14.0% with adjuvant RAI	study type? - retrospective NCDB analysis study population described (table)? - yes population well-balanced? - no ("age was found to be significantly related to higher death hazards" -- mortality rates not adjusted for this factor) drop-out reported (consort diagram)? - no / n.a. statistic methods reported? - yes definition of endpoint parameters/ treatment protocol reported? - yes (stages /	4 (unclear whether rates adjusted for full cohort; multivar. analyses for substages but many missing data, therefore high risk of bias)

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
Thyroid			tumor staging system: according to AJCC	FTC cohort - 5y mortality: 45.5% w/o RAI vs 29.2% with adjuvant RAI - 10y mortality: 51% w/o RAI vs 36.8% with adjuvant RAI hazards of death calculated for sub-stages (IV-A, -B, -C) but "*more than 70% of pat.s had missing grade data. the authors therefore advise caution when interpreting the significance of tumor grade data in this study.*"	classification) ITT analysis? - n.a. financial support/conflicts of interest reported? which? - yes (none)	
Zhang 2017 (43) *Postoperative radioactive iodine-131 ablation is not necessary among patients with intermediate-risk differentiated thyroid carcinoma: a population-based study.*	differentiated thyroid carcinoma, n=8,601 PTC: 83.6% FTC: 16.4% pat.s with intermediate risk (T1/2 N1 M0 and T3 with/ without N1 M0) T1/T2: 27.3% T3: 72.7% <u>mean age</u> 47.3y	adjuvant RAI (in 67.6% of cohort pat.s) - 68.8% of PTC - 61.6% of FTC - T1/T2: 25% no RAI, 28.3% +RAI median follow-up 10.3y	SEER database (2004-2013) univariate analyses to identify risk factors -> Cox multivariate regression analysis tumor staging system: according to AJCC TNM classification system	<u>**cohort group characteristics:**</u> significant differences: +RAI group more white pat.s, more PTC, more with tumor size of T1/T2 compared with -RAI group; fewer T3 tumors, fewer N0, fewer localized tumors without ETE, fewer solitary tumors (all p<0.001). (mean age 47 vs 48y, p=0.008) *<-- multivariate analysis: all factors associated with either OS and/or CSS but no matching (only stratification for T category)* <u>**overall survival:**</u> 5y-OS rates: 95.0% vs 96.8% (- vs +) //	study type? - retrospective SEER analysis study population described (table)? - yes population well-balanced? - no (but stratified and multivariate analyses) drop-out reported (consort diagram)? - yes (according to criteria) / n.a. statistic methods reported? - yes definition of endpoint parameters/ treatment protocol reported? - yes (classification) ITT analysis? - n.a.	2b (stratified and multivar. analyes for hazard ratios)

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				10y-OS rates: 89.8% vs 92.2% mean OS in -RAI group 112.9mo vs 114.9mo in +RAI group (p<0.001; absolute difference 2mo) subgroup analyses (univariate) for tumor size: - T1/T2: not significant (-RAI 114.4mo vs 115.8mo +RAI; p=0.113) - T3: significant diff. (-RAI 112.4mo vs 114.7mo +RAI; p<0.001) multivariate analysis (full cohort, T1-T3): significant benefit of RAI, HR=0.71 (95%CI 0.56-0.90; p=0.004) no effect of T3 in multivar.analysis --> other factors likely causal <u>thyroid cancer-specific death:</u> 5y-CSS rates: 98.8% vs 99.2% (- vs +) // 10y-OS rates: 98.2% vs 97.8% mean CSD in -RAI group 117.7mo vs 118.0mo in +RAI (p=0.164) subgroup analyses (univariate) for tumor size: - T1/T2: not significant (-RAI 118.6mo vs 118.5mo +RAI; p=0.801)	financial support/conflicts of interest reported? which? - yes (none)	

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				- T3: not significant (-RAI 117.3mo vs 117.8mo +RAI; p=0.154) *[no multivar.analysis for RAI effect on CSS because no diff. in univar.]*		
Carhill 2015 (45) *Long-Term Outcomes Following Therapy in Differentiated Thyroid Carcinoma: NTCTCS Registry Analysis 1987-2012.*	differentiated thyroid carcinoma, n=4,941 PTC 88% FTC 8% HTC 4% stage I: 43%, II: 27%, III: 24%, IV: 5% mean age: not reported (52% <45y, 48% >45y)	adjuvant RAI (in 74% of cohort pat.s) median follow-up 6y	National Thyroid Cancer Treatment Cooperative Study Group registry analysis (11 institutions) (dx between 1987-2012) tumor staging system: according to registry staging system (I-IV)	**cohort group characteristics:** significant differences between +-RAI unclear /not shown **overall survival:** multivariate analyses, per stage: - stage I: +RAI vs -RAI risk ratio RR=0.79 (95%CI 0.35-1.89; p=0.58) - stage II: +RAI vs -RAI RR=0.67 (95%CI 0.36-1.28; p=0.22) - stage III: +RAI vs -RAI RR=0.66 (95%CI 0.46-0.98; p=0.04) signif. - stage IV: +RAI vs -RAI RR=0.70 (95%CI 0.46-1.10; p=0.12) **disease-free survival:** - stage I: +RAI vs -RAI risk ratio RR=1.79 (95%CI 1.28-2.56; p<0.001) - stage II: +RAI vs -RAI RR=0.70 (95%CI 0.49-1.01; p=0.53) - stage III: +RAI vs -RAI RR=0.84	study type? - retrospective registry analysis study population described (table)? - no (not for +/- RAI groups) population well-balanced? - no / unclear drop-out reported (consort diagram)? - yes statistic methods reported? - yes definition of endpoint parameters/ treatment protocol reported? - yes (classification: see supplement) ITT analysis? - no / n.a. financial support/conflicts of interest reported? which? - yes (NTCTCS has been supported in part by research grants from Genzyme / Sanofi company, and Pfizer, and by the University of Texas)	4 (many data missing for assessment)

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				(95%CI 0.57-1.28; p=0.40) "Initial disease stage was a significant predictor of OS as well as DFS. No significant difference was observed in analysis of treatment outcomes among the histological subtypes."		
Kiernan 2015 (46) *Use of radioiodine after thyroid lobectomy in patients with differentiated thyroid cancer: does it change outcomes?*	differentiated thyroid carcinoma, n=32,119 pat.s with thyroid lobectomy as definitive procedure PTC: 83% FTC: 11% Hürthle: 6% stage I: 78%, II: 14%, III: 7%, IV: 1% mean age 48y	adjuvant RAI (in 24% of cohort pat.s) median follow-up 81-86mo	National Cancer Database (dx between 1998-2011) Cox proportional hazards regression modeling to identify factors independently associated with OS; multivariable regression analysis tumor staging system: coded according to the NCDB analytic stage group (value of reported pathologic stage group / clinical stage group if pathol. stage is not available)	<u>cohort group characteristics:</u> significant differences: pat.s +RAI younger (47 vs 49y; more FTC (18% vs 9%) and HCC (8% vs 5%) and fewer PTC (74% vs 86%) in the RAI cohort; +RAI pat.s presented at later stages (stage I 82% vs 62% +RAI, stage II 12% vs 23% +RAI, stage III 5% vs 12% +RAI), had larger cancers (2.2 vs 0.7cm), more likely with ETE (9% vs 3%) and positive LN (25% vs. 10%). <u>overall survival:</u> - unadjusted analysis: OS slightly greater in +RAI group at 5y (97% vs. 95%, p<0.001) and 10y (91% vs. 89%, p<0.001) - regression analysis (adjusting for multiple patient, tumor and hospital factors): statistically significant survival benefit in +RAI group (HR=0.53, 95%CI 0.38-0.72; p<0.001)	study type? - retrospective NCDB analysis study population described (table)? - yes population well-balanced? - no (but multivariate analysis) drop-out reported (consort diagram)? - no / n.a. statistic methods reported? - yes definition of endpoint parameters/ treatment protocol reported? - (brief) (stages / classification) ITT analysis? - n.a. financial support/conflicts of interest reported? which? - yes (none)	2b (adjusted multivar. analyses for hazard ratio)

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				[no subgroup analyses for stages] factors significantly associated with decreased OS: age ≥45, male gender, black race, Medicaid insurance, Medicare insurance, tumor size ≥ 1cm, extrathyroidal extension, distant metastases		
Ruel 2015 (47)	differentiated (papillary) thyroid carcinoma, n=21,870 adult pat.s with thyroidectomy; intermediate risk (≤4cm, T1-3 N1 M0/x or >4cm T3 N0 M0/x) mean age 43/44y	adjuvant RAI (in 70.5% of cohort pat.s) mean follow-up 6.8y / median 6.6y	National Cancer Database (dx between 1998-2006) multivariate Cox proportional hazards model to examine OS after adjustment for clinical and demographic factors across all ages and in atients aged younger than 45 years tumor staging system: according to ATA risk criteria & AJCC staging	cohort group characteristics: significant differences: +RAI group more multifocal tumors (51% vs 47%), lymph node involvement (74% vs 68%), and positive surgical margin status (19% vs 15%) overall survival: (most patients were alive as of 2006, and a median survival time could not be estimated.) multivariate analysis (adjustment for demogr. and clin. factors): RAI associated with a 29% reduced risk of death (HR=0.71; 95%CI 0.62-0.82, p<0.001) - patient factors associated with compromised OS: older age, male gender, black race	study type? - retrospective NCDB analysis study population described (table)? - yes population well-balanced? - no (but multivariate analysis) drop-out reported (consort diagram)? - yes (according to criteria) statistic methods reported? - yes definition of endpoint parameters/ treatment protocol reported? - yes (classification) ITT analysis? - n.a. financial support/conflicts of interest reported? which? - yes (none)	2b (adjusted multivar. analyses for hazard ratio)

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				- pathol. and clin. factors: larger tumor size, presence of lymph node metastases, positive surgical margins, lack of RAI therapy subgroup analysis für pat.s <45y: RAI associated with a 36% reduced risk of death (HR=0.64; 95%CI 0.45-0.92; p=0.016) - patient factors associated with compromised OS: male gender		
Nixon 2013 (48)	differentiated, papillary thyroid carcinoma, n=1,129 pT1: 45% pT2: 16% pT3: 32% pT4: 7% ATA risk groups: 41% low, 45% intermediate, 14% high median age 46y	adjuvant RAI (in 61% of cohort pat.s) - low-risk 21% (vs 72% -RAI) - interm. 60% (vs 22% -RAI) - high 19% (vs 6% -RAI) [% of entire cohort] median follow-up 63mo	Memorial Sloan-Kettering Cancer Center registry analysis (1986-2005) multivariate analyses performed [with limited variables] tumor staging system: according to MSKCC cause-specific mortality risk classification system, and ATA stratification system	**cohort group characteristics:** significant differences: +RAI group more likely male, more advanced pT and N stage disease, more likely in high-risk group **disease-specific survival:** univariate analysis: no predictive effect of RAI on DSS (5y rates +RAI 99% vs 100% -RAI, p=0.821) (multivariate analysis for DSS only possible for age, pT stage; not significant for +/-RAI [no HR reported]) **recurrence-free survival:**	study type? - retrospective registry analysis study population described (table)? - yes population well-balanced? - no (multivar. analysis with few variables) drop-out reported (consort diagram)? - yes (according to criteria) statistic methods reported? - yes definition of endpoint parameters/ treatment protocol reported? - yes (classification) ITT analysis? - n.a. financial support/conflicts of	2b (multivar. Analyses, with few variables)

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				univariate analysis: worse 5y-RFS with RAI than w/o (90% vs 97%) but not in multivariate analysis (incl. age, sex, T, N, RAI) subgroup analyses: T1/T2 N0/Nx: n=490 (178 vs 312); few events (5y-DSS 100% vs 98%, 5y-RFS 99% vs 100%), not significantly different T1/T2 N1: n=193 (142 vs 51), few events (5y-regional-RFS 93% vs 100%, 5y-distant-RFS 93% vs 100%), not significanty different T3/T4: n=444 (371 vs 73), significant difference in 5y-regional-RFS (+RAI 91% vs 98% -RAI, p=0.019), 5y-distant-RFS not significantly different (both 93%)	interest reported? which? - yes (none)	
Schvartz 2012 (50) *Impact on overall survival of radioactive iodine in low-risk differentiated thyroid cancer*	differentiated thyroid carcinoma n=1,298 PTC: 72% FTC: 28% pat.s with low risk - pT1: 62% - pT2: 38%	adjuvant RAI (in 70% of cohort pat.s) median follow-up 10.3y	retrospective cohort study (2 French registries) (tx between 1975-2004) univariate and multivariate Cox analyses, analyses stratified on propensity score (age, sex, extent of	**cohort group characteristics:** significant differences: +RAI group older, mostly thyroidectomy, less pN0 (47% vs 73%), more papillary (77% vs 62%), less pT1 (59% vs 68%) **overall survival:** unadjusted analysis: 10y OS +RAI 94.6% vs 95.8% -RAI (p<0.01)	study type? - retrospective registry analysis study population described (table)? - yes population well-balanced? - no (but propensity score adjustments) drop-out reported (consort diagram)? - n.a.	2b (adjusted multivar. analyses for hazard ratio)

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
patients.	mean age at dx 46.6y ±14y		surgery, node surgery, histology, pT) tumor staging system: according to ATA and ETA criteria	adjusted on propensity score: not significantly different (p=0.35); adjusted univariate HR=0.75 (95%CI 0.40-1.38) for RAI <u>disease-free survival:</u> unadjusted analysis: 10y DFS +RAI 88.7% vs 93.1% -RAI (p<0.01) adjusted on propensity score: not significantly different (p=0.48). adjusted univariate HR=1.11 (95%CI 0.73-1.70) for RAI "based on multivariate Cox analysis, age and sex were the only two independent prognostic factors associated with DFS and OS. If RAI had a significant and deleterious effect on survival in univariate analysis, this effect disappeared after adjustment was performed on the covariates in the multivariate analysis."	statistic methods reported? - yes definition of endpoint parameters/ treatment protocol reported? - yes (classification) ITT analysis? - n.a. financial support/conflicts of interest reported? which? - yes (none)	
studies on thyroid microcarcinoma						

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
Kwon 2017 (41) *Lack of efficacy of radioiodine remnant ablation for papillary thyroid microcarcinoma : verification using inverse probability of treatment weighting.*	papillary microcarcinoma, n=1,932 pat.s without lateral cervical LN or distant metastasis, undergoing total thyroidectomy [stages: unclear] mean age: 50y	adjuvant RAI (in 85.3% of cohort pat.s) median follow-up 8.3y	retrospective cohort study (Seoul, 1998-2009) weighted regression analysis adjusting for risk factors (age, sex, tumor size, ETE, multifocality, central cervical metastas.) [TNM system: unclear / n.a.]	cohort group characteristics: significant differences: +RAI group larger primary tumor size (0.7 vs 0.5cm), higher percentage of ETE (55% vs 33%), cervical lymph node metastasis (34% vs 4%) recurrence-free survival: univariate analysis: no significant difference [% not reported] adjusted analysis (different models): no association of RAI with RFS (HR 0.90 / 1.03 / 2.02; wide confidence intervals) regression analysis - predictive factors: older age and female gender associated with better RFS; larger primary tumor size, ETE, multifocal tumor, cervical LN metastasis significantly associated with increased recurrence	study type? - retrospective cohort analysis study population described (table)? - yes population well-balanced? - no (but adjusted analyses) drop-out reported (consort diagram)? - yes / n.a. statistic methods reported? - yes definition of endpoint parameters/ treatment protocol reported? - yes ITT analysis? - n.a. financial support/conflicts of interest reported? which? - yes (none)	2b (adjusted multivar. analyses for hazard ratio)

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
Al-Qahtani 2015 (44) *Adjuvant Radioactive iodine 131 ablation in papillary microcarcinoma of thyroid: Saudi Arabian experience [corrected].*	papillary microcarcinoma, n=326 - classic: 81.3% - follicular: 12.6% - tall cell: 3.4% - Hürthle: 2.5% stage I: 66.5% stage III: 29.5% stage IV: 4% mean age at dx 42.6y (±11.6)	adjuvant RAI (in 55.8% of cohort pat.s) median follow-up 8y	retrospective, bicentric study (Riyadh, 2000-2012) multivariate regression analysis to identify prognostic factors tumor staging system: according to AJCC	**cohort group characteristics:** significant differences: +RAI group larger tumor size (0.72 vs 0.44cm); less classic variants; more likely multifocal; higher percentage of ETE, LVSI, surgical margins, LN metastasis, stages III&IV **disease-free survival:** 5y-DFS: +RAI 95.7% vs 92.2% -RAI (unadjusted, p=0.04) 10y-DFS: +RAI 90.9% vs 84% -RAI (unadjusted, p=0.04) multivariate analysis: HR=0.30 (95%CI 0.2-0.8, p<0.001) regression analysis - prognostic factors: histopathologic variants, multifocality, ETE, nodal status, and adjuvant RAI ablation (all p<0.001)	study type? - retrospective cohort analysis study population described (table)? - yes population well-balanced? - no (but multivar. analyses for predictive factors) drop-out reported (consort diagram)? - yes / n.a. statistic methods reported? - yes definition of endpoint parameters/ treatment protocol reported? - yes(stages / classification) ITT analysis? - n.a. financial support/conflicts of interest reported? which? - yes (none)	2b (adjusted multivar. analyses for hazard ratio)
Kim 2013 (49) *Radioactive iodine ablation does not*	papillary microcarcinoma, n=704 pat.s with total thyroidectomy (considered disease-free)	adjuvant RAI (in 82% of cohort pat.s) median follow-up 64mo	retrospective cohort study (Korea, 1994-2004) propensity score included gender, age, tumour size, ETE, cervical LN metastasis	**cohort group characteristics:** significant differences: +RAI group larger primary tumor size, more likely multifocal (37% vs 12%), ETE (53% vs 15%), cervical LN metastasis (28% vs 4%); less stage I (57% vs 89%)	study type? - retrospective cohort analysis study population described (table)? - yes population well-balanced? - no (but multivar. analysis)	2b (adjusted multivar. analyses)

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
prevent recurrences in patients with papillary thyroid microcarcinoma	– low-risk: 32% – interm.risk: 68% (stage I: 63%, III: 23%, IV: 14%) mean age at dx 47y (±11)		and tumor multifocality (TNM) staging according to UICC / AJCC (7th edition)	– *subgroup characteristics reported for intermediate-risk (n=480): hardly significant differences, but very small control group (n=30)* **recurrence-free survival:** – unadjusted analysis, intermediate-risk: not significantly different (p=0.52; n=6 recurrences in +RAI group) – multivariate analysis, all pat.s: not significantly different (p=0.17); intermediate-risk: not significantly different (p=0.79) *[no hazard ratios calculated / reported]*	drop-out reported (consort diagram)? – yes statistic methods reported? – yes definition of endpoint parameters/ treatment protocol reported? – yes (stages / classification) ITT analysis? – n.a. financial support/conflicts of interest reported? which? – yes (none)	
Lin 2009 (51) Survival impact of treatment options for papillary microcarcinoma of the thyroid. Laryngoscope 2009	papillary microcarcinoma, n=7,818 [stages: unclear] mean age at dx 48.6y	adjuvant RAI (in 21.5% of cohort pat.s) [mean follow-up unclear; 5y and 10y survival rates reported]	SEER database (1988-2005) multivariable regression models (variables analyzed: extent of thyroidectomy, use of RAI, age, sex) [TNM system: unclear / n.a.]	**cohort group characteristics:** not shown **overall survival:** univariate analysis: significant benefit of RAI (204.3 vs 197.5mo, p<0.001) multivariate analysis: negative effect of age at dx and male sex, positive effect of RAI tx [no hazard ratios shown]	study type? – retrospective SEER analysis study population described (table)? – no population well-balanced? – unclear drop-out reported (consort diagram)? – no / n.a. statistic methods reported? – yes (brief)	4 (many data missing for assessment)

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	Methodische Bemerkungen	Evidenzlevel
				<u>disease-specific survival:</u> univariate analysis: no significant benefit of RAI (214.6 vs 212.2 months) multivariate analysis: negative effect of age at dx	definition of endpoint parameters/ treatment protocol reported? – no ITT analysis? – n.a. financial support/conflicts of interest reported? which? – yes (none)	

HR < 1 favorisiert RAI

AML = acute myeloid leukemia
CML = chronic myeloid leukemia
DTC = differentiated thyroid carcinoma
IQR = interquartile range
MDS = myelodysplastic syndromes
MM = multiple myeloma
Ph-MPN = myeloproliferative neoplasms
SPM = second primary malignancy
WDTC = well-differentiated thyroid carcinoma

3.9.4.2. Systematische Übersichten/Meta-Analysen

Tabelle 3: Übersicht der eingeschlossenen systematischen Reviews

Referenz	Studie	Gesamt N	+RAI	Endpunkte	Datenquelle	Patientenkohorte
(52)	Zhao 2022	Up to Dec. 2021	·	2874 (8 studies)	60.6%	Recurrence rate

Referenz	Studie	Gesamt N	+RAI	Endpunkte	Datenquelle	Patientenkohorte
(53)	Klain 2021	January 2010 to June 2020	·	6675 total, 3103 in MA (9 studies)	100%	Successful ablation rate
(54)	Verburg 2020	August 2007 to Dec. 2017	·	91,560 (11 studies)	53.8%	Overall survival and disease-free survival
(55)	Piccardo 2020	Updated systematic review, up to Jan. 2020	·	695 (5 studies)	100%	Successful ablation, Response
(56)	Altedlawi 2020	Not reported	·	63,268 (7 studies)	27.9%	DTC-related mortality, overall mortality
(57)	Reinecke 2022	Up to Dec. 2020	·	214,548 (10 studies)	49.3%	Second primary malignancies
(58)	Nappi 2022	Up to May 2021	·	200,247 (14 studies)	49,1%	Primary breast cancer
(59)	Zhang 2021	Up to Nov. 2020	·	125,591 participants (13,811 pregnancies, 7 studies)	-	Spontaneous abortion, induced abortion, preterm birth, stillbirth, congenital malformation
(60)	Piek 2021	Up to January 2020	·	36,981 (22 studies)	57.4% RAI 41.7% TT 0.9% healthy	Amenorrhea, menstrual irregularities, median age at menopause, AMH levels, pregnancy outcomes
(61)	Anagnostis 2021	Up to Dec. 2020	·	154 (4 studies), baseline vs. FU hormone levels	100%	Ovarian reserve (AMH, antral follicle count, FSH)

Referenz	Studie	Gesamt N	+RAI	Endpunkte	Datenquelle	Patientenkohorte
(62)	Adremerinas 2021	2006 -2020	·	2401 (17 studies), RAI only	100%	Sialadenitis Dry mouth Altered taste Xerostomia Dental caries Stomatitis
(63)	Sawka 2008	Review Update 2002 – August 2007	·	total 28 studies; 23 studies in previous review, + 7 in this update, 2 replacing a previous pulication	n.r.	CSM Cancer recurrence LR-recurrence DM

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse			Methodologische Validität (AMSTAR 2)	Evidenz-level
Adramerinas, 2021 (62) *Sialadenitis as a complication of radioiodine therapy in patients*	Studies (any study design) on patients with • surgical treatment of • differentiated thyroid cancer • followed by Adjuvant radioactive iodine (RAI) therapy	PubMed electronic database and related articles function of included publications Search terms: (radioiodine OR radioactive iodine) AND (salivary glands OR xerostomia) English language only		n	Sialadenitis	Other outcomes	AMSTAR-2 rating 1. PICO elements: yes 2. A priori design: No 3. Justification for design: No 4. Literature search >= 2 databases, search	2a
			Walter 2007	176	24.4%	44.3% xerostomia 24.4% caries & tooth extraction		
			Aktas 2008	30 (10 RF, 20 no RF)	n.r.	6/10 persistent xerostomia 2/20 transient xerostomia		
			Silberstein 2008	60	4/60	11 stomatitis 3 dysgeusia		
			Grewal 2009	262	16% swelling, 6% pain	17% dry mouth 13% altered taste >2 mo		

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse			Methodologische Validität (AMSTAR 2)	Evidenz-level
with thyroid cancer: where do we stand? Systematic Review without meta-analysis		March 2006 to September 2020	Almeida 2011	182	2.8%	15.6% taste alteration	strategy + other sources: no, 1 dabase only 5. Selection in duplicate: yes 6. Data extraction in duplicate: No 7. List of excluded studies: No 8. sufficient detail on studies: Partly 9. RoB assessed: no 10. Funding of incl. studies: no 11. MA appropriate: N.A. 12. RoB considered in	
			An 2013	118	34% acute 10.2% chronic	n.r.		
			Jeong 2013	213	n.r.	16.4% xerostomia		
			Rosario 2013	148	n.r.	5.4% oral symptoms		
			Lee 2015	164	24.4%	25% xerostomia		
			Wu 2015	368	3.13 – 8.59%	43.7% xerostomia (4 mo) 7.8% taste alteration 4.7% dental caries		
			Hesselink 2016	67	n.r.	34% decreased stimulated whole saliva flow rate		
			Hollingsworth 2016	143/216	25.9%	Xerostomia sign. Higher in RAI patuents than non-RAI		
			Lu 2016	117	12.9%	3.5% xerostomia		
			Iakovou 2016	121 (61 rTSH, 60 LT4 withdrawal)	33% acute 12% chronic	0.016% xerostomia in rhTSH 22% xerostomia in LT4 withdrawal		
			Daniel 2017	37	n.r.	41.7% xerostomia 11.1% dysphagia 11.1% taste alteration		
			Selvakumar 2018	65	n.r.	35.5% xerostomia		
			Riachy 2020	174	20.1	n.r.		

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse	Methodologische Validität (AMSTAR 2)	Evidenz-level
			7 retrospective 7 prospective 1 cross-sectional 1 NRSI	Conclusion: RAI-induced sialadenitis in patients with differentiated thyroid cancer, involving acute or chronic salivary gland inflammation and dysfunction, is common and has a considerable impact on their quality of life.	MA: N.A. 13. RoB in interpretation: no 14. Heterogeneity explained: no 15. Publication bias imvestigated: N.A. 16. Sources of CoI: none AMSTAR-2 score: 3.5/14	

Altedlawi 2021 (56) *Radioactive iodine following total thyroidectomy is comparable to lobectomy in low/intermediate-risk differentiated thyroid carcinoma: a meta-analysis* Systematic review with meta-analysis	Sudies on • adult humans • differentiated thyroid carcinoma • low and intermediate risk • published in English • observational and randomised studies	PubMed, Cochrane Library, EBSCO, and Google Scholar databases The keywords used were "differentiated thyroid carcinoma", "low/intermediate risk", "radioactive iodine following total thyroidectomy", "total thyroidectomy versus lobectomy and RAI", "remnants ablation", "recurrence", "survival rate", "tumor-specific cancer death", "overall mortality", and "tumorspecific mortality"	5 retrospective and 2 prospective studies Zhang 2017 Doi 2010 Hurtado-Lopez 2011 Ruel 2015 Súss 2018 Kim 2016 Wang 2020	**Overall survival and recurrence, pooled fixed effects estimate** RAI: 2466/45,608 No RAI: 848/17,660 Odds ratio: 1.13 (0.73 to 1.73)	AMSTAR-2 rating 1. PICO elements: yes 2. A priori design: No 3. Justification for design: No 4. Literature search >= 2 databases, search strategy + other sources: partly, multiple databases, but no search date reported 5. Selection in duplicate: yes 6. Data extraction in duplicate: No 7. List of excluded studies: No 8. sufficient detail on studies: Partly 9. RoB assessed: reported in methods, but not reported 10. Funding of incl. studies: no 11. MA appropriate: no* 12. RoB considered in MA: no 13. RoB in interpretation: no 14. Heterogeneity explained: no 15. Publication bias imvestigated: yes funnel plot 16. Sources of CoI: none	2a

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse	Methodologische Validität (AMSTAR 2)	Evidenz-level
					AMSTAR-2 score: 4.5/16 Additional notes MA a) the authors analysed recurrence and survival together b) fixed effects model used due to heterogeneity?	

Anagnostis 2021 (61) *Decline in anti-Müllerian hormone concentrations following radioactive iodine treatment in women with differentiated thyroid cancer: A systematic review and meta-analysis* Systematic review with meta-analysis	Studies on • premenopausal women with or without a history of DTC • administration of a single RAI dose • Comparison: self-comparison or independent controls (either healthy controls or patients with a history of low-risk DTC, not necessitating RAI treatment) • studies providing extractable data for at least one index of ovarian reserve • assessment of ovarian reserve within 12 months after RAI administration.	PubMed, Cochrane and Scopus through December 6th, 2020 Search string not accessible.	Van Velsen 2020 Rosario 2005 Evranos 2018 Yaish 2018 Follow-up: between 3.7 ± 3.3 to 15.9 ± 4.7 years	**AMH change** (3 studies, n = 104) following a single RAI dose compared with baseline: At 3 months: WMD = −1.66, 95% CI −2.42 to −0.91, p<0.0001; I2 = 0% At 6 months: (WMD = −1.58, 95% CI −2.63 to −0.52, p=0.003; I2 = 54.7% At 12 months: WMD −1.62 ng/ml, 95% CI −2.02 to −1.22, p<0.0001; I2 = 15.5% • AMH was reduced compared with baseline **FSH concentrations (**2 studies, n = 83) post-RAI At 6 months: WMD = 3.29 IU/l, 95% CI −1.12 to 7.70, *p*=0.14; I2 = 96.8% At 12 months: WMD = 0.13 IU/l, 95% CI −1.06 to 1.32, *p*=0.83; I2 =55.2% • no difference to baseline **AFC**: no data available	AMSTAR-2 rating 1. PICO elements: yes 2. A priori design: yes 3. Justification for design: No 4. Literature search >= 2 databases, search strategy + other sources: yes, multiple databases, grey literature, etc. 5. Selection in duplicate: yes 6. Data extraction in duplicate: No 7. List of excluded studies: yes 8. sufficient detail on studies: yes 9. RoB assessed: NOS, appendix 10. Funding of incl. studies: no 11. MA appropriate: yes 12. RoB considered in MA: no 13. RoB in interpretation: no 14. Heterogeneity explained: N.A. 15. Publication bias imvestigated: no 16. Sources of CoI: none AMSTAR-2 score: 8.5/14	2a

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse	Methodologische Validität (AMSTAR 2)	Evidenz-level
Klain 2021 (53) *Ablation rate after radioactive iodine therapy in patients with differentiated thyroid cancer at intermediate or high risk of recurrence: a systematic review and a meta-analysis.* Systematic review with meta-analysis	Studies including • total thyroidectomy with or without lymph node dissection for differentiated thyroid cancer (DTC) • at intermediate-high risk of recurrence • RAI administration • Adults only • >=100 patients • Follow-up >= 1 year	PubMed and Embase (conflicting information abstract vs. main text) English January 2010 to June 2020 "differentiated thyroid cancer" OR "DTC", "thyroid neoplasm", "prognosis", "outcome", "follow-up", "radioactive iodine therapy" OR "RAI therapy", "I-131 ablation", "thyroglobulin" OR "Tg".	9 studies: Caminha 2013 Han 2014 Verburg 2014 Jeon 2014 Rosario 2015 Jeong 2017 Llamas-Olier 2018 Avram 2019 Kim 2019	Mean follow-up was 4.7 ± 1.5 years **Ablation rate (successful ablation [SA]** All 9 studies, n = 3103 The SA rate in the studies ranged from 51 to 94%, pooled result 71% (95% CI 59 to 83), I^2 = 98.58% (p<0.001), no publication bias intermediate-risk patients, 7 studies, n = 1939 SA rate ranged from 51 to 94%, and the pooled SA rate was 76% (95% CI 61-86) high-risk patients, 4 studies, n = 814 SA rate ranged from 18 to 78%. The pooled SA rate was 62% (95% CI 44-77) The relative ratio of intermediate-risk patient over high-risk patient SA rates was 1.22 (95% CI 1.05-1.42, P = 0.008) late follow-up (mean 6.4 ± 1.4 years), 4 studies, n = 656 intermediate risk patients • Recurrence rate after SA ranged from 0 to 7% and the pooled recurrent disease rate was 2% (95% CI 0-5) • recurrences were observed in 18/121 intermediate-risk patients who did not achieve an SA at the first control, pooled rate = 14%.	AMSTAR-2 rating 1. PICO elements: yes 2. A priori design:Yes 3. Justification for design: No 4. Literature search >= 2 databases, search strategy + other sources: yes 5. Selection in duplicate: yes 6. Data extraction in duplicate: probably 7. List of excluded studies: No 8. sufficient detail on studies: Partly 9. RoB assessed: yes, JBI critical appraisal tool 10. Funding of incl. studies: no 11. MA appropriate: yes 12. RoB considered in MA: N.A. 13. RoB in interpretation: N.A. 14. Heterogeneity explained: yes 15. Publication bias imvestigated: yes, Egger's test and funnel plot 16. Sources of CoI: none	2a

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse	Methodologische Validität (AMSTAR 2)	Evidenz-level
					AMSTAR-2 score: 10.5/14	
Nappi 2021 (58) *Risk of primary breast cancer in patients with differentiated thyroid cancer*	Studies included: • studies reported the risk of primary breast cancer • in patients with DTC • treated with RAI and patients not treated with RAI; • studies reported an estimate of relative risk (RR) with respective 95% confidence interval (CI).	PubMed and Embase (conflicting information abstract vs. main text) English until May 2021 "differentiated thyroid cancer" [All fields] OR "DTC" [All fields] OR "thyroid cancer" OR "thyroid carcinoma" OR "thyroid neoplasm" OR "papillary	14 studies: Hall 1991 Dottorini 1995 Adjadj 2003 Rubino 2003 Bhattacharyya 2006 Lang 2012 Ahn 2015 De Souza 2015 Kuo 2015 Hirsch 2016 Lin 2016 Silva-Vieira 2017	Total 200,247 patients included; RAI: 98,368 No RAI: 101,879 **primary breast cancer** in DTC patients treated with RAI to those not treated with RAI among studies • RR ranged from 0.45 to 2.55 • pooled RR 0.83 (95% CI, 0.70–0.99), heterogeneity 71.5% ($P < 0.001$; random effects model)	AMSTAR-2 rating 1. PICO elements: yes 2. A priori design: probably yes 3. Justification for design: No 4. Literature search >= 2 databases, search strategy + other sources: yes 5. Selection in duplicate: yes 6. Data extraction in	2a

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse	Methodologische Validität (AMSTAR 2)	Evidenz-level
undergoing radioactive iodine therapy: a systematic review and meta-analysis. Systematic review with meta-anaylsis	• the length of follow-up for the development of primary breast cancer in thyroid cancer patients treated and not treated with RAI was at least 2 years	thyroid carcinoma" OR "follicular thyroid carcinoma" [MeSH terms] AND "breast carcinoma" OR "breast tumor" [MeSH terms] AND "second primary malignancy" OR "SPM" [MeSH terms] AND "radioiodine therapy" OR "radioactive iodine therapy" OR "RAI therapy" [All fields].	Drozd 2020 Mei 2021		duplicate: probably 7. List of excluded studies: No 8. sufficient detail on studies: Partly 9. RoB assessed: yes, NOS 10. Funding of incl. studies: no 11. MA appropriate: yes 12. RoB considered in MA: no 13. RoB in interpretation: no 14. Heterogeneity explained: no 15. Publication bias imvestigated: yes, Egger's test and funnel plot 16. Sources of CoI: none AMSTAR-2 score: 8.5/16	
Piccardo 2020 (55) *Radioiodine ablation of remaining thyroid lobe in patients*	Studies on • radioactive iodine (131I) therapy • in DTC patients who require a completion treatment after lobectomy • intermediateto • high-risk DTC • no further criteria listed (any stage, any	PubMed, Cochrane Central Register of Controlled Trials, Scopus, and Web of Science were searched; PubMed/ MEDLINE, Embase, Web of Science, and Scopus; until January 31, 2020; no language restriction; the references of the articles retrieved were screened.	5 studies: Randolph 2002 Hoyes 2004 Bal 2006 Santra 2011 Giovanella 2013	<u>One-year response to initial therapy (Surgey plus 131 Iodine)</u> Randolph 2002, CR: 76%; incomplete BCR: 24%, incomplete structural response: 0% Hoyes 2004: CR: 82%, incomplete BCR: 18%, incomplete structural response: 0% Bal 2006: NR Santra 2011; incomplete structural response: 3.8% Giovanella 2013: treated with 1.1 GBq: CR 76%, incomplete BCR: 24%, incomplete structural response: 0% treated with 3.7 GBq: CR 92%, BCR 8%	<u>AMSTAR-2 rating</u> 1. PICO elements: no 2. A priori design: no 3. Justification for design: No 4. Literature search >= 2 databases, search strategy + other sources: partly 5. Selection in duplicate:	2a

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse	Methodologische Validität (AMSTAR 2)	Evidenz-level
with differentiated thyroid cancer treated by lobectomy: A systematic review and metaanalysis Systematic review with meta-analysis	age, etc.) • any study design			**Pooled rate of successful ablation:** 69% (heterogeneity I2 =85%, no publication bias) **Neck pain:** 15%, 18% in two studies, and 50.7% (1.1 GBq) and 66% (3.7 GBq) in a third study.	yes 6. Data extraction in duplicate: yes 7. List of excluded studies: No 8. sufficient detail on studies: Partly 9. RoB assessed: partly 10. Funding of incl. studies: no 11. MA appropriate: no 12. RoB considered in MA: no 13. RoB in interpretation: no 14. Heterogeneity explained: no 15. Publication bias imvestigated: yes 16. Sources of CoI: none AMSTAR-2 score: 5.5/16	
Piek 2021 (60) *The effect of radioactive iodine therapy on ovarian function and fertility in*	Studies on • young adult women • who underwent treatment for DTC in their fertile years • total thyroidectomy followed by RAI therapy • comparison: total thyroidectomy or healthy women • ovarian reserve,	Pubmed, Embase, and Web of Science on the 5th of January 2020. Keywords: thyroid carcinoma, thyroid tumor, thyroid papillary carcinoma, thyroid neoplasms, thyroid cancer and RAI, iodine, radioisotope, iodine radioisotopes, 131I and fertility, Mullerian inhibiting factor, follicle stimulating	22 studies: Acibucu Anderson Azem Balenovic Bal Brandao Ceccarelli Chow Dottorini Evranos	**Menstrual irregularities in first year after RAI:** RAI: 12 up to 31% of patients **Amenorrhea in first year after RAI:** RAI: 8 to 16% **Median age at menopause:** RAI 49.5 years Control 51 years **AMH** between before and 1 year after RAI (meta-analysis of 4	AMSTAR-2 rating 1. PICO elements: yes 2. A priori design: no 3. Justification for design: No 4. Literature search >= 2 databases, search strategy + other sources: yes 5. Selection in duplicate: yes	2a

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse	Methodologische Validität (AMSTAR 2)	Evidenz-level
female thyroid cancer patients: a systematic review and meta-analysis. Systematic review with meta-analysis	ovarian function, AMH levels, fertility, menstrual cycle disorders, menopause, and pregnancy outcomes	hormone, gonadotropins, follitropin, infertility, pregnancy, spontaneous abortion, menstrual cycle, and menstruation disorder (full strategy in appendix)	Fard-Esfahani Giusti Ko Metallo Mittica Sioka Sarkar Smith Vini Wu Yaisch Van Velsen	studies, n=178), Mean difference: 1.50 (95% CI 0.82 to 2.17), I2 = 56% Pooled AMH levels after RAI, Mean raw: 1.79 (95% CI 1.47 to 2.10, 7 studies) **Pregnancy rates** OR 0.98 (95% CI 0.72 to 1.33, p = .909), I2 = 92%, 4 studies	6. Data extraction in duplicate: yes 7. List of excluded studies: No 8. sufficient detail on studies: Partly 9. RoB assessed: yes 10. Funding of incl. studies: no 11. MA appropriate: yes 12. RoB considered in MA: NA 13. RoB in interpretation: NA 14. Heterogeneity explained: partly 15. Publication bias imvestigated: no 16. Sources of CoI: none AMSTAR-2 score: 8/16	
Reinecke 2022 (57) *Second primary malignancies induced by radioactive iodine treatment of*	• thyroid cancer survivors who were treated with RAI therapy, compared to survivors treated with surgery alone • mean age at DTC diagnosis, from 39.8 to 49.0 years • number of participants per study ranged from 895-148,215	Ovid MEDLINE, Ovid MEDLINE and In-Process & Other Non-Indexed Citations, Ovid MEDLINE Epub Ahead of Print, Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed (May 2020-Dec 2020) Keywords: "thyroid cancer" combined with "second primary cancer"	Ten articles: Rubino, 2003 Khang, 2015 Hirsch, 2016 Silva-Vieira, 2017 Brown, 2008 Lang, 2007 Hakala, 2016 Teng, 2016 Fallahi, 2011 Molenaar, 2018	**Second primary malignancies;** RAI vs. No RAI **Rubino:** RR for SPM 1.2 [95% CI: 1.0-1.4] and RR for SHM: 2.5 [95% CI: 1.0-7.4] **Khang:** OR for SPM: 1.14 [95% CI: 0.67-1.92] **Hirsch**: HR for SPM 1.27 [95% CI: 0.88-1.82] **Silva-Vieira**: RR for SPM: 1.84 [95% CI: 1.02-3.31] **Hakala:** RR for SPM: 1.04 [95% CI: 0.83-1.32] vs. RR for SPM: 1.49 [95% CI: 0.96-2.30] **Teng**: HR for SPM: 1.01 [95% CI: 1.00-1.02] **Fallahi:** n.a. **Molenaar:** SIR for SHM: 1.30 [95% CI: 1.12-1.51]	AMSTAR-2 rating 1. PICO elements: yes 2. A priori design: yes 3. Justification for design: No 4. Literature search >= 2 databases, search strategy + other sources: yes 5. Selection in duplicate: yes 6. Data extraction in	sa

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse	Methodologische Validität (AMSTAR 2)	Evidenz-level
differentiated thyroid carcinoma – a critical review and evaluation of the existing evidence. Systematic review without meta-analysis				RAI vs. General population **Brown:** SIR for SPM: 1.23 [95% CI: 1.04–1.45] vs. SIR for SPM: 1.04 [95% CI: 0.9–1.2] **Lang:** SIR for SPM: 1.51 [95% CI: 1.14–1.96] vs. SIR for SPM: 0.84 [95% CI: 0.36–1.66] Summary: Effect of RAI relative to No RAI: 1.14 to 1.84 for the occurrence of SPM.	duplicate: yes 7. List of excluded studies: No 8. sufficient detail on studies: Partly yes 9. RoB assessed: yes 10. Funding of incl. studies: yes 11. MA appropriate: No MA 12. RoB considered in MA: No MA 13. RoB in interpretation: yes 14. Heterogeneity explained: yes 15. Publication bias investigated: n.a 16. Sources of CoI: none AMSTAR-2 score: 10/14	
Verburg 2020 (54) *Differentiated thyroid cancer patients potentially benefitting from postoperat*	Patients with DTC who underwent postoperative RIT vs. patients with DTC who treated by surgery alone Number of included patients ranges from n=326 to n= 32119	Medline and Cochrane Library (August 2007–December 2017) search terms: "differentiated thyroid cancer" and "radioiodine therapy" amended by specific terms for recurrence/disease-free survival or overall and/or	11 studies: Kwon, 2017 Yang, 2017 Zhang, 2017 Al-Qahtani, 2015 Carhill, 2015 Kiernan, 2015 Ruel, 2015 Nixon, 2013 Kim, 2013 Schvartz, 2012 Lin, 2009	**For studies on microcarcinoma** Al-Qahtani (microcarcinoma) **5y-Disease-free survival:** RAI: 95.7% No RAI: 92.2% **10y-Disease-free survival** RAI: 90.9% No RAI: 84% multivarble analysis: HR=0.30 (95%CI 0.2–0.8, p<0.001) Lin (microcarcinoma, n=7818) **Overall survival:** RAI: 204.3 months	AMSTAR-2 rating 1. PICO elements: yes 2. A priori design: no 3. Justification for design: no 4. Literature search >= 2 databases, search strategy + other sources: partial yes 5. Selection in duplicate: yes 6. Data extraction in	2a

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse	Methodologische Validität (AMSTAR 2)	Evidenz-level
ive I-131 therapy: a review of the literature of the past decade. Systematic review without meta-analysis		cancer-specific survival Included: systematic reviews, RCT's or cohort studies		No RAI: 197.5 months, p<.001 **Disease-specific survival:** RAI: 214.6 months No RAI: 212.2 months, p>.05 Kim (microcarcinoma, n = 740) no significant difference in recurrence-free survival [no HR calculated/ reported] Kwon (microcarcinoma, n = 1932) no significant difference in recurrence-free survival [% not reported] **Studies on Non-microcarcinoma without metastases** Zhang (n=8601) **5y-Overall survival:** RAI : 96.8% No RAI : RAI 95.0% **10y-Overall survival:** RAI : 92.2% No RAI: 89.8% **5y-Cancer-specific survival:** RAI: 99.2% No RAI: 98.8% **10y-Cancer-specific survival :** RAI 97.8% No RAI 98.2% Carhill (n=4941) Overall survival: significant positive determinant in stage IV disease Disease-specific survival: n.r. Ruel (n=21,870)	duplicate: no 7. List of excluded studies: No 8. sufficient detail on studies: no 9. RoB assessed: no 10. Funding of incl. studies: yes 11. MA appropriate: No MA 12. RoB considered in MA: No MA 13. RoB in interpretation: yes 14. Heterogeneity explained: no 15. Publication bias investigated: no MA 16. Sources of CoI: yes AMSTAR-2 score: 5/14	

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse	Methodologische Validität (AMSTAR 2)	Evidenz-level
				Overall survival: RIT was associated with a 29% reduced risk of death Kiernan (n=32,119) **5y-overall survival:** RAI: 97% No RAI: RAI 95% **10y-overall survival:** RAI: 91% No RAI: 89% HR=0.53, 95%CI 0.38-0.72 in +RAI Nixon no effect of RAI; **5y-Disease-specific survival** RAI 99% No RAI: 100% (p=0.821) **5y- Recurrence-free survival** RAI: 90% No RAI 97%; worse for RAI, but not in multivariate analysis Schvartz (n=1298) no beneficial effect of RIT on either Overall survival or disease-free survival *10y- overall survival: adjusted on propensity score: not significantly different (p=0.35); adjusted univariate HR=0.75 (95%CI 0.40-1.38) for RAI *10y disease -free survival: adjusted on propensity score: not significantly different (p=0.48). adjusted univariate HR=1.11 (95%CI 0.73-1.70) for RAI *differing results for unadjusted results		

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse	Methodologische Validität (AMSTAR 2)	Evidenz-level
				Studies on patients with distant metastases Yang PTC cohort (histological subgroups) **5y mortality:** RAI: 11.0% No RAI: 22.7% **10y mortality:** RAI: 14.0% No RAI: 25.5% *FTC cohort (histological subgroups)* 5y mortality: +RAI 29.2% vs. -RAI 45.5% 10y mortality: +RAI 36.8% vs. -RAI 51%		
Zhang 2021 (59) *The effect of I-131 therapy on pregnancy outcomes after thyroidectomy in patients with differentiated thyroid carcinoma: a meta-analysis.*	Female and pregnant DTC patients w/ or w/o postoperative RAI treatment in total: 125,591 (N) and 13,811 pregnancies	PubMed, Embase, Cochrane Library, CNKI, and VIP by November, 2020 keywords: differentiated thyroid cancer, thyroid carcinoma, thyroid neoplasm, radioiodine, I-131, 131I, pregnancy outcomes, reproduction, fertility, abortion, preterm birth, and congenital malformation	7 studies included Dottorini, 1995 Schlumberger, 1996 Chow, 2004 Garsi, 2008 Fard-Estahani, 2009 Ko, 2016 Kim, 2019	**Spontaneous abortion** Dottorini; Schlumberger; Chow; Garsi; Fard-Estahani; Ko RAI: 228 spontaneous abortions /1825 pregnancies Non-RAI:126 spontaneous abortions /1144 pregnancies OR = 1.05, 95% CI 0.82-1.33, P= 0.70 **Induced abortion** Schlumberger; Chow; Garsi; Fard-Estahani RAI: 190 induced abortions / 983 pregnancies Non-RAI: 67 induced abortions / 408 pregnancies OR= 1.06, 95% CI 0.57-1.98, P= 0.859 **Abortion** Schlumberger; Chow; Garsi; Fard-Estahani; Kim OR = 1.07, 95% CI 0.99-1.15, P= 0.098 **Preterm birth** Dottorini; Schlumberger; Chow; Ko; Kim RAI: 489 preterm birth/ 5611 pregnancies Non-RAI: 562 preterm birth/ 6327 pregnancies	AMSTAR-2 rating 1. PICO elements: yes 2. A priori design: no 3. Justification for design: no 4. Literature search >= 2 databases, search strategy + other sources: yes 5. Selection in duplicate: yes 6. Data extraction in duplicate: yes 7. List of excluded studies: No 8. sufficient detail on studies: partial yes 9. RoB assessed: partial yes	2a

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse	Methodologische Validität (AMSTAR 2)	Evidenz-level
Endocrine. Systematic review with meta-analysis				OR = 1.02, 95% CI 0.90-1.16, P = 0.756 **Stillbirth(s)** Schlumberger; Chow; Garsi RAI: 7 stillbirths /859 pregnancies Non-RAI: 3 stillbirths /307 pregnancies OR= 0.58, 95% CI 0.18-1.88, P= 0.364 **Congenital malformation (cm)** Dottorini; Schlumberger; Garsi; Fard-Estahani; Kim RAI: 302 congenital malformation/ 5851 pregnancies Non-RAI: 353 congenital malformation/ 6276 pregnancies OR= 1.00, 95% CI 0.85-1.17, P = 0.986 **Cumulative RAI dose and pregnancy outcomes** Schlumberger; Garsi; Kim Cumulative RAI dose >3.7 GBq or <3.7 GBq : Effect on abortion OR = 0.94, 95% CI 0.84-1.05, P= 0.252 Effect on conginetal malformation OR = 1.05, 95% CI 0.83-1.32, P= 0.752 **Interval time and abortion (a)** Schlumberger; Chow; Garsi; Kim Interval >1 year: 1312 abortions /3092 pregnancies Interval <1 year: 554 abortions /783 pregnancies OR = 0.60, 95% CI 0.53-0.68, P = 0.000	10. Funding of incl. studies: no 11. MA appropriate: yes 12. RoB considered in MA: yes 13. RoB in interpretation: no 14. Heterogeneity explained: no 15. Publication bias investigated: yes 16. Sources of CoI: yes AMSTAR-2 score: 10/16	
Zhao 2022 **(52)** *Radioactive Iodine Ablation Can*	PTMC patients with low-risk and intermediate risk w/ or w/o RAI treatment after TT/NT	Database PubMed, Embase, and Cochrane library through December 2021 keywords "remnant ablation" OR	8 included studies Xue, 2017 Kim and Kim, 2013 Creach, 2012 Neuhold, 2011 Moon, 2011	Any recurrence in LR - IR PTMC patients Chow, 2003; Kim, 2008; Durante, 2010; Neuhold, 2011; Creach, 2012; Moon, 2011; Kim, 2013; Xue, 2017 (RR 0.56, 95% CI 0.19-1.70, P= 0,31) Locoregional recurrence in LR - IR PTMC patients Chow, 2003; Kim, 2008; Durante, 2010; Neuhold, 2011;	AMSTAR-2 rating 1. PICO elements: yes 2. A priori design: yes 3. Justification for design: yes 4. Literature search >= 2	2a

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse	Methodologische Validität (AMSTAR 2)	Evidenz-level
Reduce the Structural Recurrence Rate of Intermediate-Risk Papillary Thyroid Microcarcinoma (PTMC): A Meta-Analysis Systematic review with meta-analysis		"radioiodine" OR "radioactive iodine" OR "iodine 131"OR "iodine-131" OR "RAI" AND "papillary thyroid microcarcinoma" OR "papillary microcarcinoma" OR "thyroid microcarcinoma" OR "PTMC" <u>Inclusion criteria</u> English; Low-risk (LR) and Intermediate-risk (IR) PTMC patients who are in a diseasefree state after Total thyroidectomy (TT) /Neartotal thyroidectomy (NT); RAI vs. Non-RAI, reporting outcome of cancer recurrence	Durante, 2010 Kim, 2008 Chow, 2003	Moon, 2011; Kim, 2013; Xue, 2017 <u>(RR 0.79, 95% CI 0.22 – 2.78, P= 0.72)</u> <u>Patients with intermediate-risk PTMC</u> Chow, 2003; Moon, 2011; Kim, 2013 (RR 0.23, 95% CI 0.11-0.49, P =0,0001) <u>Patients with risk factors for lymph node metastasis</u> Chow, 2003; Kim, 2013; Xue, 2017 (RR 0.22, 95% CI 0.10-0.49, P =0,0002) <u>Patients with microscopic extrathyroidal extension</u> Moon, 2011; Kim, 2013; Xue, 2017 (RR 0.21, 95% CI 0.07-0.65, P =0,007) <u>Patients with multifocality</u> Kim, 2013; Xue, 2017 (RR 0.15, 95% CI 0.04-0.53, P =0,003)	databases, search strategy + other sources: yes 5. Selection in duplicate: yes 6. Data extraction in duplicate: yes 7. List of excluded studies: No 8. sufficient detail on studies: partial yes 9. RoB assessed: partial yes 10. Funding of incl. studies: no 11. MA appropriate: yes 12. RoB considered in MA: no 13. RoB in interpretation: no 14. Heterogeneity explained: yes 15. Publication bias investigated: yes 16. Sources of CoI: yes AMSTAR-2 score: 12/16	
Sawka 2008 (63) *An updated systematic*	studies (RCTs or cohort studies) on adult patients with - well differentiated thyroid cancer (papillary, follicular or follicular variant of	updated search for the time period spanning from the prior review (original search in late 2002) until August 2007. databases searched: Medline and other	all studies in the original systematic review: n=21, plus n=7 additional, new studies (no long-term randomized,	systematic review of studies with adjustment for prognostic factors (no meta-analysis due to heterogenity): - 3 out of 12 adjusted studies observed a significant benefit of RRA on the risk of thyroid cancer-related mortality - 3 out of 6 adjusted studies observed a significant benefit of	1. a priori Design? – yes (update of prior syst. review) 2. selection and extraction by two independent reviewers? – yes	2a

Referenz/ Studientyp	Population	Suchstrategie, Einschlusskriterien	Eigeschlossene Studien	Ergebnisse	Methodologische Validität (AMSTAR 2)	Evidenz-level
review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer.	papillary) - surgical treatment involving bilateral resection, (total, near-total, or subtotal thyroidectomy - radioactive iodine ablation within 1yr after the operation - median or mean follow-up period of at least 5 years - reporting outcomes of any cancer-related deaths, cancer recurrence, local-regional recurrence in the thyroid bed or regional lymph nodes, or distant metastases (all at 10 years for data unadjusted for prognostic factors or interventions)	nonindexed citations, the Cochrane Database for Systematic Reviews, Database of Abstracts and Reviews, the Controlled Clinical Trials Database, American College of Physicians Journal Club, the Cochrane Clinical Trials Registry, Embase	controlled trials examining thyroid cancer-related outcomes after RRA identified --> restricted to observational data)	RAI on the risk of any thyroid cancer recurrence - significant benefit of RAI on distant metastatic recurrence in 2 adjusted studies with papillary pat.s but not in 1 study with exclusively follicular pat.s meta-analysis of pooled studies without adjustments: (- no data on mortality / survival reported) - statistically significant heterogeneity of RRA on the outcome of any recurrence, precluding meaningful estimation of an overall treatment effect "Upon carefully examining the best existing long-term observational evidence, the authors could not confirm a significant, consistent, benefit of RRA in decreasing cause specific mortality or recurrence in early stage WDTC. RRA use was associated with a significantly decreased risk of distant metastases; however, this event was relatively rare in papillary cancer. The relatively low risk of thyroid cancer-related death in early stage thyroid carcinoma patients may limit the ability to prove a significant treatment benefit for this outcome."	3. literature search min 2 databases + 1 add.source? - yes (5 db + DARE + Cochrane Clin.Trials db) 4. grey literature incl. - no 5. full list of incl. and excl. studies? - no 6. details of incl. studies? - yes 7. quality of incl. studies assessed? - no 8. reference to method. quality in conclusion? - no 9. heterogenity assessed?- yes 10. publication bias assessed (funnel plot)? - no 11. CoI / funding for review and all studies reported? - no AMSTAR score 5/11	

Abbreviations:
Outcomes: OS: overall survival; EFS: event-free survival; CSM: cause-specific mortality; TRR: tumor recurrence rate; LRR: locoregional recurrence rate; DM: distant metastases
Methods & estimates: HR: Hazard ratio; RR: Risk ratio; ITT: intention-to-treat; PP: per protocol; RCT: randomized controlled trial;
Other: Ctrl: control; BT: bilateral thyroidectomy; GBq: Gigabecquerel; RRA: radioiodine remnant ablation Tg: Thyroglobulin; Tg-Ab: Thyroglobulin Antibody

***HR < 1 favorisiert RAI**

3.9.1. GRADE-Tabelle

Summary of Findings:

Radioiodtherapie verglichen mit Therapie ohne Radioiod bei Schilddrüsenkarzinom

Patient oder Population: Schilddrüsenkarzinom
Setting:
Intervention: Radioiodtherapie
Vergleich: Therapie ohne Radioiod

Endpunkte	Erwartete absolute Effekte* (95% CI)		Relativer Effekt (95% CI)	№ der Teilnehmer (Studien)	Certainty of the evidence (GRADE)	Kommentare
	Risiko mit Therapie ohne Radioiod	Risiko mit Radioiodtherapie				
Gesamtüberleben pT1a	**Moderat**		**HR 0.585** (0.514 bis 0.666) []	32396 (1 non-randomised study)	⨁⨁◯◯ Niedrig[a]	Radioiodtherapie könnte keinen bis einen leicht positiven Effekt auf das Gesamtüberleben haben, weitere Kohortenstudien bestätigen das Ergebnis
	985 pro 1.000	**991 pro 1.000** (990 bis 992)				
Gesamtüberleben pT1b	**Moderat**		**HR 0.396** (0.347 bis 0.452) []	25204 (1 non-randomised study)	⨁⨁◯◯ Niedrig[a]	Radioiodtherapie könnte das Gesamtüberleben leicht erhöhen, weitere Kohortenstudien bestätigen das Ergebnis
	960 pro 1.000	**984 pro 1.000** (982 bis 986)				
Gesamtüberleben pT2	**Moderat**		**HR 0.363** (0.313 bis 0.420) []	17422 (1 non-randomised study)	⨁⨁◯◯ Niedrig[a]	Radioiodtherapie könnte das Gesamtüberleben leicht erhöhen, weitere Kohortenstudien bestätigen das Ergebnis
	955 pro 1.000	**983 pro 1.000** (981 bis 986)				
Gesamtüberleben pT3	**Moderat**		**HR 0.55** (0.49 bis 0.61) []	31677 (1 non-randomised study)	⨁⨁◯◯ Niedrig[a]	Radioiodtherapie könnte das Gesamtüberleben erhöhen, weitere Kohortenstudien bestätigen das Ergebnis
	910 pro 1.000	**949 pro 1.000** (944 bis 955)				
Gesamtüberleben pT4	**Moderat**		**HR 0.42** (0.37 bis 0.48) []	5718 (1 non-randomised study)	⨁⨁◯◯ Niedrig[a]	Radioiodtherapie könnte das Gesamtüberleben erhöhen, weitere Kohortenstudien bestätigen das Ergebnis
	750 pro 1.000	**886 pro 1.000** (871 bis 899)				
	7 pro 1.000	**8 pro 1.000** (6 bis 9)				

Summary of Findings:

Radioiodtherapie verglichen mit Therapie ohne Radioiod bei Schilddrüsenkarzinom

Patient oder Population: Schilddrüsenkarzinom
Setting:
Intervention: Radioiodtherapie
Vergleich: Therapie ohne Radioiod

Endpunkte	Erwartete absolute Effekte* (95% CI)		Relativer Effekt (95% CI)	№ der Teilnehmer (Studien)	Certainty of the evidence (GRADE)	Kommentare
	Risiko mit Therapie ohne Radioiod	**Risiko mit Radioiodtherapie**				

*__Das Risiko in der Interventionsgruppe__ (und das 95% Konfidenzintervall) basiert auf dem vermuteten Risiko in der Vergleichsgruppe und der **relativen Wirkung** der Intervention (und dem 95% KI).

CI: confidence interval; **HR:** hazard Ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. nicht konsekutiv
b. kleine Fallserien mit unterschiedlichen Pat. charketeristika und Ergebnissen
c. Geburtenrate selten berichtet, stattdessen AMH
d. sehr kleine Fallzahlen
e. geringe Anzahl an absoluten Sekundärneoplasien, Radioiodtherpaie könnte sowohl positive als auch negative Wirkung haben

Radioiodtherapie verglichen mit Therapie ohne Radioiod bei Schilddrüsenkarzinom

Patient oder Population: Schilddrüsenkarzinom
Setting:
Intervention: Radioiodtherapie
Vergleich: Therapie ohne Radioiod

Endpunkte	Erwartete absolute Effekte* (95% CI)		Relativer Effekt (95% CI)	№ der Teilnehmer (Studien)	Certainty of the evidence (GRADE)	Kommentare
	Risiko mit Therapie ohne Radioiod	**Risiko mit Radioiodtherapie**				
Infertilität				0 Fälle 0 Kontrollen (22 Beobachtungsstudien)	⨁◯◯◯ Sehr niedrig[a,b,c,d]	2 systematische Übersichtsarbeiten mit insgesamt 22 Beobachtungsstudien unterschiedlichen Designs und teilweise sehr kleiner Teilnehmendenzahl (ab 24 bis 6824) gaben keinen Hinweis für eine verringerte Schwangerschaftsrate. AMH könnte zumindest kurzfristig (bis zu 1 Jahr nach Therapie) verringert sein.
Sekundärneoplasien	**Moderat**					
	7 pro 1.000	**8 pro 1.000** (6 bis 9)	**HR 1.08** (0.89 bis 1.31) [Sekundärneoplasien]	10748 (1 non-randomised study)	⨁◯◯◯ Sehr niedrig[a,e]	Radioiodtherapie hat keinen Einfluss bis einen minimalen Einfluss auf die Sekundärneoplasierate, die Evidenz hierzu ist sehr unsicher. Eine weitere, nicht propensity-matched Kohorte (Pasqual 2022), zeigte einen negativen Effekt von Radioiodtherapie nach mehr als 20 Jahren nach Therapieende auf die Inzidenz von soliden Tumoren, insbesondere wenn Radioiod in jungen Jahren verabreicht wurde. Die Gesamtinzidenz von Sekundärneoplasien nach 20 Jahren lag bei 5-6 % (sowohl mit als auch ohne Radioiod)

*__Das Risiko in der Interventionsgruppe__ (und das 95% Konfidenzintervall) basiert auf dem vermuteten Risiko in der Vergleichsgruppe und der **relativen Wirkung** der Intervention (und dem 95% KI).**CI:** confidence interval; **HR:** hazard Ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

3.10. Radioiodtherapie beim papillären Mikrokarzinom - Kapitel 5.8.2.1 der Langversion

3.10.1. Schlüsselfrage

Radioiodtherapie des papillären Mikrokarzinoms

3.10.2. Schlüsselfrage im PICO-Format

Patient	PTC-Patienten – Mikrokarzinom
Intervention	Radiojodtherapie
Comparison	Keine Radiojodtherapie
Outcome	Rezidivrate, Gesamtüberleben

3.10.3. Suchstrategie vom 19.03.2020 und 05.10.2022

3.10.3.1. MEDLINE (via OVID)

#	Searches
1	exp Thyroid Neoplasms/
2	((thyroid* or thyreoid*) adj3 (carcinoma or cancer or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant*) adj5 (papillar* or differentiat* or follicular*)).tw,kf,ot.
3	(DTC or RR-DTC).tw.
4	or/1-3
5	Iodine Radioisotopes/
6	(radioiodine* or radioiodide* or radio-iodine* or radio-iodide*).tw,kf,nm.
7	((iodine* or iodide*) adj3 (radioactive* or radio-isotope* or radioisotope*)).tw,kf,nm.
8	(iodine-131 or iodine131 or Iodine I 131).tw,kf.
9	(RAIT or RRA or RAIR or RAI).tw,kf.
10	("I-131" or "I131" or "131I" or "131-I").tw,kf.
11	or/5-10
12	4 and 11
13	exp ANIMALS/ not HUMANS/
14	12 not 13

#	Searches
1	exp THYROID NEOPLASMS/
2	((thyroid* or thyreoid*) adj3 (carcinoma or cancer* or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant*) adj5 (papillar* or differentiat* or follicular*)).tw,kf,ot.
3	(DTC or RR-DTC).tw.
4	or/1-3
5	IODINE RADIOISOTOPES/
6	(radioiodine* or radioiodide* or radio-iodine* or radio-iodide*).tw,kf,nm.
7	((iodine* or iodide*) adj3 (radioactive* or radio-isotope* or radioisotope*)).tw,kf,nm.
8	(iodine-131 or iodine131 or Iodine I 131).tw,kf.
9	(RAIT or RRA or RAIR or RAI).tw,kf.
10	("I-131" or "I131" or "131I" or "131-I").tw,kf.
11	or/5-10
12	4 and 11
13	exp ANIMALs/ not HUMANS/
14	12 not 13
15	limit 14 to dt=20171231-20200310
16	14 not 15

#	Searches
1	exp Thyroid Neoplasms/
2	((thyroid* or thyreoid*) adj3 (carcinoma or cancer or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant*) adj5 (papillar* or differentiat* or follicular*)).tw,kf,ot.
3	(DTC or RR-DTC).tw.
4	or/1-3
5	Iodine Radioisotopes/
6	(radioiodine* or radioiodide* or radio-iodine* or radio-iodide*).tw,kf,nm.

#	Searches
7	((iodine* or iodide*) adj3 (radioactive* or radio-isotope* or radioisotope*)).tw,kf,nm.
8	(iodine-131 or iodine131 or Iodine I 131).tw,kf.
9	(RAIT or RRA or RAIR or RAI).tw,kf.
10	("I-131" or "I131" or "131I" or "131-I").tw,kf.
11	or/5-10
12	4 and 11
13	exp ANIMALS/ not HUMANS/
14	12 not 13
15	limit 14 to dt=20171201-20191216
16	limit 14 to dt=20191216-20200310
17	limit 14 to dt=20200310-20221005

3.10.3.2. Cochrane Central Register of Controlled Trials (via Cochrane Library)

#	Searches
#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	((thyroid* or thyreoid*) near/3 (carcinoma or cancer* or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant*) near/5 (papillar* or differentiat* or follicular*)):ti,ab,kw
#3	DTC or RR-DTC:ti,ab
#4	#1 or #2 or #3
#5	MeSH descriptor: [Iodine Radioisotopes] explode all trees
#6	(radioiodine* or radioiodide* or radio-iodine* or radio-iodide*)
#7	((iodine* or iodide*) near/3 (radioactive* or radio-isotope* or radioisotope*))
#8	(iodine-131 or iodine131 or Iodine I 131):ti,ab,kw
#9	(RAIT or RRA or RAIR or RAI):ti,ab,kw
#10	("I-131" or "I131" or "131I" or "131-I"):ti,ab,kw
#11	#5 or #6 or #7 or #8 or #9 or #10
#12	#4 and #11

#	Searches
#13	#12 with Cochrane Library publication date Between Dec 2017 and Dec 2019
#14	#12 with Cochrane Library publication date Between Dec 2019 and Mar 2020
#15	#13 or #14
#16	#12 not #15

#	Searches
#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	((thyroid* or thyreoid*) near/3 (carcinoma or cancer* or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant*) near/5 (papillar* or differentiat* or follicular*)):ti,ab,kw
#3	DTC or RR-DTC:ti,ab
#4	#1 or #2 or #3
#5	MeSH descriptor: [Iodine Radioisotopes] explode all trees
#6	(radioiodine* or radioiodide* or radio-iodine* or radio-iodide*)
#7	((iodine* or iodide*) near/3 (radioactive* or radio-isotope* or radioisotope*))
#8	(iodine-131 or iodine131 or Iodine I 131):ti,ab,kw
#9	(RAIT or RRA or RAIR or RAI):ti,ab,kw
#10	("I-131" or "I131" or "131I" or "131-I"):ti,ab,kw
#11	#5 or #6 or #7 or #8 or #9 or #10
#12	#4 and #11
#13	#12 with Cochrane Library publication date Between Dec 2017 and Dec 2019
#14	#12 with Cochrane Library publication date Between Dec 2019 and Mar 2020

3.10.3.3. Ergebnis der Recherche

Fundstellen	12.260
Volltexte	253
Ausgeschlossen mit Gründen	90 keine Studie oder SR zu Mikrokarzinomen 162 keine Angaben zu Radioiod versus kein Radioiod
Eingeschlossen	1 Systematische Übersichtsarbeit

3.10.4. Evidenztabellen

3.10.4.1. Einzelstudien

keine

3.10.4.2. Systematische Übersichten/Meta-Analysen

Referenz/ Studientyp	Untersuchte Studien	Suchstrategie	Eingeschlossene Studien	Ergebnisse	Evidenzlevel Methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Hu 2016 (64) *The Effectiveness of Radioactive Iodine Remnant Ablation for Papillary Thyroid Microcarcinoma: A Systematic Review and Meta-analysis. World Journal of Surgery*	RAI ablation-related outcomes in patients with PTMC	Databases: PubMed EMBASE OvidSP EBSCO Search period January 1966 to June 2015 English language	19 studies, non-RCTs	**any tumor recurrence** RR 0.96; 95 %CI0.63-1.48 **locoregional recurrence** RR 1.15; 95 % CI 0.75-1.76 **distant metastases** RR0.32; 95 % CI 0.08-1.32 **thyroid cancer-related mortality** RR 0.76; 95 % CI 0.22-2.63	1b AMSTAR-2 rating 1. PICO elements: yes 2. A priori design: no 3. Justification for design: no 4. Literature search >= 2 databases, search strategy + other sources: yes 5. Selection in duplicate: yes 6. Data extraction in duplicate: yes 7. List of excluded studies: partial yes 8. sufficient detail on studies: yes 9. RoB assessed: yes 10. Funding of incl. studies: no	Pedrazzini L (2013) Mihailovic J (2013) Kim HJ (2013) Riss JC (2012) Gershinsky M (2012) Neuhold N (2011) Moon HJ (2011) Mercante G (2009) Pisanu A (2009) Kim TY (2008) Hay ID (2008)

Referenz/ Studientyp	Untersuchte Studien	Suchstrategie	Eingeschlossene Studien	Ergebnisse	Evidenzlevel Methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
					11. MA appropriate: yes 12. RoB considered in MA: yes 13. RoB in interpretation: yes 14. Heterogeneity explained: yes 15. Publication bias investigated: yes 16. Sources of CoI: yes	Gu¨lben K (2008) Pelizzo (2006) Cheema Y (2006) Lo CY (2006) Roti E (2006) Chow SM (2003) Appetecchia M (2002) Baudin E (1998)

3.11. Endogene versus exogene Stimulation (Hypothyreose versus Thyrotropin alpha) - Kapitel 5.8.6.9 der Langversion

3.11.1. Schlüsselfrage

Radioiodtherapie in endogener oder exogener Stimulation

3.11.2. Schlüsselfrage im PICO-Format

Patient	DTC-Patienten – T-Stadienabhängig
Intervention	Hypothyreose
Comparison	Thyrotropin alpha
Outcome	Ablationserfolg / Rezidivrate

3.11.3. Suchstrategie vom 19.03.2020

3.11.3.1. MEDLINE (via OVID)

Gleiche Suchstrategie wie für Kapitel 3.8, keine Updatesuche

#	Searches
1	exp Thyroid Neoplasms/
2	((thyroid* or thyreoid*) adj3 (carcinoma or cancer or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant*) adj5 (papillar* or differentiat* or follicular*)).tw,kf,ot.
3	(DTC or RR-DTC).tw.
4	or/1-3
5	Iodine Radioisotopes/
6	(radioiodine* or radioiodide* or radio-iodine* or radio-iodide*).tw,kf,nm.
7	((iodine* or iodide*) adj3 (radioactive* or radio-isotope* or radioisotope*)).tw,kf,nm.
8	(iodine-131 or iodine131 or Iodine I 131).tw,kf.
9	(RAIT or RRA or RAIR or RAI).tw,kf.
10	("I-131" or "I131" or "131I" or "131-I").tw,kf.
11	or/5-10

#	Searches
12	4 and 11
13	exp ANIMALS/ not HUMANS/
14	12 not 13

3.11.3.2. Cochrane Central Register of Controlled Trials (via Cochrane Library)

Gleiche Suchstrategie wie für Kapitel 3.8, keine Updatesuche

#	Searches
#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	((thyroid* or thyreoid*) near/3 (carcinoma or cancer* or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant*) near/5 (papillar* or differentiat* or follicular*)):ti,ab,kw
#3	DTC or RR-DTC:ti,ab
#4	#1 or #2 or #3
#5	MeSH descriptor: [Iodine Radioisotopes] explode all trees
#6	(radioiodine* or radioiodide* or radio-iodine* or radio-iodide*)
#7	((iodine* or iodide*) near/3 (radioactive* or radio-isotope* or radioisotope*))
#8	(iodine-131 or iodine131 or Iodine I 131):ti,ab,kw
#9	(RAIT or RRA or RAIR or RAI):ti,ab,kw
#10	("I-131" or "I131" or "131I" or "131-I"):ti,ab,kw
#11	#5 or #6 or #7 or #8 or #9 or #10
#12	#4 and #11
#13	#12 with Cochrane Library publication date Between Dec 2017 and Dec 2019
#14	#12 with Cochrane Library publication date Between Dec 2019 and Mar 2020
#15	#13 or #14
#16	#12 not #15

3.11.3.3. Ergebnis der Recherche

Fundstellen	9275
Volltexte	20
Ausgeschlossen mit Gründen	3 narrative Reviews 7 Primärstudien, die bereits in der Übersichtsarbeit enthalten sind 10 keine Studien
Eingeschlossen	1 Systematische Übersichtsarbeit

3.11.4. Evidenztabellen

3.11.4.1. Einzelstudien

keine

3.11.4.2. Systematische Übersichten/Meta-Analysen

Referenz/ Studientyp	Population	Suchstrategie	Eigeschlossene Studien	Ergebnisse	Methodische Bemerkungen	Evidenz-level
Fu 2015 (65) *"Recombinant human thyrotropin versus thyroid hormone withdrawal in radioiodine remnant ablation for differentiated thyroid cancer: a meta-analysis"*	Inclusion: - patients with metastatic DTC - after TT or NTT followed by rhTSH and THW radioiodine treatment (RIT)	Meta-Analysis of RCTs (trials of any language). Databases: Medline, EMBASE, Cochrane Library Search date: up to September 2012	7 RCTs (N = 1325)	**rhTSH vs. THW (Primary outcomes)** Thyroid remnant ablation rate OR: 0.87 (95% CI 0.56 – 1.37), p= 0.56 Health-related quality of life Mean difference: 3.59 (95% CI 2.81 – 4.37), p=<0.00001 **rhTSH vs. THW (Secondary outcomes)** Adverse Effects (headache, neck pain, nausea, fatigue, radiation gastritis, sialadenitis) OR: 0.57 (95% CI 0.44 – 0.73), p=<0.00001 Irradiation of rhTSH vs. THW-aided iodine- 131 treatment Mean difference: -0.01 (95% CI -0.02 – 0.01), p= <0.00001	AMSTAR-2 rating 1. PICO elements: yes 2. A priori design: yes 3. Justification for design: no 4. Literature search >= 2 databases, search strategy + other sources: partial yes 5. Selection in duplicate: yes 6. Data extraction in duplicate: yes 7. List of excluded studies: partial yes 8. sufficient detail on studies: yes 9. RoB assessed: no 10. Funding of incl. studies: no 11. MA appropriate: no 12. RoB considered in MA: yes 13. RoB in interpretation: yes	2a

Referenz/ Studientyp	Population	Suchstrategie	Eigeschlossene Studien	Ergebnisse	Methodische Bemerkungen	Evidenz-level
				Dose of iodine- 131(1.11GBq and 1.85 Gbq vs. 3.7 Gbq) OR: 0.85 (95% CI 0.49 – 1.47). p= 0.56	14. Heterogeneity explained: yes 15. Publication bias investigated: no 16. Sources of CoI: no	

DTC = differentiated thyroid cancer
rhTSH = recombinant human thyrotropin
THW = thyroid hormone withdrawal
TT = total thydeoidectomy
nTT = near total thydeoidectomy

3.11.1. GRADE-Tabelle

Summary of Findings:

RhTSH verglichen mit Hypothyreose bei Schilddrüsenkarzinom

Patient oder Population: Schilddrüsenkarzinom

Setting: ambulant

Intervention: rHTSH

Vergleich: Hypothyreose

Endpunkte	Erwartete absolute Effekte* (95% CI)		Relativer Effekt (95% CI)	№ der Teilnehmer (Studien)	Certainty of the evidence (GRADE)	Kommentare
	Risiko mit Hypothyreose	**Risiko mit rHTSH**				
Gesamtüberleben Nachbeobachtung: 12 Monate	keine Todesfälle berichtet			1325 (7 RCTs)	-	
Erfolgreiche Ablation Nachbeobachtung: 12 Monate	937 pro 1.000	**928 pro 1.000** (892 bis 953)	**OR 0.87** (0.56 bis 1.37)	1207 (4 RCTs)	⨁⨁⨁◯ Moderat[a]	
Lebensqualität Nachbeobachtung: 12 Monate	Die mittlere Lebensqualität war **45 (Skala von 0-100)**	MD **3.59 höher** (2.81 höher bis 4.37 höher)	-	1183 (3 RCTs)	⨁⨁◯◯ Niedrig[b,c]	
Nebenwirkungen Nachbeobachtung: 12 Monate	348 pro 1.000	**233 pro 1.000** (190 bis 280)	**OR 0.57** (0.44 bis 0.73)	1213 (3 RCTs)	⨁⨁⨁⨁ Hoch	

***Das Risiko in der Interventionsgruppe** (und das 95% Konfidenzintervall) basiert auf dem vermuteten Risiko in der Vergleichsgruppe und der **relativen Wirkung** der Intervention (und dem 95% KI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Summary of Findings:

RhTSH verglichen mit Hypothyreose bei Schilddrüsenkarzinom

Patient oder Population: Schilddrüsenkarzinom

Setting: ambulant

Intervention: rHTSH

Vergleich: Hypothyreose

Endpunkte	Erwartete absolute Effekte* (95% CI)		Relativer Effekt (95% CI)	№ der Teilnehmer (Studien)	Certainty of the evidence (GRADE)	Kommentare
	Risiko mit Hypothyreose	**Risiko mit rHTSH**				

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Ein Punkt für unpräzise geschätztes Ergebnis abgezogen: breites Konfidenzintervall schließt sowohl positiven als auch negativen Effekt der Intervention ein

b. Ein Punkt für Bias abgezogen, da Patient*innen nicht verblindet waren

c. Ein Punkt für unpräzise geschätztes Ergebnis abgezogen: eine Veränderung von 3 Punkten auf einer Skala von 0-100 ist klinisch vermutlich nicht bedeutsam, bzw. für Patient*innen zu spüren

3.12. Therapieaktivität bei der Radioiodtherapie - Kapitel 5.8.7 der Langversion

3.12.1. Schlüsselfrage

Radioiodtherapie mit unterschiedlichen Aktivitäten

3.12.2. Schlüsselfrage im PICO-Format

Patient	DTC-Patienten, ggf. T-Stadienabhängig
Intervention	RITh high dose
Comparison	RITh low dose
Outcome	Ablationserfolg / Rezidivrate

3.12.3. Suchstrategie vom 19.03.2020

3.12.3.1. MEDLINE (via OVID)

Gleiche Suchstrategie wie für Kapitel 3.8, keine Updatesuche

#	Searches
1	exp Thyroid Neoplasms/
2	((thyroid* or thyreoid*) adj3 (carcinoma or cancer or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant*) adj5 (papillar* or differentiat* or follicular*)).tw,kf,ot.
3	(DTC or RR-DTC).tw.
4	or/1-3
5	Iodine Radioisotopes/
6	(radioiodine* or radioiodide* or radio-iodine* or radio-iodide*).tw,kf,nm.
7	((iodine* or iodide*) adj3 (radioactive* or radio-isotope* or radioisotope*)).tw,kf,nm.
8	(iodine-131 or iodine131 or Iodine I 131).tw,kf.
9	(RAIT or RRA or RAIR or RAI).tw,kf.
10	("I-131" or "I131" or "131I" or "131-I").tw,kf.
11	or/5-10
12	4 and 11
13	exp ANIMALS/ not HUMANS/

#	Searches
14	12 not 13

3.12.3.2. Cochrane Central Register of Controlled Trials (via Cochrane Library)

Gleiche Suchstrategie wie für Kapitel 3.8, keine Updatesuche

#	Searches
#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	((thyroid* or thyreoid*) near/3 (carcinoma or cancer* or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant*) near/5 (papillar* or differentiat* or follicular*)):ti,ab,kw
#3	DTC or RR-DTC:ti,ab
#4	#1 or #2 or #3
#5	MeSH descriptor: [Iodine Radioisotopes] explode all trees
#6	(radioiodine* or radioiodide* or radio-iodine* or radio-iodide*)
#7	((iodine* or iodide*) near/3 (radioactive* or radio-isotope* or radioisotope*))
#8	(iodine-131 or iodine131 or Iodine I 131):ti,ab,kw
#9	(RAIT or RRA or RAIR or RAI):ti,ab,kw
#10	("I-131" or "I131" or "131I" or "131-I"):ti,ab,kw
#11	#5 or #6 or #7 or #8 or #9 or #10
#12	#4 and #11
#13	#12 with Cochrane Library publication date Between Dec 2017 and Dec 2019
#14	#12 with Cochrane Library publication date Between Dec 2019 and Mar 2020
#15	#13 or #14
#16	#12 not #15

3.12.3.3. Ergebnis der Recherche

Fundstellen	9275
Volltexte	28

Ausgeschlossen mit Gründen	5 narrative Reviews 5 Primärstudien, die bereits in der Übersichtsarbeit enthalten sind 14 keine Studien
Eingeschlossen	1 Systematische Übersichtsarbeit, 3 Primärstudien

3.12.4. Evidenztabellen

3.12.4.1. Einzelstudien

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	methodische Bemerkungen	Evidenz-klasse
Ma 2017 (66) *Chinese Data of Efficacy of Low- and High-Dose Iodine-131* *for the Ablation of Thyroid Remnant*	**Population:** - Patients presenting for radioiodine ablation **Enrolment period:** January 2013 to December 2014 **Inclusion criteria:** - Age 16-80 - histologically confirmed papillary or follicular thyroid cancer (T1-T3, N0, NX, N1, M0), - post-total or near-total thyroidectomy. **Exclusion:** Aggressive variants, including follicular	**Interventions** I-131 ablation with 1.85GBq vs 3.7GBq	**Prospective Randomized Study;** **Sample size:** - Initially 327 patients enrolled - 278 included in analysis. **Randomized into two groups:** - Low-dose (1850 MBq) - high-dose (3700 MBq) radioiodine.	**Successful ablation:** 1.85 GBq: 82,6% 3.70 GBq: 86,2% (p=0.509) **Tg-off value ≤2 ng/mL at 6 to 9 months after ablation:** 1.85 GBq: 87.1% 3.70 GBq: 89.4% **Increased Tg-off:** 1.85 GBq: 6.5% 3.70 GBq: 5.7% (p>0.05) **Need for second dose:** 1.85 GBq: 17.4% 3.70 GBq: 13.8% **Recurrence rate:** not reported	General information • Follow-up: 2 to 3 years • Funding: National Natural Science Fund (grant 51233007, 81271612, and 81401439), Shanghai Pujiang Program (grant 13PJD022), and Shanghai Health Bureau Fund (grant 20124016). • CoI: not reported Risk of bias considerations (RoB 1): • Analysis ITT: not reported, probably mITT • Randomisation: by random number table • Allocation concealment: not reported • Blinding: no • Attrition bias: possible, 16 participants per group were lost to follow-up, without reasons provided Selective reporting: unclear; we did not identify a study protocol or trial registration number.	1b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	methodische Bemerkungen	Evidenz-klasse
	variant PTC, tall-cell, columnarcell, poorly differentiated, and diffuse sclerosing; pregnant or breastfeeding women; severe co-existing conditions; serious abnormality in hepatic function or renal function; low white blood cell count.			**Quality of Life**: not reported **Adverse events** **Abnormality in blood:** 1.85 GBq: 3.2% 3.70 GBq: 4.1%; p=0.754 **Abnormality in hepatic function:** 1.85 GBq: 3.2% 3.70 GBq: 2.4%; p=0.737 **Abnormality in renal function:** 1.85 GBq: 2,6% 3.70 GBq: 0.8%%; p=0.387 Short-term adverse effects such as nausea, taste disorders, and salivary-gland dysfunction were not evaluated in this study. Major adverse effects: not reported		

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	methodische Bemerkungen	Evidenz-klasse
Qu, 2017 (67) *Low- and high-dose radioiodine therapy for low-/intermediate-risk* *differentiated thyroid cancer: a preliminary clinical trial*	**Population:** Patients diagnosed with differentiated thyroid cancer (DTC), in stage T1N0-1M0 after total thyroidectomy and Individuals classified as low- to intermediate-risk. **Enrolment period:** October 2014 to June 2015 **Inclusion:** - DTC (PTC, FTS), - Stage T1 - T2, N0 - N1, M0 - after total thyroidectomy (+lymph node Dissection in case N1); - >18 years; **Exclusion:** Invasive subtype,	**Intervention:** I-131 ablation with 1.1 GBq vs 3.7 GBq	**Randomised controlled study** **Sample size:** 140	**Successful ablation:** 1.1 GBq: 52.7 % (29/55) 3.7 GBq: 59.1 % (26/44); p = 0.548 **Response to therapy** **Excellent response rate:** 1.1 GBq: 80% (53/66) 3.7 GBq: 85% (56/66); p = 0.087 **Indeterminate response rate:** 1.1 GBq: 19.7% (13/66) 3.7 GBq: 10.6% (7/66) **Incomplete Response:** 1.1 GBq: 0% 3.7 GBq: 4% (3/66) **Recurrence rate:** not reported **Quality of Life**: not reported **Adverse events:**	General information • Follow-up: at 6 and 24 weeks after ablation • Funding: • CoI: No potential conflicts of interest were disclosed. Risk of bias considerations (RoB 1): • Analysis ITT: not reported, probably mITT • Randomisation: by random number table • Allocation concealment: not reported • Blinding: no • Attrition bias: low risk, low number of drop-outs (2 cases in 1.1 GBq, 3 cases in 3.7 GBq) Selective reporting: study was registered under ChiCTR-IOR-15006139; the reported outcomes between registry entry and study publication differ.	1b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	methodische Bemerkungen	Evidenz-klasse
	including tall cell, insular, poorly differentiated, and diffuse sclerosing variants of anaplastic or medullary thyroid carcinoma; history of other malignancies; the presence of unstable diseases or other conditions that might prevent patient of completion of the study.			**Adverse reactions** 1.1 GBq: 18% (12/66) vs 3.7 GBq: 39% (26/66); p = 0,007 **Major adverse effects**: not reported		
Jin, 2019 (68) *Radioiodine Uptake and Thyroglobulin-Guided Radioiodine* *Remnant Ablation in Patients with Differentiated*	**Population:** Patients with differentiated thyroid cancer (DTC) who underwent total, near-total, or sub-total thyroidectomy and were referred for radioactive iodine remnant ablation (RRA).	**Intervention:** RAIU-Tg-based activity 1.1 Gbq, 1.85 Gbq, 3.7 Gbq, 5.5 Gbq, Based on: I-131 Radioiodine uptake (RAIU) (0.185	Randomized controlled study sample size: - 277 patients enrolled - analysed: 265 eligible and with data	<u>Successful ablation:</u> RAIU-Tg-based activity: 94.2% Fixed activity: 70.7%; p < 0.0001 <u>Local persistent disease</u> RAIU-Tg-based activity: 1% Fixed activity: 5.2%; p =0.063 <u>Distant metastases</u>	General information • Follow-up: • Funding: National Natural Science Fund (grant 51233007, 81271612, and 81401439), Shanghai Pujiang Program (grant 13PJD022), and Shanghai Health Bureau Fund (grant 20124016). • CoI: not reported Risk of bias considerations (RoB 1): • Analysis ITT: not reported, probably mITT • Randomisation: by random number table	1b

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	methodische Bemerkungen	Evidenz-klasse
Thyroid Cancer: *A Prospective, Randomized, Open-Label, Controlled Trial*	**Enrollment period:** between 2013 and 2017 **Inclusion:** ATA low, intermediate, and high risk DTC (PTC (97%) and FTC (3%) after total, near-total, or subtotal Tx; **Exclusion:** persistent/ recurrent locoregional disease or M1 after thyreoidectomy	Mbq) of <2% 2 – 5% 5 – 15 % > 15 % and Tg levels of <2 ng/ml 2 – 5 ng/ml 5 – 10 ng/ml > 10 ng/ml (if RAIU an Tg-levels where not in the same category (1. – 4.), the higher activity was used. **Control:** I-131 radio ablation with fixed activity of 3.7 GBq (Prednisone for RAIU > 15% for 5 days).	RAIU-Tg-based activity: 215 Fixed activity: 62	RAIU-Tg-based activity: 1% Fixed activity: 3.4%; p = 0.209 <u>Retreatment</u> RAIU-Tg-based activity: 1.4% Fixed activity: 7.7%; p =0.043 **<u>Adverse events</u>** <u>Short term AE</u> RAIU-Tg-based activity: 16.9% Fixed activity: 15.5%; p = 0.801 <u>Intermediate term AE</u> RAIU-Tg-based activity: 13% Fixed activity: 25.9%; p = 0.018 <u>Xerostomia</u> RAIU-Tg-based activity: 9.2 Fixed activity: 19.0%; p = 0.038 <u>Xerophthalmia</u> RAIU-Tg-based activity: 4.8%	• Allocation concealment: not reported • Blinding: no • Attrition bias: possible, 16 participants per group were lost to follow-up, without reasons provided Selective reporting: unclear; we did not identify a study protocol or trial registration number.	

Referenz/ Studientyp	Untersuchte Population	Intervention	Studiendesign	Hauptergebnisse	methodische Bemerkungen	Evidenz-klasse
				Fixed activity: 8.6%%; p = 0.331 <u>Amenorrhea</u> RAIU-Tg-based activity: 0.4% Fixed activity: 0%; p = 0.069 **Major Adverse effects:** not reported		

3.12.4.2. Systematische Übersichten/Meta-Analysen

Referenz/ Studientyp	Untersuchte Population	Suchstrategie, Einschlusskriterien	Eingeschlossene Studien	Ergebnisse	methodische Bemerkungen / Evidenzklasse (AMSTAR2)	Evidenz-level
Shengguang, 2016 (69) *I-131 for Remnant Ablation in Differentiated Thyroid Cancer After Thyroidectomy: A Meta-Analysis of Randomized*	Adults aged 18 years or older, not pregnant or breastfeeding, who underwent total or subtotal thyroidectomy, with histological confirmation of differentiated thyroid cancer (papillary, follicular, or mixed), and pathological tumor-node-metastasis (TNM) classification, pT1 to	<u>Databases:</u> Medline EMBASE PubMed The Cochrane Central Register of Controlled Trials Web of Science <u>Search period</u> Up to Dec 2014	14 studies RCT Giovanella, 2013 Fallahi, 2012 Caglar, 2012 Schlumberger, 2012 Mallick, 2012 Kukulska, 2010 Maenpaa, 2008 Pilli, 2007 Zaman, 2006 Sirisalipoch, 2006	<u>**Successful ablation**</u> **1.11 GBq vs 1.85 GBq:** no significant difference **1.85 GBq vs 3.7 GBq:** no significant difference **1.11 GBq vs 3.7 GBq:** pooled successful ablation rate is 5% lower (95% CI, 1-9% lower) [Subgroups: Asians: ablation success rate similar (SRRs=0.91;	<u>AMSTAR-2 rating</u> 1. PICO elements: yes 2. A priori design: yes 3. Justification for design: no 4. Literature search >= 2 databases, search strategy + other sources: partial yes 5. Selection in duplicate: yes 6. Data extraction in duplicate: yes 7. List of excluded studies: partial yes 8. sufficient detail on studies: partial yes	1b

Referenz/ Studientyp	Untersuchte Population	Suchstrategie, Einschlusskriterien	Eingeschlossene Studien	Ergebnisse	methodische Bemerkungen / Evidenzklasse (AMSTAR2)	Evidenz-level
Controlled Evidence	T3, with the possibility of lymph node involvement but no distant metastasis	Key words: "thyroid", "cancer" or "carcinoma" or "neoplasm", and "ablation"	Bal, 2004 Bal, 1996 Johansen, 1991 Creutzig, 1987	95%CI=0.72-1.14), Europeans: ablation success rate favors 3.7 GBq (SRRs=0.95; 95%CI=0.91-0.99)]. **Side effects:** Adverse effects: not reported Major adverse effects: not reported	9. RoB assessed: yes 10. Funding of incl. studies: no 11. MA appropriate: yes 12. RoB considered in MA: yes 13. RoB in interpretation: yes 14. Heterogeneity explained: yes 15. Publication bias investigated: yes 16. Sources of CoI: none	

3.12.1. GRADE-Tabellen

Summary of Findings:

Low dose verglichen mit high dose Radioiodtherapie bei Schilddrüsenkarzinom

Patient oder Population: Schilddrüsenkarzinom
Setting:
Intervention: Low dose
Vergleich: high dose Radioiodtherapie

Endpunkte	Erwartete absolute Effekte* (95% CI)		Relativer Effekt (95% CI)	№ der Teilnehmer (Studien)	Certainty of the evidence (GRADE)	Kommentare
	Risiko mit high dose Radioiodtherapie	Risiko mit Low dose				
Gesamtüberleben - nicht gemessen	-	-	-	-	-	
Erfolgreiche Ablationsrate	798 pro 1.000	**759 pro 1.000** (727 bis 790)	**RR 0.95** (0.91 bis 0.99)	1769 (9 RCTs)	⊕⊕⊕◯ Moderat[a]	

Summary of Findings:

Low dose verglichen mit high dose Radioiodtherapie bei Schilddrüsenkarzinom

Patient oder Population: Schilddrüsenkarzinom
Setting:
Intervention: Low dose
Vergleich: high dose Radioiodtherapie

Endpunkte	Erwartete absolute Effekte* (95% CI)		Relativer Effekt (95% CI)	№ der Teilnehmer (Studien)	Certainty of the evidence (GRADE)	Kommentare
	Risiko mit high dose Radioiodtherapie	**Risiko mit Low dose**				
Lebensqualität - nicht gemessen	-	-	-	-	-	
Nebenwirkungen	Tendenziell scheint es unter der Hochdosis Radiotherapie mehr Nebenwirkungen zu geben. Aufgeführt sind vermehrt Kopf- und Nackenschmerzen, Übelkeit, Muskelkrämpfe und Speicheldrüsenentzündungen mit einem trockenen Mund			455 (3 RCTs)	⨁◯◯◯ Sehr niedrig[a,b,c]	

***Das Risiko in der Interventionsgruppe** (und das 95% Konfidenzintervall) basiert auf dem vermuteten Risiko in der Vergleichsgruppe und der **relativen Wirkung** der Intervention (und dem 95% KI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Einen Punkt für Studiendesign abgezogen: die meisten Studien berichten nicht Randomisierungszuteilung und Verblindung von Endpunkterhebenden

b. Einen Punkt für unpräzise geschätzte Effekte abgezogen: insgesamt wurden nur wenige Nebenwirkungen unterschiedlichster Art aufgeführt

c. Einen Punkt für Publikationsbias abgezogen: die meisten Studien berichten nichts zu Nebenwirkungen

3.13. Labordiagnostik (Thyreoglobulin) - Kapitel 6.6 der Langversion

3.13.1. Schlüsselfrage

Arbeitstitel „Labor-Diagnostik (Tg, Tg-WF, TAK)“

3.13.2. Schlüsselfrage im PICO-Format

Patient	DTC, PTC / FTC / PDTC – Nachsorge nach Thyreoidektomie und Z.n. Radiojodtherapie; TAK negativ
Intervention	Basaler Thyreoglobulin-Wert, (Tg-WF)
Comparison	Jod131-Ganzskörperscan +- FDG-PET
Outcome	diagnostische Güte (Sensitivität, Spezifität, NPV, PPV)

3.13.3. Suchstrategie vom 05.08.2021

3.13.3.1. MEDLINE(via OVID)

ID	Search
1	exp Thyroid Neoplasms/
2	((thyr?oid* adj3 carcinoma*) or (thyr?oid* adj3 cancer*) or (thyr?oid* adj3 tumo?r*) or (thyr?oid* adj3 neoplas*) or (thyr?oid* adj3 adenom*) or (thyr?oid* adj3 adenocarcinom*) or (thyr?oid* adj3 sarcoma*) or (thyr?oid* adj3 lymphom*) or (thyr?oid* adj3 malignant*) or (thyr?oid* adj3 metasta*)).tw,kf,nm,ot.
3	(DTC or RR-DTC).tw.
4	PDTC.tw.
5	or/1-4
6	Thyroglobulin/
7	thyr?oglobulin*.tw,kf,ot.
8	Tg.tw.
9	or/6-8
10	thyroglobulin.ab. /freq=2
11	thyreoglobulin.ab. /freq=2
12	(TgR or TgAb*).tw,kf.
13	(anti-thyr?oglobulin* or antithyr?oglobulin*).tw,kf,nm.

ID	Search
14	(thyroid peroxidas* adj2 antibod*).tw,kf,nm.
15	(thyr?oglobulin* adj3 antibod*).tw,kf.
16	(Tg* adj2 antibod*).tw,kf.
17	(aftercare or recurrence detection).tw.
18	exp Biopsy, Fine-Needle/
19	(aspiration* adj3 fine-needle*).tw,kf.
20	(biops* adj3 fine needle*).tw,kf.
21	FNAB.tw.
22	or/10-21
23	5 and 9
24	5 and 22
25	5 and 9 and 22

3.13.3.2. Cochrane Central Register of Controlled Trials (via Cochrane Library)

ID	Search
#1	Thyroid Neoplasms
#2	((thyroid* OR thyreoid*) NEAR3 (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplas* OR adenom* OR adenocarcinom* OR sarcoma* OR lymphom* OR malignant* OR metasta*))
#3	((DTC OR RR-DTC OR PDTC))
#4	Thyroglobulin
#5	((thyroglobulin* OR thyreoglobulin*))
#6	Tg
#7	(thyroglobulin* OR thyreoglobulin*)
#8	(TgR OR TgAb*)
#9	(anti-thyroglobulin* OR antithyroglobulin* OR anti-thyreoglobulin* or antithyreoglobulin*)

ID	Search
#10	((thyroid peroxidas* NEAR2 antibod*) OR (thyreoid peroxidas* NEAR2 antibod*))
#11	((thyroglobulin* NEAR3 antibod*) OR (thyroglobulin* NEAR3 antibod*) OR (thyreoglobulin* NEAR3 antibod*) OR (thyreoglobulin* NEAR3 antibod*))
#12	(Tg* NEAR2 antibod*):TI,AB,KY
#13	Biopsy, Fine-Needle
#14	((aspiration* NEAR3 fine-needle*) OR (biops* NEAR3 fine needle*) OR FNAB)
#15	Recurrence
#16	Neoplasm Recurrence, Local
#17	Aftercare
#18	time factors
#19	(rezidiv* OR recurren* OR re-curren* OR failur* OR failed OR relap* OR refractor* OR pregredient* OR progredient* OR progressiv* OR follow up OR aftercare* OR after care* OR detection* OR detects OR detect OR detected OR persistent diseas*)
#20	Iodine Radioisotopes
#21	(radioiodine* OR radioiodide* OR iodine* OR iodide* OR radio-iodine* or radio-iodide* OR RAIR OR RAI)

3.13.3.3. Ergebnis der Recherche

Fundstellen	2030
Volltexte	69
Ausgeschlossen mit Gründen	60 keine Studien oder Review 8 entsprechen nicht der Fragestellunga
Eingeschlossen	1 Systematische Übersichtsarbeit

3.13.4. Evidenztabellen

3.13.4.1. Einzelstudien

Keine.

3.13.4.2. Systematische Übersichten/Meta-Analysen

Referenz/ Studientyp	Untersuchte Population	Suchstrategie, Einschlusskriterien	Eingeschlossene Studien	Ergebnisse	Methodische Bemerkungen	Evidenz-level
Giovanella 2020 (70)	Studies including … - outpatients diagnosed with DTC - treated with near-total (NTx) or total thyroidectomy (TTX) with or without RAI Age (range): 7 to 88 years PTC: 1542 FTC: 151	Databases PubMed Scopus CENTRAL Web of Science Search period until February 12, 2019 Key words (thyroid) AND (((((cancer) OR carcinoma))) AND ((((((((((high) OR highly)) AND ((sensitive) OR sensitivity))) OR	8 studies for diagnostic performance (1568 participants) Gorges (2003) Iervasi (2004) Rosario (2008) Castagna (2011) Nakabashi (2014) Rosario (2016) Trimboli (2017) Flores-Rebollar (2018)	**Diagnostic performance (Reference: differs per study, US, Chest X-ray, MRI, CT, PET, FNA, MIBI, WBS)** **Sensitivity:** 83.4% (95% CI 73.4–90.1) **Specificity:** 79.9% (95% CI 63.0–90.3) **Positive predictive value:** 21.3% (95% CI 11.9–30.7) **Negative predictive value:** 99.4 (95% CI 98.9–99.9; I2 = 13%) **Likelihood ratio for positive results:** 4.2% (95% CI 2.4–7.6) **Likelihood ratio for negative results:** 0.2% 95% CI 0.1–0.3) **Diagnostic odds ratio:** 18.7 (95% CI 6.1–57.4) **Prognostic performance (to differentiate structural from not-evidence of disease)** **Sensitivity:** 86.3% (95% CI 29.6–98.9)	AMSTAR-2 rating 1. PICO elements: yes 2. A priori design: yes, PROSPERO ID CRD42019125092 3. Justification for design: no, but RCTs would not apply, diagnostic question 4. Literature search >= 2 databases, search strategy + other sources: yes 5. Selection in duplicate: yes 6. Data extraction in duplicate: yes 7. List of excluded studies: no 8. Sufficient detail on studies: yes 9. RoB assessed: QUADAS-2 (supplemental material) 10. Funding of incl. studies: no 11. MA appropriate: yes 12. RoB considered in MA: no	2a

Referenz/ Studientyp	Untersuchte Population	Suchstrategie, Einschlusskriterien	Eingeschlossene Studien	Ergebnisse	Methodische Bemerkungen	Evidenz-level
	8 studies included only TgAb negative patients, 1 mixed, 1 unknown	ultrasensitiv*)) OR ((((second) OR new)) AND generation))) AND thyroglobulin)) <u>Restrictions</u> No language restrictions	6 studies for prognostic performance: Zöphel 2003 Rosario 2008 Castagna 2011 Nakabashi 2014 Rosario 2016 Trimboli 2017	**Specificity:** 70.7% (95% CI 52.6–83.9) **Positive predictive value:** 7.3% (95% CI 2.1–12.4) **Negative predictive value:** 99.4 (95% CI 98.8–100; I2 = 0%) **Likelihood ratio for positive results:** 2.2% (95% CI 1.2–4.1) **Likelihood ratio for negative results:** 0.3% (95% CI 0.1–1.0) **Diagnostic odds ratio:** 5.3% (95% CI 1.6–17.8)	13. RoB in interpretation: yes 14. Heterogeneity explained: NA 15. Publication bias investigated: NA 16. Sources of CoI: reported AMSTAR-2 score: 10/12	

3.14. Molekulare (funktionelle) Bildgebung - Kapitel 8.3.4.3. der Langversion

3.14.1. Schlüsselfrage

PET-Radiotracer beim metastasierten medullärem Schilddrüsenkarzinom

3.14.2. Schlüsselfrage im PICO-Format

Patient	Patienten mit metastasiertem MTC
Intervention	Funktionelle Bildgebung mit 18F-DOPA oder 18F-FDG oder DOTA-SSTR Radiopharmaka
Comparison	Morphologische Bildgebung
Outcome	Diagnostische Genauigkeit

3.14.3. Suchstrategie vom 18.02.2021

3.14.3.1. MEDLINE (via OVID)

#	Searches
1	((thyroid* or thyreoid*) adj3 (carcinoma or cancer or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant* or metasta*) adj5 medullar*).tw,kf,ot.
2	CARCINOMA, MEDULLARY/ and (thyroid* or thyreoid*).tw.
3	(medullar* adj6 (thyroid* or thyreoid*)).tw,ot.
4	or/1-3
5	Radioisotopes/
6	Gallium Radioisotopes/
7	Yttrium Radioisotopes/
8	Lutetium/
9	dota*.tw,kf,nm.
10	(gallium-68 or 68ga or ga68).tw,kf,nm.
11	(90y or 90yttrium or y90).tw,kf,nm.
12	(177LU or 177lutetium or LU177).tw,kf,nm.
13	(dopa* or FDOPA* or fluorodopa*).tw,kf.
14	fluorodopa F 18.nm.
15	(Immuno-PET or immunoPET or iPET).tw,kf.

#	Searches
16	or/5-15
17	4 and 16
18	limit 17 to yr="2010 - 2021"

3.14.3.2. Cochrane Central Register of Controlled Trials (via Cochrane Library)

3.14.3.3. ID	3.14.3.4. Search
#1	((thyroid* or thyreoid*) NEAR/3 (carcinoma or cancer or tumo?r* or neoplas* or adenom* or adenocarcinom* or sarcoma or lymphom* or malignant* or metasta*) NEAR/5 medullar*):ti,ab,kw
#2	MeSH descriptor: [Carcinoma, Medullary] this term only
#3	(thyroid* or thyreoid*):ti,ab
#4	#2 AND #3
#5	(medullar* NEAR/6 (thyroid* or thyreoid*)):ti,ab,kw
#6	#1 OR #4 OR #5
#7	MeSH descriptor: [Radioisotopes] this term only
#8	MeSH descriptor: [Gallium Radioisotopes] this term only
#9	MeSH descriptor: [Yttrium Radioisotopes] this term only
#10	MeSH descriptor: [Lutetium] this term only
#11	dota*:ti,ab,kw
#12	(gallium-68 or 68ga or ga68):ti,ab,kw
#13	(90y or 90yttrium or y90):ti,ab,kw
#14	(177LU or 177lutetium or LU177):ti,ab,kw
#15	(dopa* or FDOPA* or fluorodopa*):ti,ab,kw
#16	"fluorodopa F 18"
#17	(Immuno-PET or immunoPET or iPET):ti,ab,kw
#18	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	#6 AND #18

3.14.3.5. Ergebnis der Recherche

Fundstellen	173
Volltexte	12
Ausgeschlossen mit Gründen	11 Primärstudien
Eingeschlossen	1 Systematische Übersichtsarbeit

3.14.4. Evidenztabellen

3.14.4.1. Einzelstudien

Keine

3.14.4.2. Systematische Übersichten/Meta-Analysen

Referenz/ Studientyp	Untersuchte Population	Suchstrategie, Einschlusskriterien	Eingeschlossene Studien	Ergebnisse	Methodische Bemerkungen	Evidenz-level
Treglia 2012 (71) Diagnostic test accuracy review *Detection Rate of Recurrent Medullary Thyroid Carcinoma Using Fluorine-18 Dihydroxyphenyl alanine Positron Emission Tomography: A Meta-analysis*	**Population:** Patients with recurrent or residual medullary thyroid cancer **Intervention:** 18F-DOPA PET and PET/CT	Databases: PubMed/MEDLINE, Scopus, Embase Search period From inception of databases to 31 January 2012 Key words: (1) “PET OR positron emission tomography” AND (2) “medullary OR thyroid.” English language **Inclusion:** Recurrent MTC	8 studies Treglia 2012 Kauhanen 2011 Luster 2010 Marzola 2010 Beheshti 2009 Koopmans 2008 Beuthien-Baumann 2007 Hoegerle 2001	**Detection rates (pooled 95% CI)** **Patient-based analysis:** 66% (95% CI 58%-74% ; N = 139) **Lesion-based analysis** : 71% (95% CI 67% - 75% ; N = 124) **Calcitonin >= 1000 ng/L** : 86% (95% CI 73% - 95% ; N = 45) **Calcitonin < 150 ng/L :** 39% (95% CI 20% - 61% ; N = 28) **Calcizonin >=150 ng/L** : 73% (95% CI 63% - 82% ; N = 93) **CEA <= 5 ng/mL** : 48% (95% CI 29% - 67% N = 29)	AMSTAR-2 rating 1. PICO elements: yes, partly (diagnostic review, PI clear; comparator unclear) 2. A priori design: yes, PROSPERO ID 91505 3. Justification for design: 4. Literature search >= 2 databases, search strategy + other sources: yes, but search string quite limited 5. Selection in duplicate: yes 6. Data extraction in duplicate: unclear 7. List of excluded studies: no 8. sufficient detail on studies: partial yes 9. RoB assessed: QUADAS-2 10. Funding of incl. studies: not reported 11. MA appropriate: yes 12. RoB considered in MA: no 13. RoB in interpretation: yes 14. Heterogeneity explained: only in discussion,	3a

Referenz/ Studientyp	Untersuchte Population	Suchstrategie, Einschlusskriterien	Eingeschlossene Studien	Ergebnisse	Methodische Bemerkungen	Evidenz-level
		Exclusion: - review articles, editorials, comments, conference proceeding - case series - articles with incufficient data - studies with data overlap		**CEA>= 5 ng/mL :** 64% 95% CI 52% - 74% ; N = 69)	hypotheses, not tested 15. Publication bias investigated: no 16. Sources of CoI: not reported AMSTAR-2 score: 9,5/13* * Although formal assessment with AMSTAR showed a high score, there were errors in the content of the review. For some results reported here, primary studies were consulted.	

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