German Guideline Program in Oncology (GGPO)

Guideline on the Diagnosis, Treatment, and Follow-up of Patients with Endometrial Cancer

Short version 1.0 — April 2018
AWMF register no. 032/034-OL

Guideline (Short Version)

DKG KREBSGESELLSCHAFT
Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.
AWMF

Contents

1. Information about this guideline

1.1. Publishing body

The German Guideline Program in Oncology (GGPO) organized by the The Association of the Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.*, AWMF), German Cancer Society (*Deutsche Krebsgesellschaft e.V.,* DKG), and German Cancer Aid (*Deutsche Krebshilfe,* DKH).

1.2. Specialist societies responsible

German Society for Gynecology and Obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe, DGGG)

German Cancer Society, represented by the Working Group on Gynecological Oncology (Arbeitsgemeinschaft Gynäkologische Onkologie, AGO).

1.3. Financing of the guideline

This guideline was sponsored by German Cancer Aid (*Deutsche Krebshilfe,* DKH) within the framework of the German Guideline Program in Oncology.

1.4. Contact address

Office of the German Guideline Program in Oncology
c/o Deutsche Krebsgesellschaft e.V.
Kuno-Fischer-Strasse 8
14057 Berlin
Germany

leitlinienprogramm@krebsgesellschaft.de
www.leitlinienprogramm-onkologie.de

1.5. Suggested citation style

German Guideline Program in Oncology (German Cancer Society, German Cancer Aid, AWMF): Guideline on the Diagnosis, Treatment, and Follow-up of Patients with Endometrial cancer, short version 1.0, 2018, AWMF Registernummer: 032/034-OL, http://www.leitlinienprogramm-onkologie.de/leitlinien/endometriumkarzinom/ (accessed MM DD, YYYY).

1.6. Special note

The field of medicine is subject to a continuous process of further development, so that all details provided here, and in particular those on diagnostic and therapeutic procedures, can always only represent the state of knowledge at the time when the guideline was published. The greatest possible care has been taken with regard to the treatment recommendations given and to the choice and dosage of drugs. However, users are requested to check by referring to the patient package inserts and specialist information provided by the manufacturers, and in cases of doubt to consult a specialist. In the general public interest, readers are requested to inform the guideline editors about any questionable points found.

Users themselves remain responsible for all diagnostic and therapeutic applications, medications, and dosages.

Registered trademarks (protected proprietary names) are not specially identified in this guideline. The absence of an indication of this type can therefore not be taken to suggest that such names are unregistered product names.

1.7. Aims of the German Guideline Program in Oncology

The aim of the Working Group of Scientific Medical Specialist Societies (AWMF), the German Cancer Association (DKG), and German Cancer Aid in implementing the German Guideline Program in Oncology is to jointly promote and support the development, updating, and use of scientifically based and practicable guidelines in oncology. The program is based on medical and scientific findings established by the specialist societies and the DKG, consensus among specialist medical experts, users, and patients, as well as the AWMF's regulations for guideline development. The program receives specialist support and financing from German Cancer Aid. In order to reflect the current state of medical knowledge and to take account of medical progress, guidelines have to be regularly checked and updated. The use of the AWMF regulations is intended to provide a basis for developing high-quality oncological guidelines in this framework. As guidelines represent an important instrument for quality assurance and quality management in oncology, they are intended to be used in a targeted and sustained way in everyday medical care. Active implementation measures and also evaluation programs are therefore important components of the support provided by the German Guideline Program in Oncology. The aim of the program is to create professional preconditions, with secure medium-term financing, for the development and provision of high-quality guidelines in Germany. High-quality guidelines of this type not only serve for structured knowledge transfer but can also be used in the design of structures in the health-care system. Relevant aspects of this include evidence-based guidelines as a basis for establishing and updating disease management programs, and the use of

quality indicators derived from guidelines in the context of certification procedures for organ tumor centers.

1.8. Additional documents on this guideline

This document is the short version of the Guideline on the Diagnosis, Treatment and Follow-up of Patients with Endometrial cancer. In addition to the long version, the following supplementary documents on the guideline are also available:

- Guideline report on the process of preparing the guideline
- Document with evidence tables for the guideline
- Patient guideline (in preparation)

All of the documents for the guideline are available from the following web sites:

- German Guideline Program in Oncology (http://www.leitlinienprogramm-onkologie.de/leitlinien/endometriumkarzinom)
- AWMF (http://www.awmf.org/leitlinien/aktuelle-leitlinien.html)
- Guidelines International Network (www.g-i-n.net)

1.9. Composition of the guideline group

1.9.1. Coordination and editing

The coordinator was commissioned by the specialist society responsible, the DGGG.

Coordinator: Prof. Dr. med. Günter Emons (Göttingen)

Co-Coordinator: Prof. Dr. med. Eric Steiner (Rüsselsheim)

Editorial team: Dr. med. Nina Bock (Göttingen)
Saskia Erdogan, M.A. (Göttingen)

Steering group: Prof. Dr. med. Günter Emons (Göttingen)
Prof. Dr. med. Eric Steiner (Rüsselsheim)
Dr. med. Nina Bock (Göttingen)
Kerstin Paradies (Hamburg)
Dr. med. Christoph Uleer (Hildesheim)
Prof. Dr. med. Dirk Vordermark (Halle/Saale)

Consultancy: Physicians working at the Oncology Competence Center of the GKV central organization and for the Medical Service of the Health-Insurance Companies Association participated in the preparation of this Level 3 guideline on a consultative basis, in connection with individual aspects relevant to social medicine.

They did not take part in voting on the individual recommendations and are not responsible for the content of this guideline.

1.9.2. Participating specialist societies and organizations

Section 13.2 lists the medical specialist societies and other organizations with their mandated representatives, as well as patient representatives and methodological consultants who were involved in the developement of this guideline. Further information about the individuals' contributions and roles and the composition of the working groups is available in the long version of this guideline.

1.10. Abbreviations used

Table 1: Abbreviations

Abbreviation	Explanation
AC	Adriamycin (doxorubicin) and cyclophosphamide (chemotherapy)
ACR	American College of Radiology
AEH	atypical endometrial hyperplasia
AGO	*Arbeitsgemeinschaft Gynäkologische Onkologie* (Working Group on Gynecological Oncology)
AQUA	*Institut für angewandte Qualitätsförderung und Forschung im Gesundheitswesen GmbH*
5-ASA	5-aminosalicylic acid (mesalazine)
ASCO	American Society of Clinical Oncology
AUC	area under the curve
AWMF	*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften* (Working Group of Scientific Medical Specialist Societies)
BMI	body mass index
BSO	bilateral salpingo-oophorectomy
CI	confidence interval(s)
CT	computed tomography
DEGAM	*Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin* (German Society for General Medicine and Family Medicine)
DGP	*Deutsche Gesellschaft für Pathologie* (German Society for Pathology)
DGGG	*Deutsche Gesellschaft für Gynäkologie und Geburtshilfe* (German Society for Gynecology and Obstetrics)
DGU	*Deutsche Gesellschaft für Urologie* (German Society for Urology)

Abbreviation	Explanation
DKG	*Deutsche Krebsgesellschaft* (German Cancer Association)
EC	expert consensus
EIN	endometrioid intraepithelial neoplasia
ENT	ear, nose and throat (region)
EORTC	European Organization for Research and Treatment of Cancer
ESGO	European Society of Gynecological Oncology
ESMO	European Society for Medical Oncology
ESTRO	European Society for Radiotherapy and Oncology
FAP	familial adenomatous polyposis
FIGO	*Fédération Internationale de Gynécologie et d'Obstetrique* (International Federation of Gynecology and Obstetrics)
FN	febrile neutropenia
G-CSF	granulocyte colony-stimulating factor
GoR	Grade of Recommendation
HADS	Hospital Anxiety and Depression Scale
HE	hematoxylin–eosin (staining)
HNPCC	hereditary nonpolyposis colorectal cancer
HRT	hormone replacement therapy
5-HT_3 RA	5-hydroxytryptamine-3 receptor antagonist
ICD	International Classification of Diseases
IKNL	*Integraal Kankercentrum Nederland*
IUD	intrauterine device
LNG	levonorgestrel
LOE	level of evidence
LS	Lynch syndrome
LVSI	lymphovascular space invasion

Abbreviation	Explanation
MCP	metoclopramide
MELF	microcystic, elongated, fragmented (glandular pattern)
MGA	megestrol acetate
MMMT	malignant müllerian mixed tumor
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
NK_1 RA	neurokinin-1 receptor antagonist
PCOS	polycystic ovary syndrome
PET-CT	positron emission tomography-computed tomography
PHTS	*PTEN* hamartoma tumor syndrome
PMB	postmenopausal bleeding
QI	quality indicator
RA	receptor antagonist
RR	relative risk
SEE-FIM	sectioning and extensively examining the fimbriated end (protocol)
SEER	Surveillance, Epidemiology, and End Results (program)
SEIC	serous endometrial intraepithelial carcinoma
SEOC	synchronous endometrial and ovarian carcinoma
SIEC	serous intraepithelial carcinoma
ST	statement
TCGA	The Cancer Genome Atlas
TNM	tumor, node, metastasis (system)
UICC	Union Internationale Contre le Cancer (International Union Against Cancer)
VIP	vasoactive intestinal peptide

Abbreviation	Explanation
WHO	World Health Organization

2. Introduction

2.1. Scope of application and purpose

2.2. Patient target group and intended audience

This interdisciplinary Level 3-quality guideline on the early detection, diagnosis, treatment, and follow-up of endometrial cancer (ICD-10 C54.1 [1]) covers patients with precancerous lesions (ICD-10 N85.1 [1]) and invasive carcinomas of the endometrium. The guideline recommendations are intended for all physicians and members of professional groups concerned with the treatment of patients with endometrial cancer. These include above all gynecologists, family physicians, radiologists, pathologists, radio-oncologists, hematologists/oncologists, psycho-oncologists, palliative-medicine specialists, and nursing staff.

The guideline and the patient version of it in particular, is also aimed at all women affected by endometrial cancer and their relatives. The field of application for the guideline includes both the outpatient and in-patient care sectors: detecting early symptoms and carrying out follow-up procedures belong largely to the field of colleagues working in private medical practices, while surgical treatment takes place in the in-patient field. Radiotherapy and systemic drug treatment are carried out both by colleagues in private practice and also in the relevant outpatient departments in larger hospitals.

The guideline is also intended for:

- Medical and scientific specialist societies and professional organizations
- Special interest groups representing women (women's health organizations, patient organizations, and self-help organizations)
- Quality assurance institutions and projects at the federal and state level (AQUA, Institute for Applied Quality Assurance and Research in the Health-Care System, Working Group of German Tumor Centers, etc.)
- Health-policy institutions and decision-making bodies at federal and state level
- Funding bodies / health insurance bodies

2.3. Objectives

The aims of this interdisciplinary Level 3 Guideline on Early Detection, Diagnosis, Treatment, and Follow-up in Patients with Endometrial Cancer include providing information and counseling for women regarding the diagnosis (clinical, machine-aided, or surgical), the various treatment options (surgery, radiotherapy, drug treatment) and in particular the time course and modular combinations of these at the various stages of the disease — i.e., precancerous lesions, early stages, advanced stages, and the palliative situation. The treatment of rare histological subtypes and also of hereditary forms is also discussed.

The guideline describes the options for preserving reproductive fertility while maintaining oncological safety, rehabilitation measures, follow-up, palliative treatment, and psycho-oncological support. The latter is necessary in

endometrial cancer, which substantially alters women's sexual life particularly after the administration of radiotherapy. The recommendations are aimed at the physicians treating patients, nursing professions, and medical partners involved in the treatment of patients with endometrial cancer.

The optimal methods for early detection and diagnosis of endometrial cancer and precursor lesions are identified through reviews of the available evidence. There is potential for improvement in early detection here through rigorous and consistent observation of the relevant symptoms. On the other hand, there is also very likely to be considerable potential for reducing unnecessary worry for patients, and for reducing costs, by avoiding diagnostic measures that are not useful.

Evidence-based, risk-adapted therapy can avoid unnecessarily radical surgical procedures and unnecessary adjuvant radiotherapy and/or chemotherapy in women with endometrial cancer who are at low risk. This markedly reduces the treatment-induced morbidity and increases the patients' quality of life, on the one hand. On the other, it also avoids unnecessary costs. For women with endometrial cancer who are at high risk for recurrence, the guideline defines the optimal degree of surgical radicality and the adjuvant chemotherapy and/or adjuvant radiotherapy that may be required if appropriate. The evidence-based optimal use of the various treatment modalities is intended to improve survival rates and quality of life for these patients. This Level 3 guideline on endometrial cancer is intended to provide a basis for the work of certified gynecological cancer centers. The quality indicators based on this guideline are intended for use in certification procedures for these centers.

2.4. Period of validity and updating procedure

This Level 3 guideline is valid until the time of its next update, and the maximum period of validity is 5 years. Regular updating is planned, and in case of urgently needed changes amendments will be prepared that will be published in new versions of the guideline. The aim is to carry out updates at 2-year intervals. Comments and notes for the updating process are expressly requested and can be addressed to the guideline secretariat:

- Georg-August-Universität
  Universitätsmedizin Göttingen
  Klinik für Gynäkologie und Geburtshilfe
  Leitliniensekretariat
  Robert-Koch-Strasse 40
  37075 Göttingen
  Postal address: 37099 Göttingen
  Tel.: +49 (0) 551-39 66501
  Fax: +49 (0) 551-39 66585
  E-mail: emons@med.uni-goettingen.de

— or alternatively to the Oncology Guidelines office (see section 1.4).

2.5. Methodological basis

The methodological procedure using in compiling the present guideline is described in the Guideline Report, which is freely available on the Internet on the German Guideline Program in Oncology website (https://www.leitlinienprogramm-onkologie.de/leitlinien/endometriumkarzinom/) and also on the website of the AWMF (https://www.awmf.org).

Details on the grading of evidence and recommendations used in the recommendation boxes — grade of recommendation (GoR), level of evidence (LoE) — are explained in the Appendix in sections 13.3.1and 13.3.2.

2.5.1. Independence and presentation of potential conflicts of interest

German Cancer Aid provided the financial resources for this guideline through the German Guideline Program in Oncology. These funds were used for staffing costs, office materials, purchasing of literature sources, and the organization of consensus conferences (room rental, technology, catering, moderators' fees, participants' travel expenses). The guideline was prepared with editorial independence from the funding organization. During the guideline preparation process, all of the members provided written declarations regarding any potential conflicts of interest. The published conflicts of interest can be consulted in the Guideline Report (section 1.8) for this guideline.

Collection of declarations of conflicts of interest

Declarations of conflicts of interest were obtained from all members of the guideline group at the start of the guideline project. The AWMF's "Declaration of Conflicts of Interest" form was used for the purpose. The guideline coordinator's conflict of interest declaration was forward to the German Guideline Program in Oncology office, and the other declarations were checked by the guideline coordinator.

Handling of potential conflicts of interest

At the first consensus meeting, held in Frankfurt am Main on June 19, 2015, there was unanimous consensus that office-holders who had conducted research studies on the topic of endometrial cancer should not vote on the relevant statements and recommendations. They could, however, present documents and make further information available, and also contribute to the discussion. Details to be stated included external funding from industry and advisory boards. Company names (for external funding) were to be stated. In details regarding external funding, the company from which the funding came was to be made transparent, as well as the purposes for which it was used. Individuals who had received external funding from industry relating to endometrial cancer, or who were members of an advisory board linked to this indication, were not permitted to vote on any statements or recommendations affected by this.

We would like to take this opportunity to thank all associates and colleagues for their entirely voluntary contributions to this project.

3. Epidemiology and risk factors, prevention of endometrial cancer

3.1. Epidemiology and risk factors

3.1.1. Age

No.	Recommendation	GoR	LOE	Sources
3.1	The risk of developing endometrial cancer increases with increasing age.	ST	1	[2]

Table 2: Overview of the most important epidemiological measures for Germany, ICD-10 C54–C55 [2]

	Women (2011)	Women (2012)	Women (prognosis for 2016)
Incident cases	11,140	10,930	10,800
Crude incidence rate [1]	27.1	26.6	26.2
Standardized incidence rate [1,2]	16.9	16.6	15.8
Mean age at diagnosis [3]	69	69	
Deaths	2,442	2,515	
Crude mortality rate [1]	5.9	6.1	
Standardized mortality rate [1,2]	3.0	3.0	
5-year prevalence	45,900	45,600	
	After 5 years	After 10 years	
Absolute survival rate (2011–2012) [4]	71 (66–73)	58 (55–61)	
Relative survival rate (2012–2012) [4]	80 (75–82)	76 (73–78)	

[1] Per 100,000 population.
[2] Age-standardized relative to the old European Standard Population.
[3] Median.
[4] In percentage rates (lowest and highest values for the German federal states included).

3.1.2. Hormone replacement therapy (HRT) without gestagen protection

No.	Recommendation	GoR	LOE	Sources
3.2	Hormone therapy with estrogens alone, without gestagen protection, is a risk factor for the development of endometrial cancer in women who have not undergone hysterectomy. The effect is dependent on the duration of administration.	ST	2	[3-8]

3.1.3. Hormone replacement therapy (HRT) with gestagen protection

3.1.3.1. Continuous combined estrogen–gestagen therapy

No.	Recommendation	GoR	LOE	Sources
3.3	A reduction in the risk of endometrial cancer has been observed in patients receiving continuous combined hormone therapy with conjugated equine estrogens and medroxyprogesterone acetate as the gestagen, with a mean administration period of 5.6 years.	ST	2	[9]
3.3.1	Continuous combined hormone therapy with an administration period of < 5 years can be regarded as safe in relation to the risk of endometrial cancer.	ST	2	[3, 4, 6, 7, 9-12]

3.1.3.1.1. Long-term administration of continuous combined HRT

No.	Recommendation	GoR	LOE	Sources
3.4	An increased risk for the development of endometrial cancer has been observed during long-term administration of continuous combined hormone therapy for > 6 years or > 10 years.	ST	3	[6, 7]

3.1.3.1.2. Administration of progesterone or dydrogesterone

No.	Recommendation	GoR	LOE	Sources
3.5	Administration of progesterone or dydrogesterone during continuous combined hormone therapy may increase the risk for the development of endometrial cancer.	ST	3	[12]

Table 3: Risk of endometrial cancer relative to body mass index and administration of combined HRT [13]

BMI	RR [1]	Risk of endometrial cancer in nonusers	Risk of endometrial cancer in users
27	1.22 (1.19–1.24)	1.31 (95% CI, 1.2–1.4)	1.08 (95% CI, 1.0–1.1)
32	2.09 (1.94–2.26)	2.74 (95% CI, 2.0–3.4)	1.34 (95% CI, 1.1–1.6)
37	4.36 (3.75–5.10)	7.54 (95% CI, 4.1–13.9)	1.78 (95% CI, 1.2–2.7)
42	9.11 (7.26–11.51)	20.70 (95% CI, 8.3–51.8)	2.38 (95% CI, 1.3–4.5)

BMI, body mass index; CI, confidence interval(s); RR, relative risk.

3.1.3.2. Sequential combined estrogen–gestagen therapy

No.	Recommendation	GoR	LOE	Sources
3.6	Sequential combined hormone therapy may increase the risk for the development of endometrial cancer. The effect is dependent on the duration, type, and dosage of the gestagen administration.	ST	3	[3, 4, 6-8, 11]
3.7	Sequential combined hormone therapy with an administration period of < 5 years and with the use of a synthetic gestagen for at least 12–14 days per month can be regarded as safe in relation to the risk of endometrial cancer.	ST	2	[3, 4, 8]

3.1.4. Tibolone

No.	Recommendation	GoR	LOE	Sources
3.8	An increased risk for the development of endometrial cancer has been observed with tibolone treatment.	ST	3	[3], [14], [8]

3.1.5. Tamoxifen

No.	Recommendation	GoR	LOE	Sources
3.9	Tamoxifen treatment is a risk factor for the development of endometrial cancer. The effect is dependent on the duration of administration.	ST	1	[15-18]

[1] Data in accordance with the partially linear model.

3.1.6. Oral contraceptives

No.	Recommendation	GoR	LOE	Sources
3.10	Oral contraceptives reduce the risk for the development of endometrial cancer. The strength of the effect is dependent on the duration of use.	ST	2	[19, 20]

3.1.7. Ovarian stimulation therapy

No.	Recommendation	GoR	LOE	Sources
3.11	Ovarian stimulation therapy increases the risk of endometrial cancer in comparison with population-based controls, but not in comparison with infertile women.	ST	4	[21, 22]

3.1.8. Other biological risk factors

No.	Recommendation	GoR	LOE	Sources
3.12	Late age at menarche and late age at the birth of the last child are associated with a reduced risk of the development of endometrial cancer, while late age at menopause is associated with an increased risk.	ST	3	[23-25]
3.13	Diabetes mellitus, disturbances of glucose tolerance, metabolic syndrome, and polycystic ovary syndrome (PCOS) increase the risk for the development of endometrial cancer.	ST	3	[26-40]
3.14	An increased body mass index (BMI) increases the risk for the development of endometrial cancer.	ST	3	[41], [13], [42], [43], [44], [45]
3.15	A positive family history of endometrial cancer and/or colon carcinoma is associated with an increased risk for the development of endometrial cancer.	ST	3	[46]

3.2. Risk-reducing factors

No.	Recommendation	GoR	LOE	Sources
3.16	Physical activity is associated with a reduced risk of the development of endometrial cancer.	ST	3	[47-51]
3.17	The use of intrauterine contraceptive devices (IUDs; copper or levonorgestrel releasing devices) is associated with a reduce risk for the development of endometrial cancer.	ST	3	[52], [53]

3.3. Summary review of risk-increasing and risk-reducing factors

Table 4: The risk for the development of endometrial cancer

Increases:	Decreases:
· With increasing age · With tamoxifen treatment, depending on the duration of therapy · With hormone therapy with estrogens alone, without gestagen protection, in women who have not undergone hysterectomy, depending on the duration of administration · With long-term administration (> 6 years or > 10 years) of continuous combined hormone therapy · With sequential combined hormone therapy, depending on the duration, type, and dosage of gestagen administration · With the use of progesterone or dydrogesterone during continuous combined and sequential hormone therapy · With tibolone administration · With late age at menopause · In patients with diabetes mellitus, disturbed glucose tolerance, metabolic syndrome, and polycystic ovary syndrome · With an increased body mass index · With a positive family history of endometrial cancer and/or colon carcinoma	· With continuous combined hormone therapy with conjugated equine estrogens and medroxyprogesterone acetate as the gestagen · With administration of oral contraceptives, depending on the duration of use · With late age at menarche and late age at the birth of the last child · With physical activity · With the use of an IUD, particularly levonorgestrel IUDs · In smokers

4. Early detection and diagnosis of endometrial cancer

4.1. Early detection/diagnosis in asymptomatic women

4.1.1. Asymptomatic women who are not at increased risk

No.	Recommendation	GoR	LOE	Sources
4.1	The available data do ***not*** show that early detection examinations using transvaginal ultrasound reduce the endometrium-specific mortality rate in asymptomatic women who are not at increased risk for endometrial cancer.		EC	
4.2	Transvaginal ultrasonography must ***not*** be carried out for purposes of early detection in asymptomatic women who are not at increased risk for endometrial cancer.		EC	

4.1.2. Asymptomatic women who are at increased risk

No.	Recommendation	GoR	LOE	Sources
4.3	The available data does ***not*** show that early detection examinations with transvaginal ultrasound reduce the endometrial cancer-specific mortality rate in asymptomatic women who are at increased risk for endometrial cancer (such as those with Lynch syndrome, obesity, diabetes mellitus, hormone therapy, metabolic syndrome, PCOS).		EC	
4.4	The available data does ***not*** show that early detection examinations using endometrial biopsy, Pipelle, Tao brush, tumor markers, fractional curettage, or hysteroscopy reduce the endometrial cancer-specific mortality rate in asymptomatic women who are at increased risk for endometrial cancer (such as those with Lynch syndrome, obesity, diabetes mellitus, hormone therapy, metabolic syndrome, PCOS).	ST	4	[54], [55]
4.5	Transvaginal ultrasound examinations must ***not*** be carried out for early detection of endometrial cancer in asymptomatic women who are at increased risk for endometrial cancer (such as those with Lynch syndrome, obesity, diabetes mellitus, hormone therapy, metabolic syndrome, PCOS).		EC	

4.1.3. Asymptomatic women receiving tamoxifen therapy

No.	Recommendation	GoR	LOE	Sources
4.6	Transvaginal ultrasonography must ***not*** be carried out for early detection of endometrial cancer in asymptomatic patients who are receiving tamoxifen therapy.	A	3	[56-60]

4.1.4. Postmenopausal hormone replacement therapy (HRT)

The diameter of the endometrium is influenced by administration of hormone replacement therapy (HRT) postmenopausally, as is the risk for developing endometrial cancer. The type of HRT is also important for ultrasound assessment of the diameter of the endometrium. In the study by Van den Bosch et al. [61] including a total of 238 women, the mean endometrial thickness during continuous combined estrogen–gestagen HRT was 3.5 ± 1.6 mm, in contrast to mean endometrial thicknesses of 4.1 ± 1.9 mm during tibolone therapy and 5.5 ± 2.5 mm during sequential HRT [61]. The endometrial thickness during sequential HRT is thus significantly larger, by 1.4 mm, than during treatment with tibolone or during continuous HRT ($P = 0.0001$). If the cut-off values in patients without HRT are used in patients who are receiving HRT, there is thus a lower diagnostic specificity for detecting endometrial cancer, particularly in patients receiving sequential HRT.

4.2. Diagnostic clarification of abnormal premenopausal uterine bleeding

No.	Recommendation	GoR	LOE	Sources
4.7	The risk for endometrial cancer or atypical endometrial hyperplasia in premenopausal women with abnormal uterine bleeding is below 1.5%.	ST	2	[62]
4.8	In women with premenopausal abnormal uterine bleeding who do not have any risk factors (suspicious cytology, obesity, Lynch syndrome, diabetes, polyps, etc.), an attempt at conservative treatment should initially be made, provided that the bleeding is not hemodynamically relevant. If conservative therapy fails, hysteroscopy/curettage should be carried out.	EC		
4.9	The gold standard for a definite diagnosis of endometrial cancer is hysteroscopy in combination with fractional curettage.	ST	3	[63], [64], [65]
4.10	In smaller series with symptomatic patients, diagnostic procedures such as Pipelle and the Tao brush have shown comparable positive and negative predictive values for diagnosing endometrial cancer as curettage plus hysteroscopy. However, there is still a lack of larger studies.	ST	3	[66]

No.	Recommendation	GoR	LOE	Sources
4.10.1	These diagnostic procedures are ***not*** at present comprehensively available on a quality-assured basis throughout Germany.	EC		

4.2.1. Diagnostic algorithm for abnormal premenopausal uterine bleeding

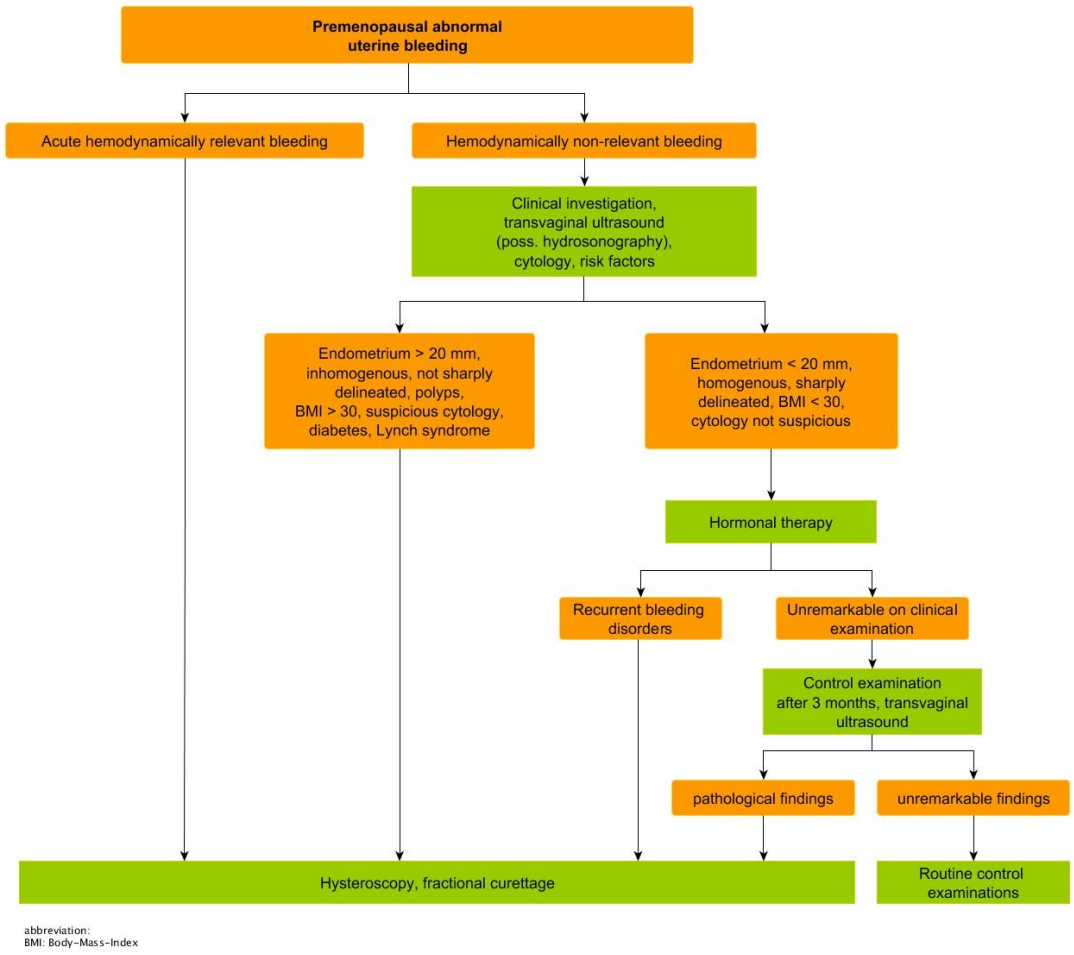

Figure 1: Algorithm for diagnostic procedure for abnormal premenopausal uterine bleeding

4.3. Procedure with postmenopausal bleeding (PMB)

No.	Recommendation	GoR	LOE	Sources
4.11	In a woman with a first episode of postmenopausal bleeding and an endometrial thickness ≤ 3 mm, ultrasound and clinical check-up examinations should take place after 3 months.	B	1	[67]

No.	Recommendation	GoR	LOE	Sources
4.12	Persistence or recurrence of the clinical symptoms, or an increase in the endometrial thickness, must prompt histological clarification.		EC	

4.3.1. Diagnostic algorithm for the procedure in women with perimenopausal or postmenopausal bleeding

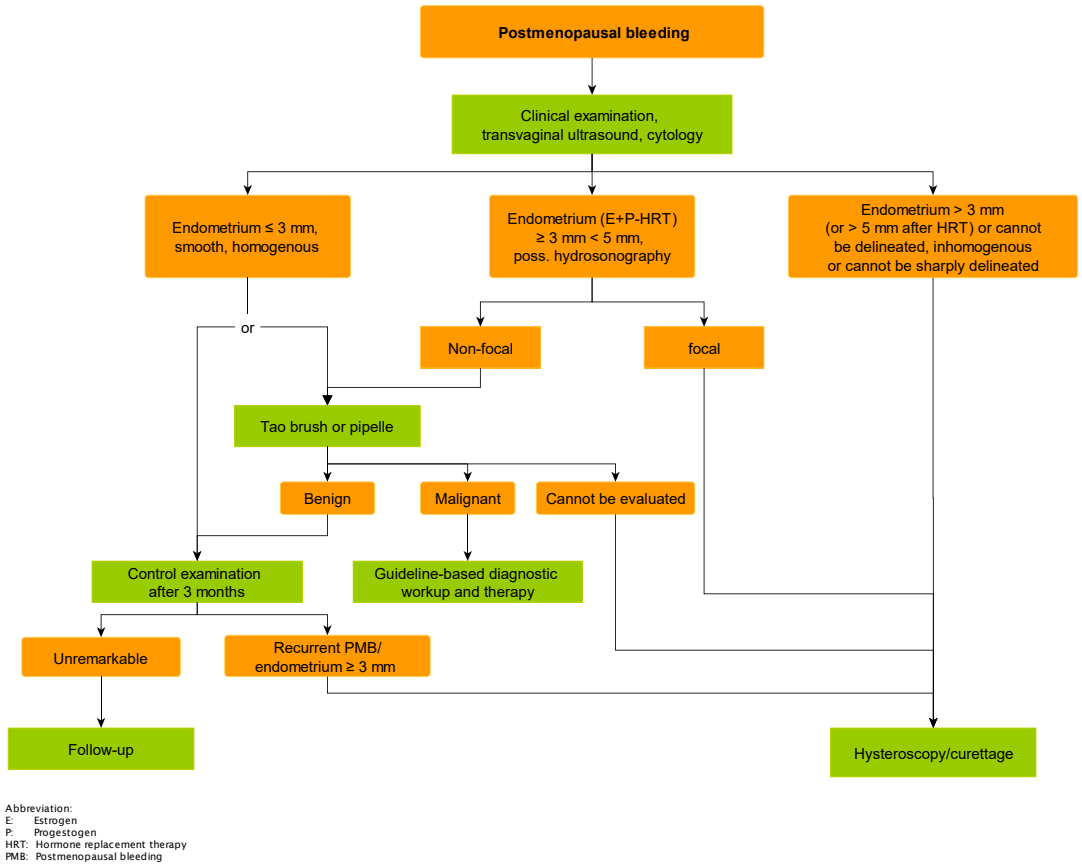

Figure 2: Algorithm for the diagnostic procedure in women with perimenopausal or postmenopausal bleeding [68], [67], [62]

4.4. Imaging diagnosis

4.4.1. General information about imaging

No.	Recommendation	GoR	LOE	Sources
4.13	Surgical staging with histopathological examination is the reference method for diagnosing the extent of local spread in patients with endometrial cancer. Imaging is the primary diagnostic method for distant metastases outside of the usual surgical field.		EC	

4.4.2. Basic imaging diagnosis

4.4.2.1. Chest radiography

In the IKNL and ACR guidelines, chest radiographs at two levels are recommended for primary diagnosis of endometrial cancer [69], [70]. As the basic examination, this is primarily used to assess the patient's preoperative cardiopulmonary status, while at the same time allowing assessment of any rare pulmonary metastases. Preoperative chest radiography is also used to establish the baseline findings for any check-ups during the later course.

Although distant pulmonary metastases are generally rare at the initial manifestation of endometrial cancer, they lead to FIGO stage IV. In a retrospective multicenter study, Amkreutz et al. [71] report that pulmonary metastases from endometrial cancer were found on chest radiographs in 1.3% of patients (seven of 541). All of the patients affected had high-risk subtypes (serous, clear cell, or poorly differentiated endometrioid), and the incidence of pulmonary metastases was 4.1% for these subtypes. No pulmonary metastases were found on chest radiographs in patients with low-risk subtypes of endometrial cancer. A total of 243 other patients did not undergo chest imaging during primary diagnosis. The authors conclude that chest radiography can be dispensed with for metastasis detection in patients with low-risk subtypes of endometrial cancer. According to the study by Amkreutz et al. [71], approximately 4% of patients with high-risk subtypes have pulmonary metastases for which detection is relevant to the subsequent treatment.

4.4.2.2. Abdominal ultrasonography

Abdominal ultrasound is a basic examination, particularly for assessing the internal organs, including possible prior urinary flow disturbances. However, assessment of the lower pelvis and retroperitoneum is limited due to superimposed intestinal gas. In accordance with the ACR guideline [70], transabdominal ultrasonography is not regarded as appropriate for the staging of endometrial cancer.

4.4.2.3. Transvaginal ultrasonography

No.	Recommendation	GoR	LOE	Sources
4.14	When there is histological confirmation of primary endometrial cancer, a transvaginal ultrasound examination should be carried out to assess the extent of infiltration into the myometrium and cervix.	B	3	[72]
4.15	Preoperative imaging using transvaginal ultrasound is used for documentation and surgical planning, although the final locoregional staging classification takes place postoperatively based on the histological findings.	EC		

4.4.3. Tomographic imaging for diagnosing local spread

No.	Recommendation	GoR	LOE	Sources
4.16	If the transvaginal ultrasound findings show limited imaging quality, magnetic resonance imaging (MRI) should be offered for preoperative assessment of the extent of infiltration into the myometrium and cervix in patients with primary endometrial cancer.	B	3	[72]
4.17	If there is a need for noninvasive assessment of locoregional lymph nodes, tomographic imaging should be carried out.[2,3]	B	3	[69, 70, 73-76]
4.18	In patients receiving primary radiotherapy, the extent of locoregional spread should be diagnosed if possible using MRI.[4]	EC		

4.4.4. Imaging for distant metastases

No.	Recommendation	GoR	LOE	Sources
4.19	If there is a justified suspicion of distant metastases, the latter should be evaluated for purposes of treatment planning using tomographic imaging (and skeletal scintigraphy if appropriate).	B	3	[69, 70, 75]

[2] E.g. for imaging diagnosis of the extent of spread before primary radiotherapy, or when planning the surgical procedure in patients with advanced carcinomas (cT3).

[3] Transabdominal and transvaginal ultrasonography are not suitable for this.

[4] If MRI is not possible, computed tomography (CT) or positron emission tomography plus computed tomography (PET-CT) are possible alternatives. It should be noted that the costs of PET-CT are at present only accepted by the statutory health-insurance companies in individual cases, on application.

4.5. Pathology

4.5.1. Dual model for the pathogenesis of endometrial cancer (see Table 5)

A simplified model originally developed by Jan Bokhman [77] describes two types of endometrial cancer, with differing biology and pathogenesis, to which specific histomorphological and molecular subtypes can be assigned.

Endometrioid and mucinous carcinomas — type I carcinomas — typically arise under the influence of hyperestrogenism on the basis of atypical endometrial hyperplasia, and are mainly characterized by low stage and a favorable course. Their relationship to estrogens is also indicated by the perimenopausal age peak and usually high levels of expression of estrogen and progesterone receptors. Their pathogenesis follows an adenoma–carcinoma sequence, with subsequent progression from low-grade to high-grade malignancy, and it has often been compared with the pathogenesis of sporadic colorectal carcinoma.

Important molecular changes that usually occur at an early stage affect the *PTEN, KRAS,* and *CTNNB1* (catenin beta 1) genes, as well as the mismatch repair system [78], whereas *TP53* mutations only appear during the course of carcinoma progression. Endometrioid carcinomas without associated hyperplasia probably show differences in the molecular pathogenesis and prognosis [79], [80]. Type II carcinomas typically arise on the basis of atrophic endometrium or inside (glandular-cystic) endometrial polyps.

Histologically, these include non-endometrioid carcinomas, particularly serous ones, and currently clear cell carcinomas as well. The peak age of occurrence is in the very elderly, and expression of estrogen receptors and progesterone receptors is usually lacking or weak, so that a clear pathogenetic relationship to the female sexual hormones is absent. The development of these lesions is thought to be de novo on the basis of an intraepithelial carcinoma, but this has only been reported for serous carcinoma (serous intraepithelial carcinoma, SIEC).

At the molecular level, *TP53* mutations and overexpression of cyclin E occur at an early stage in the pathogenesis, as well as changes in the *PIK3CA* pathway [81]. The genetic changes in *PTEN, KRAS, CTNNB1* and in the mismatch repair system that are characteristic of type I carcinomas are extremely rare.

Table 5: Dualistic model of endometrial cancer

	Type I carcinomas	Type II carcinomas
Estrogen relationship	Yes	No
Endometrium	Usually hyperplasia	Usually atrophy, SIEC
Estrogen or progesterone receptors	Usually positive	Usually negative or weakly positive
Age	55–65 years	65–75 years
Prognosis	Stage-dependent, usually favorable	Stage-dependent, usually unfavorable

	Type I carcinomas	Type II carcinomas
Stage	Usually FIGO stage I	Usually FIGO stages II–IV
Histological subtype	Endometrioid + variants; mucinous	Serous, clear cell
Molecular changes	*PTEN* inactivation, microsatellite instability, *CTNNB1* mutations, *KRAS* mutations	p53 mutations, E-cadherin inactivation, *PIK3CA* changes
Molecular types (TCGA)	*POLE* ultramutated, microsatellite instability hypermutated, copy number low	Copy number high (serous-like)
TCGA, The Cancer Genome Atlas.		

4.5.2. Precursor lesions for endometrial cancer

In the WHO classification, atypical endometrial hyperplasia (ICD-10 N85.1) [1] is listed as a precursor lesion for type I carcinoma [82]. The synonymous term "endometrioid intraepithelial neoplasia" (EIN) may be used. By contrast, endometrial hyperplasia without atypia (ICD-10 N85.0) [1] is regarded not as a precursor lesion, but rather as a disease involving a risk for the development of endometrial cancer. SIEC is classified not as a preneoplastic condition, but rather as a superficial carcinoma, since it is rarely diagnosed in isolation and is associated with an extensive extrauterine serous carcinoma in more than 50% of cases.

4.5.2.1. Endometrial hyperplasias

Endometrial hyperplasias are characterized by an increase in glands and stroma due to increased proliferation. In some endometrial hyperplasias, particularly atypical hyperplasias, the ratio of glands to stroma is additionally shifted in favor of glands in comparison with an increased proliferation phase [82]. Atypical hyperplasia is characterized by clonal expansion of densely packed glands with cellular atypia. In the WHO classification, there is a two-stage subdivision into hyperplasia without atypia and atypical hyperplasia [82], which is summed up in Table 5 in comparison with earlier classifications.

Table 6: The 2014 WHO classification of endometrial hyperplasia in comparison with earlier classifications [82]

Dallenbach-Hellweg classification	1994/2003 WHO classification	2014 WHO classification
Glandular-cystic hyperplasia Adenomatous hyperplasia Grade 1	Simple hyperplasia without atypia	Endometrial hyperplasia without atypia
	Complex hyperplasia without atypia	
Grade 2		
Grade 3	Simple atypical endometrial hyperplasia	Atypical endometrial hyperplasia/EIN
	Complex atypical endometrial hyperplasia	
EIN, endometrial intraepithelial neoplasia.		

4.5.2.2. Endometrial hyperplasia without atypia

Endometrial hyperplasia without atypia arises due to protracted stimulation of the endometrium by estrogens. The risk for the development of an endometrioid endometrial cancer (type I carcinoma) is low, at 1–4% [83], [84], [85]. Endometrial hyperplasia without atypia is polyclonal in around 95% of cases [86].

4.5.2.3. Atypical endometrial hyperplasia (AEH)

Atypical endometrial hyperplasia also arises in the majority of cases due to hyperestrogenism, and in rare cases with hereditary cancers it may occur with an increased risk for endometrial cancer. These cases include in particular Cowden syndrome (germline mutation in the tumor suppressor gene *PTEN* [87]) and Lynch syndrome (inactivation of the mismatch repair gene) [88].

In comparison with hyperplasia without atypia, a complex pattern of densely packed glands occurs, with the appearance of cellular atypia [82]. Changes similar to those seen in endometrioid endometrial cancer are already identifiable using molecular pathology — such as microsatellite instability, inactivation of *PTEN* (mainly due to mutation) and *PAX2,* as well as mutations in *KRAS* and *CTNNB1* [78], which are in some cases diagnostically helpful. The risk for endometrioid endometrial cancer (type I carcinoma) is markedly increased, at a mean of 45 [83], [84], [85].

A carcinoma is already found concordantly in 40–50% of cases in hysterectomy specimens taken within 6 months of curettage [89]. Atypical hyperplasia needs to be distinguished from SIEC in the differential diagnosis; the latter is characterized among other things by its high degree of nuclear atypia and a mutation-specific immunohistochemical staining pattern for p53.

4.5.3. Morphology of endometrial cancer

No.	Recommendation	GoR	LOE	Sources
4.20	The terminology and morphological diagnosis of endometrial hyperplasia must be based on the currently applicable edition of the WHO classification.		EC	
4.21	Carcinosarcomas (malignant müllerian mixed tumors, MMMTs) are assigned to the carcinomas in molecular pathology. The histological assessment of carcinosarcomas must be based on the currently applicable WHO classification. The FIGO and TNM classification must be carried out on analogy with the classification for endometrial cancer.		EC	

4.5.3.1. Tumor typing (see Table 7)

Precise tumor typing is relevant for treatment and for the prognosis. In cases of doubt, additional immunohistochemical examinations can be recommended [90], [91], [92], [82].

In the majority of cases (70–80%), the lesions are endometrioid carcinomas, the histological variants of which have no clinical relevance. Around 10–25% of endometrioid carcinomas show squamous differentiation; less frequent findings are secretory differentiation and a villoglandular or sertoliform pattern. By contrast, all other types of carcinoma are much more rare. Mucinous differentiation may occur in endometrioid carcinomas, or rarely as mucinous carcinoma with a more than 50% proportion of the tumor. Serous carcinoma, clear cell carcinoma, and undifferentiated carcinoma represent 5% or fewer of the lesions, and neuroendocrine carcinomas are rarities.

Although serous endometrial intraepithelial carcinoma (SEIC) is regarded as a directly noninvasive precursor lesion for serous carcinoma, it represents a superficial carcinoma biologically, as it is not uncommon for it to be associated with peritoneal spread [93]. In SEIC, the surface epithelium and/or glandular epithelium is replaced by epithelium showing high-grade atypia [82].

Since invasion is often difficult to diagnose, the use of the synonymous term “minimal uterine serous carcinoma” is recommended specifically for biopsies and curettage material [82]. SEIC shows the same molecular-pathological changes as those seen in invasive serous endometrial cancer. Mixed carcinomas consist of at least two different histological types, one of which corresponds to a type II carcinoma (serous, clear cell) and must represent at least 5% of the total tumor mass [82].

Table 7: Histopathological classification of endometrial cancer [82], [94]

• Endometrioid adenocarcinoma
• Variants of endometrioid adenocarcinoma
➢ Secretory variants
➢ Ciliated cell variants
➢ Villoglandular variants
➢ Variants with squamous epithelial differentiation
• Mucinous adenocarcinoma
• Serous adenocarcinoma
• Clear cell adenocarcinoma
• Mixed carcinoma
• Undifferentiated carcinoma
➢ Monomorphic type
➢ Dedifferentiated type
• Neuroendocrine tumors
➢ Well-differentiated neuroendocrine tumors (carcinoid)
➢ Poorly differentiated small cell neuroendocrine carcinoma
➢ Poorly differentiated large cell neuroendocrine carcinoma
• Other carcinomas

Undifferentiated carcinomas do not show any differentiation at all. In addition to the monomorphic variant, a dedifferentiated carcinoma is now distinguished that contains a low-grade (G1 or G2) component of an endometrioid carcinoma. In the differential diagnosis, dedifferentiated carcinomas have to be distinguished from carcinosarcomas, which are also rare (synonym: malignant müllerian mixed tumors, MMMTs; ICD-O 8980/3) [95]. Previously, carcinosarcoma of the endometrium was discussed in the consensus-based (Level 2) guideline on "Uterine Sarcomas," version 1.0 (2015), AWMF registry number 015/074 (https://www.awmf.org/leitlinien/detail/ll/015-074.html) [96]. It is now included in the evidence-based and consensus-based (Level 3) guideline on the "Diagnosis, Treatment, and Follow-up of Patients with Endometrial cancer" (the present document).

These lesions have biological similarities to high-grade carcinomas, but in the WHO classification they are assigned to the group of mixed epithelial-mesenchymal tumors. They typically consist of a highly malignant epithelial component and a malignant mesenchymal component. In contrast to dedifferentiated carcinomas, these are arranged in a biphasic pattern. Depending on the degree of tissue differentiation, the mesenchymal component is described as homologous (structures that occur in the uterus — e.g., smooth muscle) or heterologous (structures that do not occur in the uterus — e.g., cartilage and bone).

Molecular-pathological studies indicate that these lesions arise from a single original cell and that they are related to carcinomas [97], [98], [99]. In the TNM system, carcinosarcomas are classified in the same way as endometrial cancers [100], [101].

The classification of neuroendocrine tumors of the endometrium is roughly based on the classification of neuroendocrine tumors in the gastrointestinal tract [82], [102], although precise criteria for this are not stated.

4.5.3.2. Grading in endometrial cancer

The grading depends on the histological tumor type. In the FIGO system, endometrioid and mucinous carcinomas are graded according to the proportion of solid, nonsquamous areas [82]: G1 carcinomas contain less than 5%, G2 carcinomas have 6–50%, and G3 carcinomas have more than 50%. If higher-grade cellular atypia is present, the grading is increased by one step in each case, but the possibility of a serous carcinoma should also be excluded. Serous and clear cell carcinomas are not graded and are classified as G3 by definition, as are carcinosarcomas.

4.5.3.3. Staging of endometrial cancer

No.	Recommendation	GoR	LOE	Sources
4.22	The staging of endometrial cancer must be carried out in accordance with the applicable FIGO/TNM classification.		EC	

Table 8: The new (2010) FIGO/TNM classification of endometrial cancer [100]

TNM category	FIGO stages	Definition
TX		The primary tumor cannot be assessed
T0		No evidence of a primary tumor
T1	I [1]	The tumor is limited to the body of the uterus
T1a	IA [1]	The tumor is limited to the endometrium, or is infiltrating less than halfway through the myometrium
T1b	IB	The tumor is infiltrating half or more of the myometrium

TNM category	FIGO stages	Definition
T2	II	The tumor is infiltrating into the cervical stroma, but is not spreading outside the uterus
T3 and/or N1	III	Local and/or regional spread, as described below:
T3a	IIIA	The tumor is affecting the serosa and/or adnexa (direct spread or metastases)
T3b	IIIB	Vaginal or parametrial involvement (direct spread or metastases)
N1	IIIC	Metastases to the pelvic and/or para-aortic lymph nodes [2]
	IIIC1	Metastases in the pelvic lymph nodes
	IIIC2	Metastases in the para-aortic lymph nodes
T4	IVA	The tumor is infiltrating the bladder and/or rectal mucosa [3]
M1	IVB	Distant metastases, including intra-abdominal metastases (excluding metastases in the vagina, pelvic serosa or adnexa, including metastases in the inguinal lymph nodes and intra-abdominal lymph nodes other than para-aortic and/or pelvic lymph nodes

1. Assessment of the endocervical glands alone must be classified as stage I.

2. Positive cytology must be diagnosed separately and documented without changing the stage.

3. The presence of bullous edema is not sufficient to classify a tumor as T4. Infiltration into the mucosa of the bladder or rectum requires biopsy confirmation.

4.5.3.4. Definition of TNM-relevant parameters

The depth of invasion is defined as the extent of tumor invasion into the myometrium, measured from the adjoining normal/hyperplastic endometrium as far as the deepest point of tumor infiltration. In tumors with exophytic growth, an imaginary line from the nearest detectable endometrium through the tumor is used as the uppermost measuring point [103], [104] (Figure 3: Determination of invasion depth in endometrium). Evidence of lymphatic infiltration below the deepest point of tumor infiltration is not included in the depth measurement and is classified as L1.

If the carcinoma has arisen in an endometriosis, the depth of invasion is measured from the most superficial normal/hyperplastic gland in each endometriosis as far as the deepest point of infiltration.

Measuring the depth of infiltration can be difficult, as there is no sharp boundary between the endometrium and myometrium [104], [105]. Infiltrative growth is present when tumor glands are in direct contact with the surrounding myometrium; sometimes there is slight peritumoral desmoplasia and an absence of surrounding endometrial stroma. Van Gieson staining to

identify desmoplasia and CD-10 immunohistochemistry to demonstrate endometrial stroma may be helpful in cases of doubt.

Growth of a carcinoma into a preexisting endometriosis may simulate myometrial infiltration and does not have any prognostic significance. The following findings argue in favor of a diagnosis of endometriosis involvement [105], [106]:

- Evidence of benign endometrial glands in the immediate vicinity of tumor glands
- Evidence of benign glands between tumor glands
- An absence of peritumoral desmoplasia
- An absence of peritumoral inflammation
- Round external contours of the lesion, with a sharp delineation from the surrounding myometrium on low magnification

The anterior and posterior wall of the uterus usually have the same thickness [107], so that it may be possible to use the thickness of the opposite wall as a reference value for myometrial thickness when measuring depth of invasion.

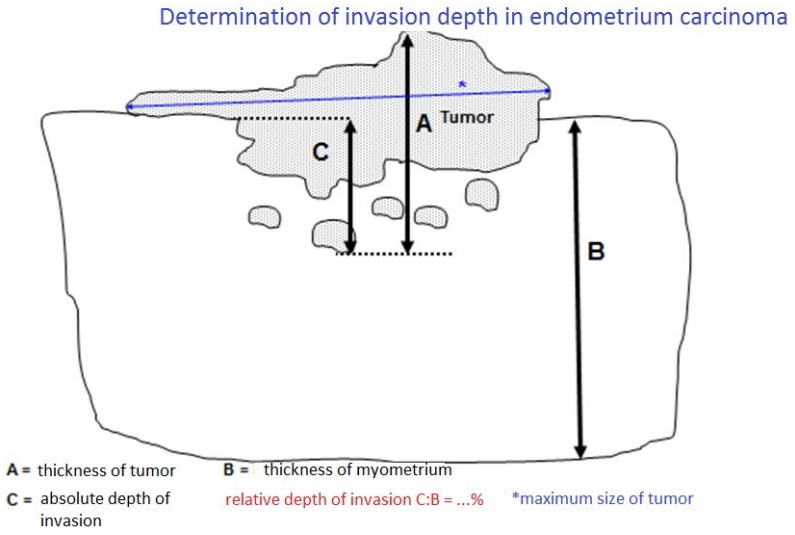

Figure 3: Determination of invasion depth in endometrium cancer [104], [103]

The tumor thickness is the distance measured between the tumor surface and the deepest point of invasion [104], [105].

Infiltration into the perineural sheath (the Pn category) is of subordinate importance for endometrial cancer and is defined as evidence of tumor cells in perineural spaces, independently of the spread of tumor cells within the spaces and independently of whether or not the nerve itself is infiltrated [108], [109].

Lymphatic infiltration (the L category) consists of evidence of individual or grouped tumor cells within spaces that are clearly covered in (lymphatic) endothelium (L1) [110]. The TNM committee has stated that when there is evidence of tumor cells inside spaces without clear endothelial cover, the findings are to be classified as L0 (no lymphatic infiltration) [110], since this

usually represents contraction-related artifacts. There is currently no indication for immunohistochemical examinations (e.g., D2-40) to confirm lymphatic invasion in endometrial cancer.

For invasion into veins (the V category), a distinction is made between macroscopically visible (V2) and histologically confirmed venous infiltration (V1) [100]. Macroscopic venous infiltration has no relevance in endometrial cancer. The microscopic V1 category is defined in the TNM system as evidence of tumor cells inside the venous lumen and/or evidence of tumor cells infiltrating the wall of the vein [110].

The grading of endometrial cancer depends on the histological tumor type, as discussed above.

4.5.4. Frozen-section examination in endometrial cancer, malignant müllerian mixed tumor, and atypical endometrial hyperplasia (AEH)

No.	Recommendation	GoR	LOE	Sources
4.23	An intraoperative histological examination may be carried out if there is a suspicion of stage pT1b and/or pT2.		EC	
4.24	If the surgeon decides to assess the depth of myometrial infiltration and/or endocervical stroma infiltration by the endometrial cancer on a frozen section examination, then these two parameters must be assessed macroscopically and microscopically.		EC	
4.25	A frozen-section examination must not be carried out to assess the grading and determine the histological tumor type.		EC	
4.26	The tubes and ovaries must be assessed macroscopically during the intraoperative frozen-section examination, and findings suspicious for metastases must be examined histologically.		EC	

4.5.5. Tissue processing

No.	Recommendation	GoR	LOE	Sources
4.27	Tissue from a (fractional) curettage or endometrial biopsy must be fully embedded.		EC	
4.28	The report on findings from a (fractional) curettage or endometrial biopsy must include a statement on the evidence and type of any endometrial hyperplasia. In the presence of carcinoma, the histological tumor type must be stated in accordance with the current WHO classification. When there is evidence of tumor tissue in the cervical part		EC	

No.	Recommendation	GoR	LOE	Sources
	of a fractional curettage, a clear statement must be made on the detection or absence of endocervical stroma infiltration.			
4.29	The morphological processing of a hysterectomy specimen must be carried out in such a way that all therapeutically and prognostically relevant parameters can be assessed. The findings must be based on the currently applicable WHO classification on tumor typing and the current TNM classification for staging.		EC	
4.30	The report on findings in a hysterectomy specimen must include the following details for endometrial cancer: • WHO histological type • With mixed carcinomas, details of the percentage proportion of each type in the overall tumor • Grading • Evidence/absence of lymphatic or vascular invasion (L and V status) • Evidence/absence of perineural sheath infiltration (Pn status) • Staging (pTNM) • Measurement of the depth of invasion relative to the thickness of the myometrium, in millimeters • Three-dimensional tumor size, in centimeters • In the presence of vaginal infiltration, measurement of the minimum distance to the vaginal resection margin • R classification (UICC)		EC	
4.31	Mixed carcinomas in the endometrium are defined in accordance with the WHO classification as tumors containing two or more histological subtypes, each of which is detected microscopically in > 5% of the extent of the overall tumor. The percentage proportion of each of the individual histological subtypes must be stated in the report on histological findings.		EC	

4.5.5.1. Curettage/endometrial biopsies

The tissue removed during curettage or endometrial biopsy due to dysfunctional or postmenopausal bleeding must be fully processed in accordance with the site of removal (samples from the cervical part or body of the uterus).

The report on the histopathological findings must make a statement regarding the presence and type of any endometrial hyperplasia. When there is evidence of carcinoma, the histopathological tumor type (type I carcinoma versus type II carcinoma; MMMT) must be stated in accordance with the current WHO

classification [82]. If there is evidence of tumor tissue in the cervical sample, a statement must be made on whether infiltration of the endocervical stroma is present or the tumor tissue is isolated due to dislocation from the uterine cavity [111, 112].

4.5.5.2. Specimens after simple and radical hysterectomy in endometrial cancer

The report on pathological findings must make a statement regarding the size, weight, and characteristics of the specimen, with special attention to the characteristics of the serosa [113], [92].

The macroscopic description of the endometrial cancer or MMMT must include the precise anatomic location (isthmus or body of the uterus, anterior or posterior wall or roof of the uterus), three-dimensional measurements of the extent of the tumor, the growth type (polypoid, sessile, diffusely infiltrating), and its relationship to the endocervix [113], [92]. It is recommended that details should be given on the removal of the tumor as far as the external and internal orifices of the uterine cervix.

In addition, details must be given on evidence or absence, as well as the length, of the resected vaginal cuff [113], [92]. The distal vaginal resection margin must be fully processed circularly (preferably after separation into a posterior and anterior vaginal cuff).

Studies in recent years have shown that malignant mixed müllerian tumors (MMMTs) represent a special type of endometrial cancer [98], and their processing, histopathological reporting, and staging correspond to those for endometrial cancer [100].

The morphological processing of the hysterectomy specimen must be carried out in such a way that all of the details given in the following list can be given [114], [115], [116], [113], [92]. The report must be based on the currently applicable WHO classification for tumor typing [82] and the current pTNM classification for staging [100].

Requirements for reporting histological findings in hysterectomy specimens [115], [116], [113], [92]:

- WHO histological type
- With mixed carcinomas, details of the percentage proportion of each in the overall tumor
- Grading
- Evidence/absence of lymphatic or vascular invasion (L and V status)
- Evidence/absence of perineural sheath infiltration (Pn status)
- Staging (pTNM)
- Measurement of the depth of invasion relative to the thickness of the myometrium, in millimeters
- Three-dimensional tumor size, in centimeters
- In the presence of vaginal infiltration, measurement of the minimum distance to the vaginal resection margin
- R classification (UICC)

For the definition of how to assess depth of invasion and tumor thickness, as well as other parameters, see section 4.5.3.4, ‘Definition of TNM-relevant parameters’, above.

Measurement of the distance to each resection margin is carried out from the point of deepest tumor infiltration to the surgical resection margin, either after marking using a ruler on the specimen slide or using an ocular micrometer for small distances.

There are probably differences in the molecular pathogenesis and in the prognosis for endometrioid carcinomas with and without associated endometrial hyperplasia [79], [80]. It therefore seems useful to include details of whether there is any evidence of endometrial hyperplasia in the endometrium near the tumor. Measurements of the absolute and relative depth of invasion into the cervical stroma are not relevant for staging or therapy at present, although some clinicians request these.

To ensure adequate documentation of the tumor type, it is recommended to embed one paraffin block per 2 cm of the largest tumor extent for purely endometrioid or serous carcinomas diagnosed during curettage; and one block per 1 cm of the largest tumor extent for mixed endometrioid/serous/clear cell/neuroendocrine carcinomas or MMMTs [113], [92].

If a macroscopically visible tumor is not detected in the hysterectomy specimen, it is useful to embed three blocks each from the anterior and posterior walls [103]. If there is also no histological evidence of a carcinoma (known as "vanishing endometrial cancer") [117], complete embedding of the endometrium is recommended, and several samples from the endometrial-myometrial transition zone may be embedded in one block.

The WHO classification defines a mixed carcinoma as a tumor with two or more histological subtypes, each of which can be identified microscopically in > 5% of the overall extent of the tumor [82]. Several studies describing mixed carcinomas have reported that a type II tumor component has prognostic significance even at a proportion of 5% [118]. The percentage proportion of a type II tumor part must therefore always be stated in the report on histological findings.

Various patterns of invasion into the myometrium also exist in endometrial cancer as well. In addition to the classic invasion pattern with infiltration of glands located in groups, with different degrees of peritumoral desmoplasia and an inflammatory reaction, there are also carcinomas with growth similar to that of malignant adenoma [119] and what is known as MELF pattern (microcystic, elongated, fragmented glands) [111]. The latter two types are thought to have a less favorable prognosis [119], [120], [121], [122]. It is therefore recommended that the pattern of invasion should be stated in the report on the histological findings.

Particularly with serous endometrial cancers, involvement of the adnexa may not be macroscopically visible [112], [123], although it is relevant for staging. Macroscopically unremarkable-looking ovaries should therefore be fully embedded with the immediately adjoining hilar tissue, and lamination along the short axis of the ovary is recommended, since this allows more tissue to be histologically assessed [105], [124]. Processing based on the SEE-FIM protocol is recommended for the tubes [125], [126], [127].

4.5.6. Processing and reporting of omentectomy specimens in endometrial cancer

No.	Recommendation	GoR	LOE	Sources
4.32	In patients with endometrial cancer, the ovaries should be completely embedded, including the hilum of the ovary. Processing of the tubes should be based on the SEE-FIM protocol.		EC	
4.33	When there is macroscopic tumor infiltration, at least one representative paraffin block must be examined during pathological processing of an omentectomy specimen in patients with endometrial cancer. If there is no macroscopic tumor infiltration, four to six paraffin blocks must be examined (several samples may be embedded in a single block). All additional abnormal findings (e.g., intra-omental lymph nodes) must be described macroscopically and examined histologically.		EC	

4.5.7. Processing and reporting of lymph-node specimens in endometrial cancer

No.	Recommendation	GoR	LOE	Sources
4.34	In lymphadenectomy specimens obtained during surgical treatment for endometrial cancer, all removed lymph nodes must be fully embedded and histologically examined.		EC	
4.35	Lymph nodes with a maximum extent of up to approx. 0.3 cm should be embedded in toto, and larger lymph nodes should be divided in two along their long axis or laminated and also fully embedded.		EC	
4.36	Isolated tumor cells are defined as evidence of individual tumor cells, or tumor cell components that are < 0.2 mm in total extent. Micrometastases are defined as histological evidence of tumor cells in lymph nodes ≥ 0.2 mm, but no larger than 0.2 cm.		EC	
4.37	The report on findings in lymphadenectomy specimens from patients with endometrial cancer must include the following details: · Number of lymph nodes affected relative to the number of lymph nodes removed, specifying the site of removal (pelvic, para-aortic)		EC	

No.	Recommendation	GoR	LOE	Sources
	· Size of the largest lymph-node metastasis, in millimeters/centimeters · Absence/evidence of capsular invasion by the lymph-node metastasis · Evidence of isolated tumor cells in lymph nodes and evidence of lymphatic vessel invasion in the perinodal fatty tissue and/or lymph-node capsule.			

4.5.8. Sentinel lymph nodes (examination in research studies)

No.	Recommendation	GoR	LOE	Sources
4.38	In the setting of research studies, sentinel lymph nodes that are removed in patients with endometrial cancer must be fully embedded and examined in step sections. In addition, immunohistochemical examinations must be carried out ("ultrastaging") on sentinel lymph nodes that are negative on hematoxylin–eosin (HE) morphology.		EC	

4.5.9. Morphological prognostic factors

A detailed discussion of morphological prognostic factors is given in the long version of this guideline.

Table 9 summarizes a risk stratification for endometrial cancer, based on morphological factors and on consensus agreement among the European Society for Medical Oncology (ESMO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Gynecological Oncology (ESGO) [128], [129].

Table 9: Risk stratification in endometrial cancer, based on consensus agreement among the European Society for Medical Oncology (ESMO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Gynecological Oncology (ESGO) [128], [129].

Risk group	Characteristics
Low risk	Endometrioid endometrial cancer, G1, G2, < 50% myometrial infiltration, L0
Low intermediate risk	Endometrioid endometrial cancer, G1, G2, ≥ 50% myometrial infiltration, L0
High intermediate risk	Endometrioid endometrial cancer, G3, < 50% myometrial infiltration, L0 or L1

Risk group	Characteristics
High risk	Endometrioid endometrial cancer, G3, ≥ 50% myometrial infiltration, L0 or L1, FIGO/TNM stage II/T2
	Endometrioid endometrial cancer, FIGO/TNM stage III/T3, R0
	Non-endometrioid endometrial cancer (serous/clear cell, undifferentiated, MMMT)

Table 10: Prognostic factors in endometrial cancer / MMMT

Name	Standard factor	Risk	Treatment relevance
Tumor stage	Yes	Yes	Yes
Depth of myometrial invasion	Yes	Yes	Yes
Lymph-node status	Yes	Yes	Yes
Histological tumor type	Yes	Yes	Yes
Size of lymph-node metastases	Yes	Unclear	No
No. of lymph nodes with metastatic involvement	Yes	Unclear	No
Extracapsular spread of lymph-node metastases	Yes	Unclear	No
Peritoneal cytology status	Yes	Unclear	No
Perineural sheath infiltration (Pn status)	Yes	Unclear	No
Lymphatic infiltration (L status)	Yes	Yes	Yes
Venous invasion (V status)	Yes	Unclear	No
Resection margins (residual tumor status; R classification)	Yes	Yes	Yes
Grading	Yes	Yes	Yes
Three-dimensional tumor size (cm)	Yes	Unclear	No

Name	Standard factor	Risk	Treatment relevance
Associated endometrial hyperplasia	No	No	No
Invasion pattern	No	Unclear	No
Hormone receptor status	No	Unclear	No
DNA cytometry	No	No	No
Intrinsic/molecular subtypes	No	Unclear	No
Molecular markers	No	No	No

5. Treatment of precancerous lesions and early endometrial cancer

5.1. Endometrial hyperplasia

5.1.1. Endometrial hyperplasia without atypia

No.	Recommendation	GoR	LOE	Sources
5.1	Endometrial hyperplasia without atypia must not be treated using hysterectomy.	A	3	[82]

5.1.2. Atypical endometrial hyperplasia (AEH)

5.1.2.1. Procedure for AEH in postmenopausal women or premenopausal women who do not wish to have children

No.	Recommendation	GoR	LOE	Sources
5.2	In postmenopausal patients and in premenopausal patients not wishing to have (any more) children who have atypical hyperplasia of the endometrium, total hysterectomy and bilateral salpingo-oophorectomy if appropriate must be carried out.	A	1	[82, 130]

5.1.2.2. Procedure for AEH in premenopausal women

No.	Recommendation	GoR	LOE	Sources
5.3	In the presence of atypical hyperplasia, the ovaries may be left in place when hysterectomy and bilateral salpingectomy are carried out, provided that there is no evidence of any hereditary predisposition for ovarian carcinoma (e.g., *BRCA* mutation or Lynch syndrome).		EC	

5.1.2.3. Fertility preservation in women with AEH

No.	Recommendation	GoR	LOE	Sources
5.4	If there is a desire to preserve the uterus in the presence of atypical hyperplasia, the uterus and adnexa may be left in place, provided that the patient has been informed that the standard treatment, almost always leading to cure, is total hysterectomy and she has agreed to tightly scheduled follow-up checks and has been informed that hysterectomy will be necessary once she has had children or no longer wishes to have children.		EC	
5.5	If there is a desire to preserve the uterus in the presence of		EC	

No.	Recommendation	GoR	LOE	Sources
	atypical hyperplasia, the uterus and adnexa may be left in place, provided that targeted biopsy or curettage have been carried out to confirm the diagnosis and the diagnosis of "atypical hyperplasia" has been established or confirmed by a pathologist with experience in gynecological pathology.			
5.6	If there is a desire to preserve the uterus in the presence of atypical hyperplasia, the uterus and adnexa may be left in place, provided that laparoscopy with vaginal ultrasound or magnetic resonance imaging (MRI) has been carried out to achieve the best possible assessment of the risk of adnexal involvement and/or myometrial infiltration.	EC		
5.7	If complete remission of the AEH is observed after 6 months of conservative treatment, the planned pregnancy should be attempted.	EC		
5.8	If the patient is not currently wishing to have children, maintenance therapy must be carried out. An endometrial biopsy must be taken every 6 months.	EC		
5.9	After the patient has had children or no longer wishes to have children, a total hysterectomy (with or without bilateral salpingectomy and with or without bilateral oophorectomy) must be carried out.	A	4	[131-135]

5.2. Early endometrial cancer

5.2.1. Procedure in early endometrial cancer

No.	Recommendation	GoR	LOE	Sources
5.10	In the presence of early endometrial cancer, hysterectomy and bilateral salpingo-oophorectomy must be carried out.	A	3	[136]
5.11	In the presence of endometrioid endometrial cancer, G1, G2 pT1a, the ovaries may be left in place when hysterectomy and bilateral salpingectomy are carried out in premenopausal women, provided that there is no evidence of any hereditary predisposition for ovarian carcinoma (e.g., *BRCA* mutation or Lynch syndrome) and the patient has received information about the risk.	EC		

5.2.2. Synchronous endometrial and ovarian carcinoma

In rare cases, women with endometrial cancer may have a synchronous ovarian carcinoma. In an analysis carried out in the Surveillance, Epidemiology, and End Results (SEER) program in the United States, synchronous endometrial cancer was found in 1709 of 56,986 women with ovarian carcinoma (3%) [137]. However, young women with endometrial cancer

have a markedly increased risk for synchronous endometrial and ovarian carcinoma (SEOC), which is reported in the literature to be in the range of 11–36% [138], [139], [140], [141], [142]. This has important implications for counseling and treatment in young women with endometrial cancer.

In over 70% of these cases, SEOC involves synchronous endometrioid adenocarcinomas both in the endometrium and in the ovary. On the basis of this histological correspondence and also clonality analyses, a common monoclonal origin for SEOC has been suggested [143]. In most cases of SEOC, both the endometrial cancer and the ovarian carcinoma are diagnosed at an early stage, and the prognosis for women with SEOC is therefore good. Oranratanaphan et al. [138], for example, report a 5-year survival rate of 64% in women with SEOC, in comparison with only 48% in women with endometrial cancer and ovarian metastases.

It is sometimes difficult to distinguish between SEOC, on one hand, and endometrial cancer with ovarian metastases on the other, and the distinction is based both on clinicopathological criteria and also on immunohistochemical analyses such as PAX-8, which is expressed in primary ovarian carcinomas but not in metastases from endometrial cancer [144]. In the literature, the reported rates of ovarian metastases vary widely, ranging from 12% [141] to 87% [138], indicating the difficulty of histopathological classification.

However, diagnosing and distinguishing precisely between SEOC and endometrial cancer with ovarian metastases is extremely important clinically, since patients with endometrial cancer and ovarian metastases are candidates for adjuvant chemotherapy or radiotherapy, but not patients with two early carcinomas, as is the case when SEOC is diagnosed. Consulting a reference pathologist is therefore recommended in cases of doubt.

Young women with SEOC are at increased risk for carrying a mutation associated with hereditary nonpolyposis colon cancer (HNPCC) syndrome (Lynch syndrome). Whereas the rate of Lynch syndrome in women with endometrial cancer is around 4–11% [145], young women with SEOC have Lynch syndrome in around 40% of cases [142]. Screening for Lynch syndrome must therefore be carried out in young women with SEOC (see also 10, “Hereditary endometrial cancers” in the long version of this guideline, recommendation 10.6).

5.2.3. Fertility preservation in women with early endometrial cancer

No.	Recommendation	GoR	LOE	Sources
5.12	In women with endometrial cancer who are still planning to have children and wish to have fertility preservation, the uterus and adnexa may be left in place, provided that the patient has been informed that the standard treatment, almost always leading to cure, is total hysterectomy; and if she is willing on her own responsibility to temporarily dispense with curative treatment for a malignancy and is aware of the potentially fatal consequences (progression of the disease, metastases) even if a pregnancy is successful.		EC	

No.	Recommendation	GoR	LOE	Sources
5.13	In patients with early endometrial cancer who wish to preserve the uterus, the uterus and adnexa may be preserved if the patient has been recommended to receive counseling from a reproductive medicine specialist to assess the chances of a successful pregnancy.		EC	
5.14	In patients with early endometrial cancer who wish to preserve the uterus, the uterus and adnexa may be left in place, provided that the patient agrees to tightly scheduled check-up appointments and has received information about the need for hysterectomy after she has had children or no longer wishes to do so.		EC	
5.15	In patients with early endometrial cancer who wish to preserve their fertility, the uterus and adnexa may be left in place if a hysteroscopy with targeted biopsy or with curettage and assessment by a pathologist experienced in gynecological pathology have established a diagnosis of a well-differentiated (G1) endometrioid endometrial cancer expressing progesterone receptors.		EC	
5.16	In patients with early endometrial cancer (pT1a, G1) who wish to preserve their fertility, the uterus and adnexa may be left in place if adnexal involvement or myometrial infiltration have been excluded as far as possible using laparoscopy with vaginal ultrasound or with MRI.		EC	
5.17	In patients with early endometrial cancer who wish to preserve their fertility, the uterus and adnexa may be left in place if adequate drug treatment with medroxyprogesterone acetate or megestrol acetate or a levonorgestrel IUD is administered.		EC	
5.18	If complete remission of the endometrial cancer is observed after 6 months of conservative treatment, the planned pregnancy should be attempted, if necessary in collaboration with a reproductive medicine specialist.		EC	
5.19	In patients with endometrial cancer (pT1a without myometrial infiltration, G1) who are not currently wishing to have children, maintenance therapy (levonorgestrel IUD, oral contraceptives, cyclic gestagens) should be administered and an endometrial biopsy should be taken every 6 months.		EC	
5.20	If there is no response in the carcinoma after 6 months of conservative treatment, hysterectomy should be carried out.			
5.21	If the uterus is to be preserved in the presence of an endometrioid adenocarcinoma in the endometrium, cT1A,		EC	

No.	Recommendation	GoR	LOE	Sources
	G1 with no evidence of myometrial infiltration, with expression of the progesterone receptor, then the uterus and adnexa may be left in place, provided that the following prerequisites are met: • The patient has been informed that the standard treatment, almost always leading to a cure, is total hysterectomy. • The patient agrees to tightly scheduled check-up appointments. • The patient has received information about the need for hysterectomy after she has had children or no longer wishes to have children. • Hysteroscopy with targeted biopsy or curettage have been used to confirm the diagnosis. • Laparoscopy with vaginal ultrasound or with MRI have been used to exclude adnexal involvement and myometrial infiltration. • The diagnosis has been established or confirmed by a pathologist with experience in gynecological pathology. • Treatment with medroxyprogesterone acetate (MPA) or megestrol acetate (MGA) or a levonorgestrel (LNG) IUD. • Repeat hysteroscopy after 6 months with curettage and imaging. If there is no response, hysterectomy. • Pregnancy can be attempted if there is complete remission (reproductive medicine specialist) • If the patient is not currently wishing to have a child: maintenance therapy and endometrial biopsy every 6 months. • Once the patient has had children or no longer wishes to have children: total hysterectomy and bilateral salpingo-oophorectomy should be recommended.			

6. Surgical treatment for endometrial cancer

6.1. Foundations of surgical treatment

Surgical treatment for endometrial cancer is based on total hysterectomy and bilateral salpingo-oophorectomy (BSO) (see section 5 above, "Treatment of precancerous lesions and early endometrial cancer"). In exceptional cases, surgical removal of the ovaries may be avoided (see recommendations 5.11–5.17 and 5.21 in section 5).

6.1.1. Parametrial resection

No.	Recommendation	GoR	LOE	Sources
6.1	Radical hysterectomy (parametrial resection) must not be carried out in patients with cT2 or pT2 endometrial cancer (with histological evidence of involvement of the cervical stroma) with no clinical suspicion of parametrial infiltration.	A	3	[146]

6.2. Lymphadenectomy

No.	Recommendation	GoR	LOE	Sources
6.2	All suspicious lymph nodes or lymph nodes that are enlarged on palpation or macroscopically must be removed.	EC		
6.3	Lymph-node sampling of unsuspicious lymph nodes must not be carried out.	EC		
6.4	In type I endometrial cancer (ICD-0: 8380/3, 8570/3, 8263/3, 8382/3, 8480/3) pT1a, G1/2, systemic lymphadenectomy must not be carried out when the lymph nodes are clinically unsuspicious.	A	1	[147]
6.5	Systematic lymphadenectomy may be carried out in type I, pT1a, G3, pT1b, G1/2 endometrial cancer.	0	4	[148, 149]
6.6	Systematic lymphadenectomy should be carried out in type I, pT1b, G3 endometrial cancer.	B	4	[148, 149]
6.7	Systematic lymphadenectomy should be carried out in type I, pT2 to pT4, M0, G1–3 endometrial cancer if a macroscopically tumor-free status can be achieved.	B	4	[148, 149]
6.8	Systematic lymphadenectomy should be carried out in type II endometrial cancer if a macroscopically tumor-free status can be achieved.	EC		

No.	Recommendation	GoR	LOE	Sources
6.9	Systematic lymphadenectomy should be carried out in patients with uterine carcinosarcomas.	B	4	[150]
6.10	If there is lymphovascular space invasion, lymphadenectomy may be carried out in patients with endometrial cancer even if no other risk factors are present.	EC		
6.11	If systematic lymphadenectomy is indicated, it should be carried out in the pelvic and infrarenal–para-aortic areas.	B	4	[148, 151, 152]
6.12	Sentinel lymph-node biopsy alone in patients with endometrial cancer must only be carried out in the framework of controlled studies.	EC		

6.3. Laparoscopic surgery

No.	Recommendation	GoR	LOE	Sources
6.13	In endometrioid adenocarcinomas of the endometrium with a suspected early stage, hysterectomy and bilateral salpingo-oophorectomy should be carried out using a laparoscopic or laparoscopy-assisted vaginal procedure.	B	1	[153]

6.4. Robot-assisted surgical procedures

No.	Recommendation	GoR	LOE	Sources
6.14	Robot-assisted laparoscopic procedures may be used in the same way as conventional laparoscopy in surgery for endometrial cancer.	EC		

6.5. Tumor reduction in advanced endometrial cancers

No.	Recommendation	GoR	LOE	Sources
6.15	In advanced endometrial cancer (including carcinosarcomas), surgical tumor reduction can be carried out in order to achieve macroscopic removal of all tumor manifestations.	0	4	[154, 155]

7. Radiotherapy for endometrial cancer

7.1. Postoperative external pelvic radiotherapy in endometrial cancer type I, stages I–II

No.	Recommendation	GoR	LOE	Sources
7.1	Neither brachytherapy nor percutaneous radiotherapy should be carried out in patients with stage pT1a, pNX/0, G1 or G2 endometrioid endometrial cancer (type I) after hysterectomy with or without lymph-node dissection.	B	1	[156-158]

7.2. Postoperative vaginal brachytherapy in endometrial cancer type I, stages I–II

No.	Recommendation	GoR	LOE	Sources
7.2	In stage pT1a, pNX/0 without myometrial involvement, G3, endometrioid endometrial cancer (type I), vaginal brachytherapy may be carried out in order to reduce the risk of vaginal recurrence.	0	4	[156, 159]
7.3	In stage pT1b, G1 or G2 pNX/0 and in stage pT1a (with myometrial involvement), G3 pNX/0, endometrioid endometrial cancer (type I), vaginal brachytherapy alone should be carried out postoperatively in order to reduce the risk of vaginal recurrence.	B	2	[160-162]
7.4	Patients with stage pT1b pNX G3 or stage pT2 pNX endometrioid endometrial cancer (type I) should receive vaginal brachytherapy; alternatively, percutaneous radiotherapy may be carried out.	EC		
7.5	Patients who have undergone systematic lymphadenectomy in stage pT1b pN0 G3 or in stage pT2 pN0 endometrioid endometrial cancer (type I) should receive vaginal brachytherapy. Percutaneous radiotherapy must not be carried out in these patients.	EC		
7.6	In patients with stage pT1 pNX (any grading) with “substantial lymphovascular space invasion” (LVSI; the highest level in the three-level grading of lymphatic invasion), percutaneous pelvic radiotherapy may be carried out instead of vaginal brachytherapy.	EC		

7.3. Postoperative radiotherapy in endometrial cancer type I, stages III–IVA

No.	Recommendation	GoR	LOE	Sources
7.7	In patients with positive lymph nodes, involvement of the uterine serosa, adnexa, vagina, bladder, or rectum (i.e., stages III to IVA) with endometrioid endometrial cancer (type I), postoperative external pelvic radiotherapy may be carried out in addition to chemotherapy, in order to improve local control.		EC	

7.4. Vaginal brachytherapy as a booster in postoperative percutaneous pelvic radiotherapy

No.	Recommendation	GoR	LOE	Sources
7.8	In the presence of specific risk factors for a vaginal recurrence (stage II or stage IIIB vaginal, each with narrow or positive resection margins), vaginal brachytherapy may be carried out additionally for boost treatment after postoperative external pelvic radiotherapy following hysterectomy due to endometrioid endometrial cancer.		EC	

7.5. Postoperative radiotherapy in type II endometrial cancer

No.	Recommendation	GoR	LOE	Sources
7.9	The indication for postoperative vaginal brachytherapy or external pelvic radiotherapy in type II carcinoma (serous or clear cell) should be based on the recommendations for type I carcinomas (endometrioid) at grade 3 for the same stage.		EC	

7.6. Primary radiotherapy alone for inoperable internal findings

In patients with endometrial cancer who are inoperable due to comorbidity, radiotherapy alone represents a treatment approach with curative intent.

In the absence of randomized studies, the Gynecological Cancer Group of the European Organization for Research and Treatment of Cancer recently published a systematic review describing the use of radiotherapy for this indication, along with the results [163].

Overall, a total of 2694 patients from 25 case series were included. They had been treated with brachytherapy alone (51%) or with a combination of brachytherapy plus percutaneous radiotherapy (47%). After 5 years, the

disease-specific survival was 78.5%, local control was 79.9%, and the overall survival, reflecting the preexisting comorbidities, was 53.2%. The risk for late sequelae ≥ grade 3 was 2.8% (with brachytherapy alone) or 3.7% (with the combination). On the basis of these data, brachytherapy alone is only recommended for stage I, grade 1 when the patient is inoperable for internal-medicine reasons; for the rest of stage I and for stages II to IV, a combination of percutaneous radiotherapy and brachytherapy is recommended.

7.7. Radiotherapy for carcinosarcoma

No.	Recommendation	GoR	LOE	Sources
7.10	To improve local control in patients with carcinosarcoma, postoperative radiotherapy should be carried out in the presence of FIGO stages I or II.	B	3	[164]

7.8. Supportive therapy

When radiotherapeutic measures are being carried out, the recommendations of the Level 3 guideline on "Supportive Therapy in Oncology Patients" should be observed (long version 1.1, April 2017, AWMF Registry No. 032/054OL, https://www.leitlinienprogramm-onkologie.de/index.php?id=95&type=0) [165]. See also recommendation 9.9 in section 9, "Follow-up for / recurrence of / metastases from endometrial cancer" in the long version of this guideline.

The following text is taken from the Level 3 guideline on "Diagnosis, Treatment, and Follow-up in Patients with Cervical Carcinoma) (version 1.0, September 2014, AWMF Registry No. 03/033OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/zervixkarzinom/) [166] and has been updated and adapted.

Supportive therapy is an integral component of the treatment approach. Side effects may occur in the form of acute changes during or immediately after treatment, or as late sequelae.

7.8.1. Radiotherapy-induced nausea and vomiting

In patients who are receiving radiotherapy, the emetogenic risk should also be checked using the risk categories (Table 11: Emetogenic potential of radiotherapy) and guideline-appropriate prophylaxis and treatment should be started [165].

Table 11: Emetogenic potential of radiotherapy [165]

Emesis risk	Body area irradiated
High	Whole-body irradiation
Moderate	Upper abdomen, thoracic spine, lumbar spine, neuraxis, depending on the technique used
Low	Pelvis, neurocranium, ENT areas, chest
Minimal	Extremities, breast

Table 12: Summary of prophylactic antiemetic treatment in radiotherapy (in accordance with the Level 3 guideline on Supportive Therapy [165])

Emesis risk	Body area irradiated	Antiemetic prophylaxis
High	Whole-body irradiation	5-HT_3 RA and dexamethasone
Moderate	Upper abdomen, thoracic spine, lumbar spine, neuraxis, depending on the technique used	5-HT_3 RA and dexamethasone; "may" for dexamethasone
Low	Pelvis, neurocranium, ENT areas	5-HT_3 RA or rescue therapy
Minimal	Extremities, breast	No routine prophylaxis

Table 13: Rescue antiemetic treatment (in accordance with the Level 3 guideline on Supportive Therapy [165])

Rescue antiemetic treatment
In patients who have nausea and/or vomiting despite optimal antiemetic treatment, the following drugs can be used as rescue antiemetic treatment for radiotherapy-induced vomiting:
Neurokinin-1 receptor antagonist (off-label use)
Neuroleptic agents and other dopamine receptor antagonists
• Olanzapine, initially 1 × 5 mg p.o. (off-label use)
• Haloperidol, initially 1–3 × 1 mg p.o.
• Metoclopramide, initially 3 × 10 mg p.o. (max. daily dosage 0.5 mg/kg body weight or 30 mg)
• Levomepromazine, initially 3 × 1–5 mg p.o.
• Alizapride, initially 3 × 50 mg
Benzodiazepines:
• Lorazepam, initially 1 × 1–2 mg p.o.
• Alprazolam, initially 1 × 0.25–1.0 mg p.o.
H1 blockers:
• Dimenhydrinate, initially 3 × 50–100 mg p.o. or 1–2 × 150 mg rectally

7.8.2. Locoregional side effects

7.8.2.1. Radiogenic proctitis

No prophylactic drug treatments against radiogenic proctitis are known of. 5-Aminosalicylic acid (5-ASA) is contraindicated during abdominal radiotherapy, due to increased complication rates. For acute proctitis, topical therapy with butyrates is possible (see specialist information) [167]. Treatment for late radiogenic changes in the rectum is an interdisciplinary task. Individual reports on endoscopic sclerotherapy have been published. If treatment fails, local anti-inflammatory treatments and enemas with sucralfate (2 × 2 g in 20 mL water suspension/day), sodium, pentosan polysulfate, or metronidazole with cortisone can be given. These treatments are carried out on an interdisciplinary basis in experienced centers (with gynecological oncologists, radio-oncologists, and gastroenterologists), for example.

7.8.2.2. Radiogenic cystitis

Acute radiotherapy-induced cystitis leads to symptoms such as dysuria, increasing micturition frequency, and nocturia. The focus is on treatment of the symptoms using analgesia and spasmolysis — with metamizole (dipyrone), centrally active analgetic agents, hyoscine butylbromide, oxybutynin. Alkalinization of the urine and iron substitution, or even transfusions in case of recurrent microhematuria and macrohematuria, supplement the treatment. Bacterial superinfections require the appropriate antibiotic treatment.

According to the American Society of Clinical Oncology (ASCO) guideline [168], preventive use of amifostine (= aminothiol) to reduce radiotherapy-related toxicity may be considered. Ethyol® (amifostine) is not approved for this indication in Germany. The side effects and benefits of amifostine need to be weighed up critically for this off-label use [168].

7.8.2.3. Radiogenic vulvovaginitis

Acute radiogenic vulvovaginitis occurs up to 90 days after the start of radiotherapy and is often reversible. Dexpanthenol, camomile sitz baths and sitz baths with synthetic tannins such as phenol-methanal-urea polycondensate are available for the treatment of vulvovaginitis. Suppositories with freeze-dried cultures of *Lactobacillus acidophilus* are used to restore the physiological pH value in the vagina, as a prerequisite for restoring the physiological vaginal flora. Benzydamine-containing creams are also used. On the use of estrogen-containing creams, gels, Ovula, etc., see section 9.6.2, “Local estrogen treatment,” in the long version of this guideline.

7.8.2.4. Lymphedema

In clinical practice, combination therapy with manual lymphatic drainage and compression therapy is carried out for lymphedema. The frequency and duration of these combined measures are based on stages I–III of lymphedema. After contraindications have been excluded, treatment can be carried out after the expected benefit has been weighed up (for more details, see section 11.4.4, “Treatment for lymphedema,” in the long version of this guideline).

7.8.2.5. Vaginal dryness, vaginal stenosis, and vaginal fibrosis

Radiogenically induced or chemotherapy-induced dryness in the vagina can be reduced in patients with endometrial cancer by applying inert lubricant gels.

In individual cases when there is severe pain, local estrogen therapy may be carried out after careful consideration of the risks and after the patient has been given the appropriate information. Approximately 4–6 weeks after the end of radiotherapy that has included the vaginal region, mechanical dilation (with vaginal dilators or Bepanthen tampons) may be a suitable method for prophylaxis against vaginal stenosis (see section 9, "Follow-up/recurrence/metastases in endometrial cancer," in the long version of this guideline).

7.8.2.6. Disturbances of sexual function

Providing patients with sufficient information about the effects of the treatment on their sexual life and options for prophylactic treatment measures (e.g., vaginal dilation) is a vital component of therapy for patients with endometrial cancer (for further details, see section 11.1.4, "Sexuality and endometrial cancer," in the long version of this guideline).

8. Adjuvant medical therapy for endometrial cancer

8.1. Adjuvant medical therapy in endometrial cancer

8.1.1. Adjuvant gestagen therapy

No.	Recommendation	GoR	LOE	Sources
8.1	Adjuvant gestagen therapy must not be administered after surgery for endometrial cancer.	A	1	[169]

8.1.2. Adjuvant chemotherapy

No.	Recommendation	GoR	LOE	Sources
8.2	Patients with endometrioid or other type I endometrial cancers (ICD-0: 8380/3, 8570/3, 8263/3, 8382/3, 8480/3) at stage pT1a/b G1 and G2 cN0/pN0 must not receive adjuvant chemotherapy.	EC		
8.3	Sufficient data regarding the benefit of adjuvant chemotherapy are not available for patients with endometrioid or other type I endometrial cancer in stage pT1a G3 cN0 or pN0.	ST	2	[170]
8.4	Adjuvant chemotherapy may be administered in patients with type II endometrial cancer and patients with type I endometrial cancer G3 pT1b and stage pT2 (both pN0).	0	2	[171], [170]
8.5	Patients with endometrial cancer at stage pT3 and/or pN1 should receive adjuvant chemotherapy.[5]	B	1	[171], [170]
8.6	Patients with endometrial cancer at stage pT4a or M1 who have undergone macroscopically tumor-free resections or have a maximum postoperative residual tumor less than 2 cm in size should receive adjuvant chemotherapy.[5]	B	1	[171], [170]
8.7	In patients with endometrial cancer, adjuvant chemotherapy should be administered with carboplatin and paclitaxel.[5]	EC		

[5] It should be noted that the chemotherapies listed here are not approved for adjuvant therapy for endometrial cancer and that using them for these indications represent "off-label" usage.

8.2. Adjuvant medical therapy for carcinosarcomas

No.	Recommendation	GoR	LOE	Sources
8.8	Patients with carcinosarcoma at FIGO stage I or II may receive adjuvant chemotherapy with cisplatin/ifosfamide at a dosage of ifosfamide 1.6 g/m² i.v. on days 1–4 and cisplatin 20 mg/m² i.v. on days 1–4 or carboplatin/paclitaxel at a dosage of paclitaxel 175 mg/m² on day 1 and carboplatin AUC 5.[6]	0	4	[172]
8.9	In patients with a carcinosarcoma in FIGO stages III or IV, a significant survival benefit has been demonstrated for adjuvant chemotherapy with ifosfamide/paclitaxel or ifosfamide/cisplatin in comparison with ifosfamide monotherapy.	ST	1	[173], [174], [175]
8.10	In view of the high toxicity of ifosfamide-containing combinations, the combination of carboplatin and paclitaxel may also be offered for adjuvant chemotherapy in patients with carcinosarcoma.	EC		

8.3. Supportive therapy

The required supportive measures must of course also be carried out during the administration of systemic therapies, in accordance with the Level 3 guideline "Supportive Therapy in Oncology Patients" (long version 1.1, April 2017, AWMF Registry No. 032/054OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/supportive-therapie/) [165].

The following text is taken from the Level 3 guideline on "Diagnosis, Treatment, and Follow-up in Patients with Cervical Carcinoma" (version 1.0, September 2014, AWMF Registry No. 03/033OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/zervixkarzinom/) [166] and has been updated and adapted.

8.3.1. Chemotherapy-induced nausea and vomiting

As both intravenous and oral cytostatic agents, and also hormonal and biological agents, have now been stratified into four risk classes (Table 14), each antiemetic treatment regimen can be selected according to whether it belongs to the highly, moderately, slightly, or minimally emetogenic group.

8.3.1.1. Antiemetic strategy

Before the start of chemotherapy, it is important to establish the antiemetic strategy for the acute and delayed phase of vomiting (Table 15).

Symptomatic therapy that first starts during the course of treatment only has limited effectiveness, particularly for prophylaxis during the delayed phase of vomiting. First, the emetogenic potential of the chemotherapy is established.

[6] It should be noted that the chemotherapies listed here are not approved for adjuvant therapy for endometrial cancer and that using them for these indications represents "off-label" usage.

The cytostatic agent with the highest emetogenic potential is decisive here; there is no additive effect with additional cytostatics. A single daily dose of the antiemetic is often sufficient. Oral intake of antiemetic agents is equivalent in its effectiveness to intravenous administration, with equipotent dosage, taking bioavailability into account (see specialist information). Chemotherapy treatments lasting several days, with unchanged emetogenic potential on the individual days, require administration of the antiemetics on each chemotherapy day as on day 1, or, if palonosetron is being used, on every second day (e.g., d1, d3, d5). Particularly in patients who are receiving outpatient treatment, it is indispensable to produce a written medication plan and give it to the patient (see Table 15).

Table 14: Emetogenic potential of parenteral antineoplastic agents (in accordance with the Level 3 guideline on supportive therapy [165])

Emetogenic potential	Agents	
High, > 90%	Anthracycline/cyclophosphamide combination [1]	
	Cisplatin	
	Cyclophosphamide ≥ 1500 mg/m²	
Moderate, > 30–90%	Carboplatin	Ifosfamide
	Cyclophosphamide < 1500 mg/m²	Treosulfan
	Doxorubicin	
	Epirubicin	
Low, 10–30%	Docetaxel	Ixabepilone
	Doxorubicin, liposomally pegylated	Methotrexate
	Etoposide	Mitoxantrone
	5-Fluorouracil	Nab-paclitaxel
	Gemcitabine	Paclitaxel
		Pertuzumab
		Temsirolimus
		Topotecan
Minimal, < 10%	Fulvestrant	Trastuzumab
	Goserelin	Triptorelin
	Leuprorelin	Vinblastine
		Vincristine

Emetogenic potential	Agents	
		Vinorelbine

[1] The combination of anthracycline and cyclophosphamide in patients with breast cancer is classified as highly emetogenic.

Table 15: Summary of antiemetic prophylaxis in the acute and delayed phases (in accordance with the Level 3 guideline on supportive therapy [165])

Emetogenic risk (risk of vomiting without antiemetic treatment)		Acute phase (before anticancer drug treatment)			Delayed phase (starting 24 h after anticancer drug treatment)
High, > 90%	Highly emetogenic and AC-based chemotherapy in patients with breast carcinoma	5-HT_3 RA			–
		NK_1 RA[1]			NK_1 RA[1]
		Dexamethasone			Dexamethasone on days 2–4
Moderate, 30–90%	Carboplatin-containing chemotherapy[3]	5-HT_3 RA			–
		NK_1-RA ("may")			[1]
		Dexamethasone			Optional dexamethasone on days 2–3
	Moderate (except carboplatin)	5-HT_3 RA			–
		Dexamethasone			[2]
Low, 10–30 %		Dexamethasone	or 5-HT_3 RA	or MCP	–
Minimal, < 10%		No routine prophylaxis			No routine prophylaxis

AC, Adriamycin (doxorubicin) and cyclophosphamide; MCP, metoclopramide.

[1] Administration of aprepitant on days 2 and 3 in accordance with approval; administration of fosaprepitant or netupitant/palonosetron only on day 1.

[2] Administration of dexamethasone in the delayed phase is recommended only in chemotherapies in which there is an increased potential for delayed vomiting (e.g., oxaliplatin, doxorubicin, cyclophosphamide, bendamustine).

[3] Randomized studies have only been published for combination therapies with carboplatin AUC > 4.

8.3.2. Diarrhea/enteritis

In addition to more frequent bowel movements, typical symptoms of diarrhea include abdominal pain and tenesmus. Discharges of blood and mucus, as

well as fever and nausea, are also potential accompanying symptoms. In extreme cases, hypovolemia and electrolyte disturbances can lead to life-threatening situations, with renal failure and metabolic acidosis [176], particularly in patients with tumor-related urinary stasis and raised creatinine levels. The main risk factors for which there is clinical evidence for increased severity and also a higher incidence of diarrhea are parallel radiotherapy of the abdomen and pelvis, simultaneous neutropenia and concomitant symptoms such as stomatitis, emesis, anorexia, anemia, abdominal cramping, or a combination of these symptoms.

8.3.2.1. Chemotherapy-induced diarrhea/enteritis

The 2004 ASCO consensus guidelines still only recommend loperamide, octreotide, and opium tincture in the treatment of diarrhea induced by cytostatic agents, with loperamide being the drug of choice [177]. The initial dose is 4 mg, followed by 2 mg every 2–4 hours or after each discharge of loose stools, up to a maximum of 12 mg. Opium tincture (e.g., 15 drops three times daily) is more recommendable in treatment-resistant cases of diarrhea. Octreotide, a synthetic somatostatin analogue, reduces the secretion of a number of hormones, including vasoactive intestinal peptide (VIP), prolongs gastrointestinal transit time, and increases the absorption of liquids and electrolytes. Although octreotide (e.g., 100–150 µg three times daily; up to 500 µg three times daily) proved to be superior to loperamide in a randomized study (90% versus 15% freedom from diarrhea after 3 days), it must be regarded as a reserve agent for treatment-resistant patients in view of its high treatment costs [178], [179].

8.3.3. Treatment for anemia

Patients with cancer often suffer from anemia, which may trigger clinical symptoms. Possible causes include the cancer itself, as well as the cancer treatment. The frequency and severity of the anemia are dependent on the tumor type and stage; it affects approximately 50% of patients with solid tumors, for example. Possible treatments for anemia that are available include blood transfusions and substitution of essential nutrients for erythropoiesis. An accurate risk–benefit analysis is necessary here. In addition, functional iron deficiency and the resulting potential treatment options also need to be taken into account [180].

8.3.4. Prophylaxis against febrile neutropenia with G-CSF

Myelotoxicity may be dose-limiting for chemotherapy and can lead to the interruption of treatment. The ASCO guidelines (2006) [181] and EORTC guidelines (2011) [182] recommend already using G-CSF even when there is a risk of febrile neutropenia (FN) ≥ 20%. With a moderate FN risk of 10–20% (e.g., with cisplatin/topotecan, cisplatin/paclitaxel weekly, or cisplatin in radio(chemo)therapy, the guidelines recommend calculating the individual overall FN risk before each cycle of chemotherapy (Tabelle 16) so that G-CSF prophylaxis can be planned if needed. Prophylaxis against neutropenia with G-CSF is not required with radiotherapy alone and is not recommended in the guidelines.

Tabelle 16: Patient-related risk factors for febrile neutropenia (FN) [182]

Patient-related risk factors for febrile neutropenia (FN)	
High risk	• Age > 65 years
Increased risk	• Advanced disease
	• Prior episodes of FN
	• No antibiotic prophylaxis, no use of G -CSF
Other factors	• Poor performance status and/or poor nutritional condition
	• Female sex
	• Hemoglobin < 12 g/dL
	• Liver, kidney, or cardiovascular diseases

8.3.5. Mucositis

Mucositis is a fairly rare side effect during the treatment of patients with endometrial cancer. Supportive therapy for prophylaxis against and to minimize the symptoms should follow the recommendations given in the Level 3 guideline 'Supportive Therapy in Oncology Patients' (long version 1.1, April 2017, AWMF Registry No. 032/054OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/supportive-therapie/) [165].

9. Follow-up / recurrence / metastases from endometrial cancer

9.1. Procedures during follow-up

No.	Recommendation	GoR	LOE	Sources
9.1	There is no evidence that follow-up examinations in women with endometrial cancer lead to longer survival.	ST	4	[69, 183-191]
9.2	A patient history including targeted questions about symptoms should be taken and clinical gynecological examinations with speculum examination and rectovaginal palpation examination should be carried out at 3–6-month intervals in the first 3 years after the completion of primary therapy and at 6-month intervals in the fourth and fifth years.	EC		
9.3	Imaging examinations and tumor marker assessments should not be carried out in asymptomatic patients.	B	4	[69, 183, 184, 189]

9.2. Procedures for locoregional recurrences

No.	Recommendation	GoR	LOE	Sources
9.4	If a local recurrence is suspected in the area of the vagina or lower pelvis, or if distant metastases are suspected, histological confirmation must be attempted.	EC		
9.5	Tomographic imaging should be carried out if a vaginal recurrence, pelvic recurrence, or distant metastasis is suspected, or after histological confirmation of a vaginal recurrence, pelvic recurrence, or distant metastasis.	A	3	[69, 70, 192]

9.2.1. Isolated vaginal recurrence or vaginal stump recurrence

No.	Recommendation	GoR	LOE	Sources
9.6	In women with an isolated vaginal recurrence or vaginal stump recurrence after endometrial cancer who have not undergone radiotherapy during the primary treatment, radiotherapy with curative intent consisting of external pelvic radiotherapy and brachytherapy, with or without local tumor resection, should be carried out.	EC		
9.7	In women with an isolated vaginal recurrence or vaginal stump recurrence after endometrial cancer who have only received adjuvant brachytherapy during the primary	EC		

No.	Recommendation	GoR	LOE	Sources
	treatment, radiotherapy with or without local tumor resection may be carried out with curative intent.			
9.8	If there is a vaginal recurrence or vaginal stump recurrence in patients who have received external radiotherapy, with or without brachytherapy, it should be checked whether repeated radiotherapy with external irradiation or brachytherapy, with or without local tumor resection, is possible with curative intent.		EC	
9.9	Local late sequelae of radiotherapy must be treated in accordance with the Level 3 guideline "Supportive Therapy in Oncology Patients" [165].[7]		EC	

9.3. Surgical treatment for recurrence

No.	Recommendation	GoR	LOE	Sources
9.10	Surgical treatment may be carried out for recurrent endometrial cancer if complete resection of the recurrent tumor appears possible and tomography does not show any evidence of distant metastases.		EC	
9.11	There is no evidence that exenteration leads to improvements in the survival period, survival rate, or progression-free survival in comparison with other treatments or with best supportive care in women with recurrent endometrial cancer.		EC	
9.12	Exenteration may be considered in individual cases in women with recurrent endometrial cancer.		EC	

9.4. Endocrine therapy for recurrence

No.	Recommendation	GoR	LOE	Sources
9.13	There are no data showing that endocrine therapy leads to improvements in the survival period, survival rate, or progression-free survival in comparison with other treatments or with best supportive care in women with recurrent endometrial cancer.		EC	
9.14	Endocrine therapy with MPA (200 mg/d) or MGA (160 mg/d) may be administered in women with recurrent endometrial cancer.	0	3	[193], [194]

[7] On this topic, see also section 7.8, "Supportive therapy," in the long version of this guideline.

No.	Recommendation	GoR	LOE	Sources
9.15	In women with recurrent endometrial cancer, endocrine therapy with MPA leads to higher response rates if there is evidence of progesterone receptor expression or estrogen receptor expression, or good to moderate differentiation of the tumor (G1/G2).	ST	3	[194], [195]

9.5. Chemotherapy for recurrence

No.	Recommendation	GoR	LOE	Sources
9.16	Systemic chemotherapy may be carried out in women with recurrent endometrial cancer that is not locally treatable, or with distant metastases.	0	1	[69, 196]
9.17	There is no evidence that any specific chemotherapy regimen is superior in women with recurrent endometrial cancer. Platinum salts, anthracyclines and taxanes are thought to be the most effective agents for chemotherapeutic treatment of advanced or recurrent endometrial cancer. A combination of carboplatin and paclitaxel has become established as a relatively well tolerable and safely usable treatment.[8]	ST	3	[196]

9.6. Postactinic changes in the irradiation field

9.6.1. Vaginal atrophy

No.	Recommendation	GoR	LOE	Sources
9.18	Symptoms of vaginal atrophy in patients who have undergone treatment for endometrial cancer must be treated primarily with inert lubricant gels or creams.	A	3	[197]

9.6.2. Local estrogen treatment

No.	Recommendation	GoR	LOE	Sources
9.19	Local estrogen treatment after primary therapy for endometrial cancer may be considered if the results of treatment with inert lubricant gels or creams are unsatisfactory.	EC		

[8] The remarks above concerning "off-label use" should be noted (see section 8, "Adjuvant medical therapy for endometrial cancer"). However, the criterion of life-threatening disease is certainly met in these cases. Robust phase III studies have been published on the administration of Adriamycin/cisplatin, Adriamycin/cisplatin/paclitaxel, and carboplatin/paclitaxel for these indications.

9.6.3. Treatment of and prophylaxis against vaginal stenoses

No.	Recommendation	GoR	LOE	Sources
9.20	Vaginal dilators may be used for treatment of and prophylaxis against vaginal stenoses in patients with endometrial cancer, after the completion of radiotherapy and resolution of the acute sequelae of radiotherapy.		EC	

9.7. Palliative radiotherapy

No.	Recommendation	GoR	LOE	Sources
9.21	As a palliative measure for vaginal bleeding or pain caused by a vaginal stump recurrence or pelvic wall recurrence, radiotherapy at a low total dosage may also be used even after prior radiotherapy.		EC	

10. Hereditary endometrial cancer

10.1. Introduction

Up to 5% of all endometrial cancers are due to a monogenic hereditary disposition (hereditary or inheritable endometrial cancer) and thus occur in the context of a hereditary tumor syndrome. Individuals, who have been confirmed clinically, or using molecular genetics, as carriers of specific hereditary tumor syndromes and their first-degree relatives (high-risk individuals) have a markedly increased lifetime risk of developing endometrial cancer.

The overwhelming majority of hereditary endometrial cancers occur in the setting of Lynch syndrome (LS)/hereditary nonpolyposis colorectal cancer (HNPCC). There is also known to be a markedly increased risk of endometrial cancer in Cowden syndrome or *PTEN* hamartoma tumor syndrome (PHTS). Carriers of these and a few other extremely rare hereditary tumor syndromes have a 6–20 times greater risk of endometrial cancer in comparison with the general population (Table 17).

The causes of hereditary tumor syndromes are mutations particularly in DNA repair genes and tumor suppressor genes. These mutations are present in all of the body's cells (germline mutations), in contrast to sporadic tumors, in which the relevant mutations occur only in the tumor itself (somatic mutations).

Most hereditary tumor syndromes have autosomal-dominant inheritance. This means that first-degree relatives of those affected by hereditary endometrial cancer (high-risk individuals) have a 50% risk of having inherited the genetic disposition and thus the increased tumor risk. Numerous high-risk individuals are therefore often found in these families.

10.2. Hereditary tumor syndromes with an increased risk of endometrial cancer

No.	Recommendation	GoR	LOE	Sources
10.1	The hereditary tumor syndromes in which there is a confirmed marked increase in the risk of endometrial cancer are Lynch syndrome (hereditary nonpolyposis colorectal cancer, HNPCC) and Cowden syndrome or *PTEN* hamartoma tumor syndrome (PHTS). Carriers of these hereditary tumor syndromes are also at increased risk of developing other syndrome-specific intestinal and extraintestinal benign and malignant tumors.	ST	3	[198], [199], [200], [201], [202], [203], [204], [205], [206], [207]

Table 17: Tumor risks and mutation detection rates

	Lynch syndrome	Cowden syndrome
Inheritance	Autosomal-dominant	Autosomal-dominant
Causative genes	MLH1, MSH2, MSH6, PMS2, EPCAM	PTEN
Frequency in the general population	1 : 300–500	1 : 200,000? [208]
Frequency in unselected endometrial cancer cohorts	2–4%	< 0.5%
Frequency in endometrial cancer patients < 50 y	9–10%	
Endometrial cancer in the lower uterine segment	14–29% [206]	
Mutation range in Lynch syndrome-associated endometrial cancers	*PMS2:* 5%, *MLH1:* 16%, *MSH2:* 26%, *MSH6:* 53%	
Lifetime risk of endometrial cancer up to age 70 (general population approx. 2.6%) [209]	**Overall: 16–54%** *MLH1:* 18–54%, *MSH2:* 21–30%, *MSH6:* 16–49%, *PMS2:* 12–15% [210], [201], [198], [211], [212], [213]	19–28% [214], [215]
Mean age at onset of Lynch/Cowden-associated endometrial cancer (y)	**Overall: 50 y** *MLH1:* 44 (29–54), *MSH2:* 50 (36–66), *MSH6:* 55 (26–69), *PMS2:* 57 (44–69) [203], [199], [202], [216], [204]	48–53 [217], [218]
Metachronous carcinoma after endometrial cancer diagnosis	10 y: 25%, 15 y: 50%, 20 y: > 50% [199], [202], [200], [219]	
Endometrioid type	57–85%	84% [218]
Other major tumors/tumor range	Colorectal carcinoma, duodenal carcinoma, gastric carcinoma, ovarian carcinoma, cerebral tumor, urothelial carcinomas	Thyroid carcinoma, breast cancer, renal cancer, cerebral tumors, skin tumors

10.3. Risk assessment

No.	Recommendation	GoR	LOE	Sources
10.2	An important tool for assessing a genetically caused	EC		

No.	Recommendation	GoR	LOE	Sources
	increased risk of endometrial cancer is a patient history and family history obtained by a physician, taking specific clinical criteria into account (in Lynch syndrome: Amsterdam I/II criteria, revised Bethesda criteria).			

10.4. Procedure for suspected hereditary forms of endometrial cancer

No.	Recommendation	GoR	LOE	Sources
10.3	If a hereditary form of endometrial cancer is suspected, the patient should be referred to a certified gynecological cancer center.	EC		

10.5. Psychosocial counseling and care services

No.	Recommendation	GoR	LOE	Sources
10.4	Individuals who have already developed the disease, carriers, and those at high risk for monogenic hereditary diseases and other malignancies should be informed about the availability and benefits of psychosocial counseling and care services.	EC		

10.6. Clarifying a suspected clinical diagnosis

No.	Recommendation	GoR	LOE	Sources
10.5	If at least one of the revised Bethesda criteria has been met, a more detailed (molecular-)pathological examination of the tumor tissue for changes typical of Lynch syndrome must be carried out. This includes an examination of immunohistochemical expression of DNA mismatch repair proteins, a microsatellite analysis, and if appropriate an examination of methylation of the *MLH1* promoter.	A	3	[199, 202-204, 216]
10.6	A (molecular-)pathological examination for Lynch syndrome in tumor tissue should be carried out in patients under the age of 60 in whom an endometrial cancer is diagnosed.	B	3	[199, 202-204, 216, 220]
10.6.1	It is still a matter of controversy whether these examinations of tumor material require medical information and counseling to be provided and consent to be given in accordance with the requirements of the law on genetic diagnosis. Until an authoritative interpretation of the gene	EC		

No.	Recommendation	GoR	LOE	Sources
	diagnosis law relative to Lynch syndrome screening in endometrial cancer tumor material becomes available, the appropriate information and consent in accordance with the genetic diagnosis law should be ensured before the above molecular-pathological analyses of tumor material are carried out.			
10.7	In patients from families in which the Amsterdam criteria are met, but whose tumor tissue does not show the abnormalities typical of Lynch syndrome, Lymph syndrome is not excluded. For further assessment and additional diagnosis if appropriate, genetic counseling should therefore be carried out.		EC	

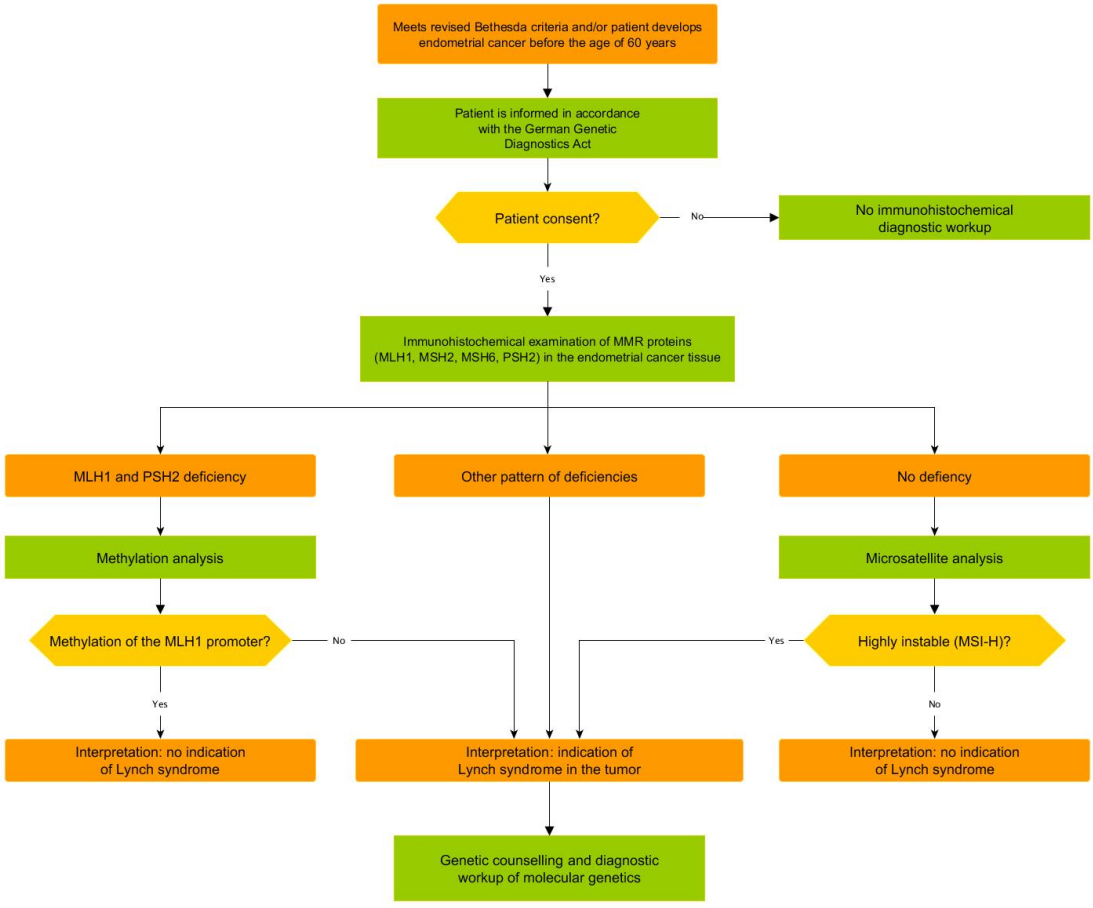

Figure 4: Algorithm for diagnosing Lynch syndrome in tumor issue

10.6.1. Searching for germline mutations

No.	Recommendation	GoR	LOE	Sources
10.8	If Lynch syndrome is suspected due to an abnormal molecular-pathological finding, the patient must be offered a germline mutation search in the *MMR* gene(s) that are probably affected.	A	3	[199, 202, 204, 216]
10.8.1	If the clinical criteria for another hereditary tumor syndrome with an increased risk of endometrial cancer are met, a mutation search in the genes probably affected must be directly carried out.	EC		

10.6.2. Approach with absent or uncertain evidence of mutation

No.	Recommendation	GoR	LOE	Sources
10.9	If the molecular-genetic examination of the patient does not definitely diagnose any pathogenic germline mutations, this does not exclude the presence of a hereditary tumor syndrome.	EC		

10.7. Primary prevention in the risk group

No.	Recommendation	GoR	LOE	Sources
10.10	Due to a lack of data on the risk groups mentioned, no specific recommendations can be given for primary prevention through dietary measures or chemoprevention in comparison with the general population.	EC		

10.8. Approach in individuals at high risk for Lynch or Cowden syndrome

No.	Recommendation	GoR	LOE	Sources
10.11	Individuals who are at risk for Lynch syndrome or Cowden syndrome must be recommended to receive human genetics counseling before the start of the recommended screening/early detection examinations.	EC		
10.12	As soon as the causative mutation in the family is known, the patient must be informed that other potentially affected family members also need to be told about the increased risk.	EC		

No.	Recommendation	GoR	LOE	Sources
10.13	If the familial mutation has been excluded in an at-risk individual, the general cancer early detection measures apply.		EC	

10.9. Screening for endometrial cancer in patients with Lynch or Cowden syndrome

No.	Recommendation	GoR	LOE	Sources
10.14	It has not yet been shown that any of the screening methods used for early detection of endometrial cancer in patients with Lynch syndrome and Cowden syndrome leads to a prolongation of life. The limited data therefore do not allow any recommendations to be made either for or against a specific screening examination for early detection of endometrial cancer in patients with Lynch syndrome or Cowden syndrome.	ST	4	[54, 55, 69, 221, 222]

10.9.1. Syndrome-specific early detection examinations in patients with Lynch or Cowden syndrome and those at risk

No.	Recommendation	GoR	LOE	Sources
10.15	Due to the wide range of possible tumors, patients with Lynch syndrome or Cowden syndrome and those who are at risk must be recommended to undergo syndrome-specific early detection examinations, particularly colonoscopies. Detailed instructions can be found in the corresponding guidelines.		EC	

10.10. Procedure in genetic carriers of Lynch or Cowden syndrome

No.	Recommendation	GoR	LOE	Sources
10.16	The advantages and disadvantages of prophylactic hysterectomy - and bilateral salpingo-oophorectomy as well if appropriate in Lynch syndrome patients - must be discussed with carriers of Lynch syndrome and Cowden syndrome starting at age 40, or 5 years before the earliest age at diagnosis in the family, particularly when a surgical intervention for a different indication is planned.		EC	

11. Palliative medicine, psycho-oncology, rehabilitation, psychosocial care, patient information

11.1. Psycho-oncological aspects

No.	Recommendation	GoR	LOE	Sources
11.1	Patients with endometrial cancer and their relatives may face many different physical, psychological, social, and spiritual/religious burdens.		EC	

11.1.1. Psychosocial support

No.	Recommendation	GoR	LOE	Sources
11.2	Cancer patients and their relatives must be informed as early as possible in all phases of the disease about the availability of psychosocial support, counseling and treatment services and must be given access to these services as appropriate for their individual needs.		EC	

11.1.2. Screening to assess the psychosocial burden

No.	Recommendation	GoR	LOE	Sources
11.3	All patients must receive screening for psychosocial burdens. Psycho-oncological screening should be carried out at the earliest time possible and repeated at appropriate intervals during the course of the disease when it is clinically indicated or when there are changes in the patient's disease status (e.g., recurrence or progression of the disease).		EC	

Table 18: Recommendations of the Level 3 guideline on "Psycho-Oncological Diagnosis, Counseling and Treatment in Adult Cancer Patients," version 1.1, January 2014 [223]

7.1	Assessment of the psychosocial burden and individual need for psycho-oncological treatment should take place at the earliest possible time and should then be repeated during the course of the disease.
7.2	All patients must receive screening for psychosocial burdens. Psycho-oncological screening should be carried out at the earliest time possible and repeated at appropriate intervals during the course of the disease when it is clinically indicated or when there are changes in the patient's disease status (e.g., recurrence or progression of the disease).

7.3	Validated and standardized screening instruments must be used to assess the psychosocial burden. Recommended screening instruments include, for example, the Distress Thermometer and the Hospital Anxiety and Depression Scale (HADS). The patient should also be asked about her individual preferences for psychosocial support.
7.4	When there are positive screening findings and/or if the patient so wishes, a diagnostic discussion to clarify psychosocial burdens and psychological comorbidity must take place.
7.5	More detailed diagnostic clarification should take place in accordance with the individual problems in the psychological/social/somatic field that are identified during the discussion.

11.1.3. Establishing an indication for psycho-oncological intervention

No.	Recommendation	GoR	LOE	Sources
11.4	The indication for psycho-oncological interventions must be established in accordance with individual need, the setting and the phase of the patient's disease (first diagnosis, surgery, adjuvant therapy, recurrence-free phase, recurrence phase, palliative phase) and must taken the patient's wishes into account.		EC	

11.1.4. Sexuality and endometrial cancer

No.	Recommendation	GoR	LOE	Sources
11.5	The topic of sexuality must be actively addressed in the various phases of the treatment process and follow-up in patients with endometrial cancer, in order to assess the need for support and allow the appropriate assistance to be offered.		EC	

11.2. Patient information

This section has been compiled with close attention to the following Level 3 guidelines:

- "Diagnosis, Treatment, and Follow-Up of Breast Carcinoma" [224]
- "Diagnosis, Treatment, and Follow-Up of Malignant Ovarian Tumors" [225]
- "Diagnosis, Treatment, and Follow-Up in Patients with Cervical Carcinoma" [166]
- "Psycho-Oncological Diagnosis, Counseling, and Treatment of Adult Cancer Patients" [223]
- "Early Detection, Diagnosis, and Treatment of the Various Stages of Prostate Carcinoma" [226]

11.2.1. Patient information and its content

11.2.1.1. Information materials

No.	Recommendation	GoR	LOE	Sources
11.6	High-quality and pertinent information materials (in print or Internet media) compiled in accordance with the defined quality criteria for health-care information must be made available to patients in order to support them in their independent decision-making for or against medical measures by communicating levels of risk in a generally comprehensible way (e.g., with details of absolute risk reductions).		EC	

11.2.1.2. Explaining the diagnosis

No.	Recommendation	GoR	LOE	Sources
11.7	The patient must be offered an opportunity for her partner or a relative/confidant to be present at the discussion when the diagnosis is being explained and during additional discussions in the course of treatment and follow-up.		EC	
11.8	The patient's individual preferences, needs, worries, and anxieties must be explored and taken into account during the discussion with the doctor. If the patient needs several discussions for this purpose, an offer to hold additional discussions must be made.		EC	

11.2.1.3. Providing and explaining information

No.	Recommendation	GoR	LOE	Sources
11.9	Information and explanations must be communicated to the patient as early as possible and in accordance with the basic principles of patient-centered communication that allows participatory decision-making.		EC	

11.2.1.4. Information about self-help groups

No.	Recommendation	GoR	LOE	Sources
11.10	The patient must be informed about the option of contacting self-help groups.		EC	

Contact data for self-help groups in the local area can be obtained from the Contact and Information Office for Promoting and Supporting Self-Help Groups (NAKOS):

- Nationale Kontakt- und Informationsstelle zur Anregung und Unterstützung von Selbsthilfegruppen (NAKOS)
  Wilmersdorfer Strasse 39, 10627 Berlin, Germany
  Tel.: 030 31018960
  Fax: 030 31018970
  E-mail: selbsthilfe@nakos.de
  Internet: www.nakos.de

Contact data for counseling services and centers for patients with endometrial cancer will also be made available in the accompanying patient guideline, which will be freely available on the Internet after publication on the page of the Oncology Guidelines Program and AWMF pages:

- https://www.leitlinienprogramm-onkologie.de/patientenleitlinien/
- https://www.awmf.org/leitlinien/patienteninformation.html

11.2.1.5. Information about treatment options

No.	Recommendation	GoR	LOE	Sources
11.11	Patients with endometrial cancer must be informed about the treatment options described in this guideline that are relevant to them and the prospects of success and the potential side effects of these treatments. In particular, details must be given of effects on the patient's physical appearance, sexual life, urinary and fecal control (incontinence), and aspects of female identity (self-image, fertility, menopausal symptoms).	EC		

11.3. Palliative-medicine aspects during treatment for endometrial cancer

No.	Recommendation	GoR	LOE	Sources
11.12.1	After a diagnosis of incurable cancer, all patients must be offered palliative care, independently of whether tumor-specific therapy is carried out.	A	2	[227-236]
11.12.2	Specialized palliative care must be incorporated into oncological decision-making processes — e.g., with involvement of palliative care specialists in interdisciplinary tumor conferences.	EC		
11.12.3	Patients with incurable cancer and in highly complex situations must receive specialized palliative care.	A	2	[227-236]

11.4. Rehabilitation

This section is closely based on and adapted from the existing Level 3 guideline "Diagnosis, Treatment, and Follow-Up in Patients with Cervical Carcinoma," version 1.0, September 2014, AWMF Registry No. 032/033OL (available at http://www.leitlinienprogramm-onkologie.de/leitlinien/zervixkarzinom/) [166].

No.	Recommendation	GoR	LOE	Sources
11.13	Medical-oncological rehabilitation is aimed at specific treatment of disturbances following disease and treatment. All patients with endometrial cancer must receive information and counseling about statutory entitlement to apply for and receive rehabilitation services.		EC	
11.14	Treatment-related disturbances — for example, abdominal wall and adhesion symptoms, disturbances of sexual function, pain during intercourse, vaginal dryness, urinary and bowel disturbances — must be inquired about and treated not only during primary therapy but also during rehabilitation and follow-up.		EC	

11.4.1. Employment rehabilitation

Oncological rehabilitation measures are provided in in-patient and outpatient rehabilitation institutions qualified for the purpose. The bodies funding these institutions are usually the statutory pension insurance funds or health insurance funds. Patients usually wish to return to work in order to regain as much normality as possible in their lives. The charges that qualify for insurance refunding cover in particular assistance in keeping or obtaining a job, including costs of activation and professional reintegration (see sections 33 of the German Social Security Code (*Sozialgesetzbuch,* SGB) X, and section 74 SGB V) [237].

11.4.2. Physiotherapeutic treatment during rehabilitation after endometrial cancer

The physiotherapeutic part of follow-up treatment focuses on the treatment of the various side effects of cancer treatment (surgery, radiotherapy, and chemotherapy). This includes treatment for incontinence (see below for ICD-10 codes), lymphedema (in this case the lower extremities: ICD-10 I89.0– [1]) and extends to interventions used to alleviate fatigue syndrome (ICD-10 G93.3 [1]).

Surgical or radiotherapeutic treatment for gynecological tumors may cause functional disturbances in the pelvis. These involve symptoms of urinary incontinence (urgency incontinence, stress incontinence, mixed incontinence; ICD-10 N39.42, N39.3, N39.48 [1]) and fecal incontinence (ICD-10 R15 [1]), pain, dyspareunia (N94.1 [1]; e.g., due to a shortened or scarred vagina), circulatory changes and inadequate elasticity in scar tissue.

Various passive physiotherapeutic techniques (scar mobilization, dilation of vaginal tissue, positioning, complex physical decongestive therapy, etc.) and

also active techniques (guidance on low-pain everyday behavior, circulation exercises, decongestive exercises, measures involving physical exercise therapy and training methods) may reduce these disturbances.

11.4.3. Treatment for incontinence

No.	Recommendation	GoR	LOE	Sources
11.15	If urinary incontinence develops in patients after endometrial cancer, treatment in accordance with the "Interdisciplinary Level 2 Evidence-Based Guideline on the Diagnosis and Treatment of Stress Incontinence in Women" [238] must be offered.		EC	
11.16	If fecal incontinence develops in patients after endometrial cancer, pelvic floor training should be offered.		EC	

11.4.4. Treatment for lymphedema

No.	Recommendation	GoR	LOE	Sources
11.17	When there is manifest lymphedema, combined treatment with compression, skin care, manual lymph drainage, and exercise therapy should be offered.		EC	

11.4.5. Alleviation of fatigue syndrome

No.	Recommendation	GoR	LOE	Sources
11.18	For fatigue, patients should be offered active forms of training (strength training and/or stamina training).	B	2	[239-256]

12. Care structures and quality indicators

12.1. Care structures

12.1.1. Preliminary remarks

Endometrial cancer is the most frequent type of gynecological carcinoma. The mean age at diagnosis is constantly around 70 years, and the incidence and mortality are continuing to gradually increase [257], [2]. Health-care structures must be available to comprehensively regulate the prevention, diagnosis, treatment and follow-up and thereby lead to good results. For the treatment of ovarian carcinoma and cervical carcinoma, it has been shown that treatment at specialized centers leads to treatment benefits and thus to better overall survival for the patients [166, 225, 258, 259].

Due to the often unclear diagnosis of endometrial cancer at the stage in which there is lymph-node metastasis, and the good prognosis when the lymph nodes are not involved, treatment recommendations for endometrial cancer have in the past been unclear. The aims of improving early cancer detection, developing oncological care structures further, ensuring effective oncological treatment, and promoting patient-centered care have been included in the National Cancer Plan (https://www.bundesgesundheitsministerium.de/themen/praevention/nationaler-krebsplan.html). The need to evaluate the health-care situation in Germany and the need for research studies to survey the long-term follow-up and the training situation have been clearly recognized.

12.1.2. Treatment in oncological centers

No.	Recommendation	GoR	LOE	Sources
12.1	Patients with endometrial cancer should be treated by an interdisciplinary team. The team should include all of the necessary specialist disciplines in a cross-sector network. This is most easily achieved in a certified center.		EC	

12.1.3. Interdisciplinary and cross-sector care

Caring for patients with suspected endometrial cancer, or with a diagnosis of endometrial cancer, is an interdisciplinary and cross-sectoral task. To achieve the optimal treatment result for the patient, it is necessary for the various structures and persons acting along the chain of care to be coordinated in an interdisciplinary way and to work collaboratively with one another [260], [261]. The basis for this type of care is the definition of centers set out in the framework of the National Cancer Plan: “A center represents a network of qualified and jointly certified interdisciplinary and trans-sectoral institutions, spread over different locations if appropriate (hospitals, medical practices, rehabilitation institutions) which so far as the discipline requires reflect as much of the entire chain of care as possible for the affected patients” [260]. The results of questionnaires in certified breast cancer centers and bowel cancer centers have shown that implementing the concept of a center

described above has positive effects from the point of view of the funding bodies on the quality of care for patients in the certified networks [262], [263] and also that patient satisfaction is very high [264], [265], [266]. In addition, analyses of the guideline-based quality indicators in certified centers have shown that the content of the guidelines is well implemented and that patients are accordingly treated in accordance with the guidelines [267].

In this system, high quality standards need to be aimed for in prevention, diagnosis, and treatment, extending to rehabilitation and palliative treatment for the patients. For this purpose, procedures and structures within the network have to be optimized in an interdisciplinary and cross-sectoral way. The three-level center model, with the establishment of organ cancer centers, oncological centers, and comprehensive cancer centers along with collaborating partners (e.g., private practices) at all levels of care provision forms the basis for this high-quality health-care structure [260], [268].

Gynecological cancer centers have been certified since 2008 by the German Cancer Association (*Deutsche Krebsgesellschaft,* DKG) in collaboration with the German Association for Gynecology and Obstetrics (*Deutsche Gesellschaft für Gynäkologie und Geburtshilfe,* DGGG) and the Working Group on Gynecological Oncology (*Arbeitsgemeinschaft für Gynäkologische Onkologie,* AGO). In July 2016, a total of 123 of these centers had been certified [269].

By analogy with the breast cancer centers, the aim is also to establish comprehensive care here as well, so that care for patients with gynecological carcinomas takes place in a quality-assured, certified, interdisciplinary, and cross-sectoral form.

Particularly in view of the increasing numbers of new cases in patients over 70 years of age, with the corresponding comorbidities, interdisciplinary collaboration among recognized and tested experts is all the more important. Despite the generally good prognosis with endometrial cancer, it has in the meantime been shown that patients with endometrial cancer have a treatment advantage when they are treated by specialized gynecological oncologists [270], [271]. Patients with a primary diagnosis of endometrial hyperplasia with evidence of atypia should therefore already be treated at a specialized center, due to the often simultaneous presence of endometrial cancer [130]. Particularly with the more aggressive histological type, higher grades, and advanced stages, treatment by specialized gynecological oncologists results in a marked improvement in the recurrence-free interval and overall survival [272].

The qualitative and quantitative expertise of the physicians treating the patients must therefore be demonstrated in certified centers — e.g., through the focus of expertise description “gynecological oncology” [273] or the numbers of surgical and systemic treatments carried out [274]. Patients with endometrial cancer who undergo surgery in centers with large numbers of cases have lower mortality rates [274], [275]. Minimum case numbers are necessary in order to allow quality-assured care in accordance with the current standard [274], [275]. In addition, the gynecological cancer centers treating the patients must ensure a timely start to therapy. Delayed treatment has been shown to have a negative influence on patients’ survival [276]. The aim must be for a patient with a diagnosis of endometrial cancer to be able to turn to centers that present their quality standards transparently and meet the relevant criteria [260], [268], [277].

12.1.4. Interdisciplinary tumor conference

No.	Recommendation	GoR	LOE	Sources
12.2	Patients with endometrial cancer must have their cases presented at an interdisciplinary tumor conference.		EC	

12.1.5. Interdisciplinary chain of care

The first element in the chain of care is the private-practice gynecologist, who identifies a patient with endometrial cancer particularly as a result of abnormal symptoms, or through her participation in statutory early cancer detection examinations. This is followed by vaginal ultrasonography for further clarification. Abnormal findings are then clarified histologically with the relevant expert opinion, either locally, by a specialized gynecologist, or at a certified gynecological cancer center (Figure 5: Consensus-agreed care algorithm).

12.1.6. Algorithm of care agreed by consensus in the guideline group

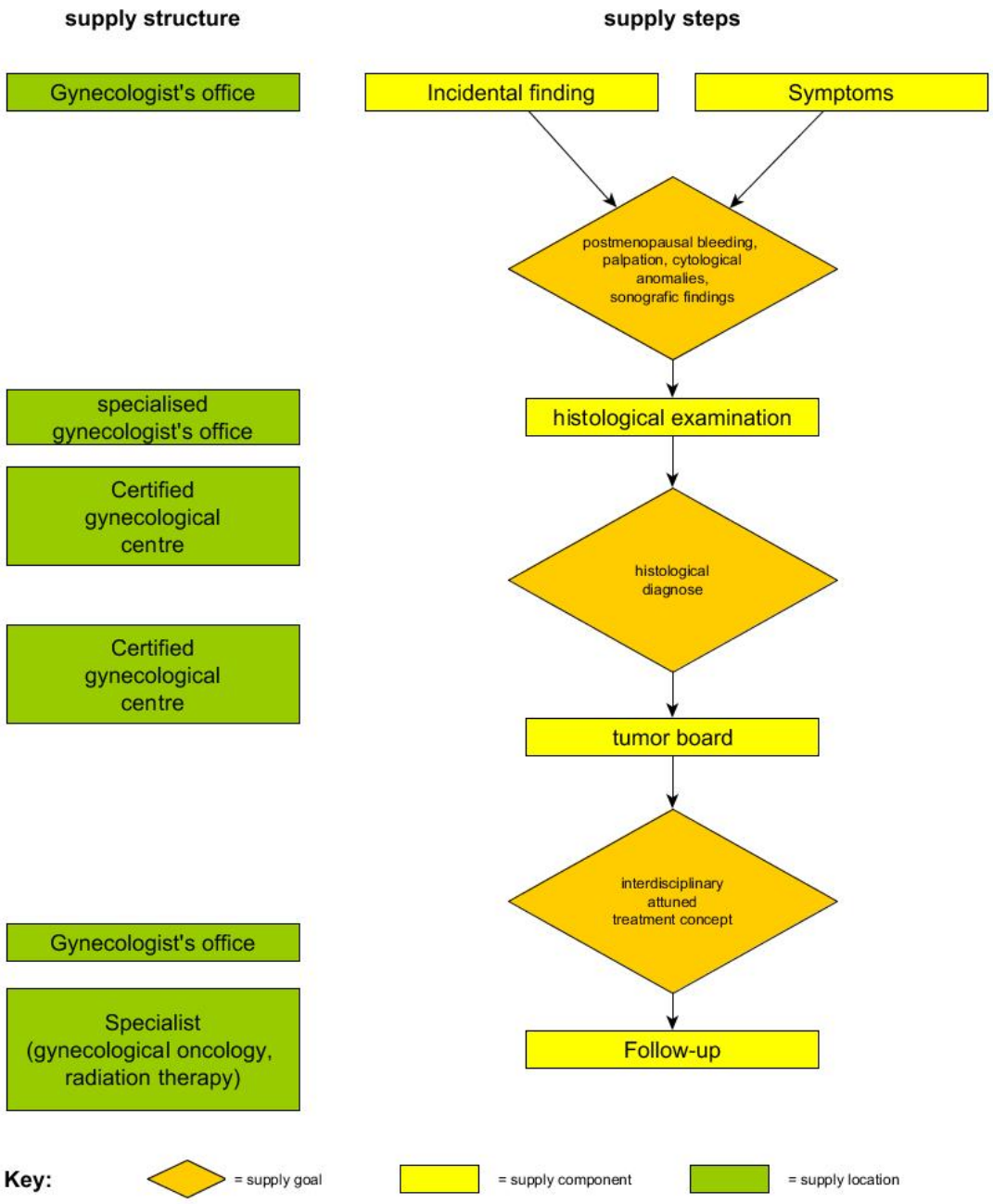

Figure 5: Consensus-agreed care algorithm

12.1.7. Longitudinal documentation of patient history

The decisive element in the entire chain of care is that information from the individual areas of care should be collected and systematically documented in order to allow statements to be made that are relevant to the patient's care in relation to the quality of the process, structure, and results. Quality indicators are defined in the framework of the certification process. The extent to which these are met and assessed is analyzed and reported back to the health-care institution, as well as to the guideline group, etc.

This information approach follows the Cancer Early Detection and Registry Law (*Krebsfrüherkennungs- und -registergesetz,* KFGoR), which specifies that data must be combined centrally so that they can be collected on both a cross-sectoral and also multiple-site basis in order to be used to present the quality of the results.

For this purpose, the Working Group on Data-Minimizing Standard Tumor Documentation (*Arbeitsgruppe Datensparsame Einheitliche Tumordokumentation,* DET), initiated by the Federal Ministry of Health in Germany, has defined a basic dataset with which the data are to be documented on a cross-sectoral basis. Following decentralized input by all health-care institutions, central data documentation and analysis returns the necessary information back to physicians and patients [278].

12.1.8. Opportunities for further training and further education

The guideline group is not aware of any existing meta-analyses, randomized studies, or observational studies on the specific training and further education situation in relation to endometrial cancer in Germany. Further training and further education basically take place when specialists are working in the field or during training in a focus of expertise. The overall topic here is the treatment of gynecological malignancies, in which the principles of treatment are often similar.

Training for physicians who treat patients with endometrial cancer should focus on certified networks, so that large numbers of cases, interdisciplinarity, and bundling of expertise will ensure high-quality training in relation to the implementation of the guideline and the latest standards [260], [268], [277]. The basic precondition for this is the guidelines established in the 2004 Further Education Regulations on the performance figures that need to be met during further training for specialist physicians, further training in a focus of expertise, and/or in optional further training courses. It is only possible to carry out major surgical interventions in the framework of further training in the focus of expertise "gynecological oncology," or disease-specific chemotherapy in the framework of additional further training in drug therapy for cancer, when minimum numbers of patients with these clinical pictures are being treated on an interdisciplinary basis by physicians with the appropriate further training and qualifications and proven oncological experience.

The currently large numbers of specialist physicians and holders of "focus of expertise" qualifications in the various fields of health care mean that provision of comprehensive care is at present possible. However, the numbers of physicians authorized to conduct further training are stagnating or have been declining slightly in recent years. It appears that the numbers of individuals receiving specialized further training are likely to decline in the future, so that care for patients with gynecological carcinomas may become more difficult [273], [277].

12.2. Quality indicators

Quality indicators (QIs) are measurement variables for which data are collected to assess the quality of the structures, processes, and results they represent [279]. The quality indicators developed by the guideline group may be consulted in the long version of this guideline.

13. Appendices

13.1. Criteria for diagnosing Lynch syndrome: extracolonic manifestations

13.1.1. Amsterdam II criteria

1. At least three family members with histologically confirmed colorectal cancer or cancer of the **endometrium,** small bowel, ureter, or renal pelvis, one of whom is a first-degree relative of the other two; familial adenomatous polyposis (FAP) must be excluded.

2. At least two successive generations are affected.

3. First diagnosis before the age of 50 in at least one of the patients.

Source: [280], Institut für Humangenetik Bonn: https://www.humangenetics.uni-bonn.de/de/beratung/diagnostik/Molekulargenetische-Diagnostik/hereditaeres-nicht-polypoeses-kolonkarzinom-hnpcc-lynch-syndrom/hereditaeres-nicht-polypoeses-kolonkarzinom-hnpcc-lynch-syndrom/ (accessed on August 24, 2017).

13.1.2. Revised Bethesda criteria

Patients' tumors should be examined for the presence of a mismatch repair defect in the following cases:

1. Patients with colorectal cancer under the age of 50.

2. Patients with synchronous or metachronous colorectal carcinomas or other HNPCC-related tumors,* regardless of age.

3. Patients with colorectal cancer with histological findings with MSI-H histology** under the age of 60.

4. Patients with colorectal carcinoma (regardless of age) who have one first-degree relative with a colorectal carcinoma or an HNPCC-associated tumor under the age of 50.

5. Patients with colorectal cancer (regardless of age) who have at least two first-degree or second-degree relatives in whom a colorectal cancer or an HNPCC-associated tumor (regardless of age) has been diagnosed.

* HNPCC-related tumors include tumors in: the colorectum, **endometrium,** stomach, ovaries, pancreas, urothelium, bile duct, small bowel, and brain (usually glioblastomas, as in Turcot syndrome), as well as sebaceous gland adenomas and keratoacanthomas (as in Muir–Torre syndrome).

** Presence of tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, or a medullary growth pattern.

Source: [281], Institut für Humangenetik Bonn: https://www.humangenetics.uni-bonn.de/de/beratung/diagnostik/Molekulargenetische-

Diagnostik/hereditaeres-nicht-polypoeses-kolonkarzinom-hnpcc-lynch-syndrom/ (accessed on August 24, 2017).

13.2. Overview of participating organizations and individuals

Table 19: Participating specialist societies and organizations

Participating specialist societies and organizations	Office-holders	Deputies
ADT (AG Deutscher Tumorzentren)	Prof. Dr. med. Olaf Ortmann, Regensburg	
AET (AG Erbliche Tumorerkrankungen der DKG)	Prof. Dr. med. Stefan Aretz, Bonn	Prof. Dr. med. Rita Katharina Schmutzler, Cologne
AGO (Arbeitsgemeinschaft Gynäkologische Onkologie in der DGGG und DKG)	Prof. Dr. med. Peter Mallmann, Cologne	
AGO Studiengruppe (Arbeitsgemeinschaft Gynäkologische Onkologie [AGO] Studiengruppe)	PD Dr. med. Christian Kurzeder, Basel	Prof. Dr. med. Felix Hilpert, Hamburg
AIO (Arbeitsgemeinschaft Internistische Onkologie der DKG)	Dr. med. Volker Hagen, Dortmund	PD Dr. med. Anne Letsch, Berlin
APM (Arbeitsgemeinschaft Palliativmedizin der Deutschen Krebsgesellschaft)	Prof. Dr. med. Birgitt van Oorschot, Würzburg	Dr. med. Joan Elisabeth Panke, Essen
ARO (Arbeitsgemeinschaft Radiologische Onkologie der DKG)	Prof. Dr. med. Stefan Höcht, Saarlouis	Prof. Dr. med. Vratislav Strnad, Erlangen
ASORS (AG Supportive Massnahmen in der Onkologie, Rehabilitation und Sozialmedizin der DKG)	Prof. Dr. med. Petra Feyer, Berlin	[Dr. med. Christiane Niehues, Berlin], Dr. med. Timm Dauelsberg, Nordrach
BLFG (Bundesarbeitsgemeinschaft Leitender Ärztinnen und Ärzte in der Frauenheilkunde und Geburtshilfe)	Prof. Dr. med. Michael Friedrich, Krefeld	
BNGO (Berufsverband Niedergelassener Gynäkologischer Onkologen in Deutschland)	Dr. med. Christoph Uleer, Hildesheim	
BVF (Berufsverband der Frauenärzte)	Dr. med. Wolfgang Cremer, Hamburg	

Participating specialist societies and organizations	Office-holders	Deputies
BVDST (Bundesverband Deutscher Strahlentherapeuten)	Prof. Dr. med. Franz-Josef Prott, Wiesbaden	Prof. Dr. med. Peter Niehoff, Offenbach
BV Pathologie (Bundesverband Deutscher Pathologen)	Prof. Dr. med. Lars-Christian Horn, Leipzig	Prof. Dr. med. Doris Mayr, Munich
DEGRO (Deutsche Gesellschaft für Radioonkologie)	Prof. Dr. med. Dirk Vordermark, Halle	
DEGUM (Deutsche Gesellschaft für Ultraschall in der Medizin)	Prof. Dr. med. Heinrich Prömpeler, Freiburg	Prof. Dr. med. Dieter Grab, Munich
DGAV (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie)	Prof. Dr. med. Jan Langrehr, Berlin	
DGCH (Deutsche Gesellschaft für Chirurgie)	Prof. Dr. med. Steffen Leinung, Grimma [*d.* November 25, 2016]	
DGE (Deutsche Gesellschaft für Endokrinologie)	Prof. Dr. Matthias W. Beckmann, Erlangen	
DGGG (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe)	Prof. Dr. med. Rainer Kimmig, Essen	
DGHO (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie)	PD Dr. med. Anne Letsch, Berlin	Dr. med. Volker Hagen, Dortmund
DGN (Deutsche Gesellschaft für Nuklearmedizin)	Prof. Dr. med. Michael J. Reinhardt, Oldenburg	Prof. Dr. med. Michael Kreissl, Magdeburg
DGP (Deutsche Gesellschaft für Palliativmedizin)	Prof. Dr. med. Bernd Alt-Epping, Göttingen	
DGP (Deutsche Gesellschaft für Pathologie)	Prof. Dr. med. Lars-Christian Horn, Leipzig	Prof. Dr. med. Doris Mayr, Munich
DMG (Deutsche Menopause Gesellschaft)	Prof. Dr. med. Ludwig Kiesel, Münster	Dr. med. Ralf Witteler, Münster

Participating specialist societies and organizations	Office-holders	Deputies
DGoR (Deutsche Röntgengesellschaft)	Prof. Dr. med. Jan Menke, Göttingen	
FSH (Frauenselbsthilfe nach Krebs)	Marion Gebhardt, Forchheim	Annemarie Schorsch, Bad Soden
GFH (Deutsche Gesellschaft für Humangenetik)	Dr. med. Verena Steinke-Lange, Munich	
KOK (Arbeitsgemeinschaft der DKG: Konferenz Onkologische Kranken- und Kinderkrankenpflege)	Kerstin Paradies, Hamburg	
NOGGO (Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie)	Prof. Dr. med. Werner Lichtenegger, Berlin	Prof. Dr. med. Alexander Mustea, Greifswald
OEGGG (Österreichische Gesellschaft für Gynäkologie und Geburtshilfe)	Prof. Dr. med. Alain-Gustave Zeimet, Innsbruck	Prof. Dr. med. Edgar Petru, Graz
PRIO (Arbeitsgemeinschaft der DKG Prävention und integrative Medizin in der Onkologie)	Prof. Dr. med. Volker Hanf, Fürth	Prof. Dr. med. Jutta Hübner, Jena
PSO (Deutsche Arbeitsgemeinschaft für Psychoonkologie)	Prof. Dr. phil. Joachim B. Weis, Freiburg	Dr. med. Anne D. Rose, Berlin
SGGG (Schweizer Gesellschaft für Gynäkologie und Geburtshilfe)	Prof. Dr. med. Michael D. Mueller, Bern	PD Dr. med. Edward Wight, Basel
ZVK (Zentralverband der Physiotherapeuten/ Krankengymnasten)	Ulla Henscher, Hannover	Reina Tholen, Bremen/Cologne

The following specialist societies were also contacted for the guideline process:

- Working Group on Oncological Pathology (*Arbeitsgemeinschaft Onkologische Pathologie*) of the German Cancer Association; the group is represented by the German Society for Pathology (*Deutsche Gesellschaft für Pathologie,* DGP).
- German Society for General Medicine and Family Medicine (*Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin,* DEGAM); however, this society did not nominate a representative.

- German Society for Urology (*Deutsche Gesellschaft für Urologie,* DGU); the office-holder, Prof. Stephan Roth, suspended participation due to lack of free time.

13.2.1. Patient participation

Marion Gebhardt, the representative of the Women's Self-Help after Cancer (*Frauenselbsthilfe nach Krebs e.V.*) patient organization, was directly involved in the compilation of the guideline. She also took part in the Working Group on Palliative Medicine/Psycho-Oncology/Rehabilitation/Psychosocial Care/Patient Information and the Working Group on the compilation of the quality indicators (meeting with personal attendance on October 9, 2017 in Berlin) and had voting rights at the consensus conferences.

13.2.2. Methodological supervision

By the German Guideline Program in Oncology:

- Dr. Monika Nothacker, MPH (AWMF-Institut für Medizinisches Wissensmanagement (AWMF-IMWi)
- Dipl. Biol. Susanne Blödt, MScPH (AWMF-Institut für Medizinisches Wissensmanagement (AWMF-IMWi)
- Dr. Markus Follmann, MPH, MSc, Office of the German Guideline Program in Oncology c/o DKG
- Dipl.-Soz.Wiss Thomas Langer, Office of the German Guideline Program in Oncology c/o DKG

By external contractors:

- Dr. Heike Raatz, MSc; Basel Institut für Klinische Epidemiologie & Biostatistik (CEB) (compilation of an evidence report; see section 1.8)
- Dr. Simone Wesselmann, MBA; Deutsche Krebsgesellschaft – Bereich Zertifizierung (coordination for compiling the quality indicators)

13.3. Methodological and editorial notes

13.3.1. Oxford level of evidence scheme (2011 version)

Table 20: Oxford level of evidence scheme (2011 version) [282]

Question	Level 1*	Level 2*	Level 3*	Level 4*	Level 5
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local nonrandom sample**	Case series**	Not applicable
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross-sectional studies with consistently applied reference standard and blinding	Individual cross-sectional studies with consistently applied reference standard and blinding	Nonconsecutive*** studies, or studies without consistently applied reference standards**	Case-control studies, or poor or nonindependent reference standard**	Expert opinion based on pathophysiological considerations
What will happen if we do not apply a therapy? (Prognosis)	Systematic review of cohort studies that observe patients in the initial stage of the disease (inception cohort studies)	Individual cohort studies of patients in the initial stage of the disease (inception cohort studies)	Cohort study or control arm of a randomized trial*	Case series or case-control study, or prognostic cohort study with poor methodological quality**	Not applicable
Does this intervention help? (Benefits of the intervention)	Systematic review of randomized studies or *n*-of-1 studies [2]	Randomized trial or observational study with dramatic effect	Controlled cohort study/follow-up study**	Case series, case-control studies, or historically controlled studies**	Expert opinion based on pathophysiological considerations

Question	Level 1*	Level 2*	Level 3*	Level 4*	Level 5
What are the *common* side effects? (Treatment harms)	Systematic review of either randomized studies or nested case–control studies,[4] or *n*-of-1 study with the patient you are raising the question about, or observational study with dramatic effect	Randomized study or (exceptionally) observational study with dramatic effect	Controlled cohort study/follow-up study (postmarketing surveillance), with sufficient case numbers to identify a common side effect. If long-term side effects are to be identified, the duration of follow-up must be sufficient**		
What are the *rare* side effects? (Treatment harms)	Systematic review of randomized studies or *n*-of-1 studies	Randomized study or (exceptionally) observational study with dramatic effect			
Is this early detection test worthwhile? (Screening)	Systematic review of randomized studies	Randomized study	Controlled cohort study/follow-up study**		

* The level may be graded down on the basis of study quality, wide confidence intervals (imprecise effect estimate), inconsistencies between studies, or because the absolute effect size is very small, as well as due to insufficient transferability (the question addressed by the study does not correspond to the clinically relevant question). The evidence level may be graded up if there is a large or very large effect size.
** As always, a systematic review is generally better than an individual study.
*** Consecutive inclusion = patients are continually recruited.
1. For quality assessment, the STROBE statement may also be used: http://www.strobe-statement.org/index.php?id=strobe-aims.
2. Individual patient studies in which the patients alternately receive an intervention and a control intervention.
3. Observational follow-up studies of a population from a completed randomized controlled trial.
4. A study in which cases and controls are drawn from a cohort study that is currently in progress.

13.3.2. Scheme for grades of recommendation

The methodology used in the Oncology Guidelines program involves the issuing of grades of recommendation by the authors of the guideline, within the framework of a formal consensus procedure. Accordingly, a complex nominal group process and structured consensus conferences moderated by the AWMF were carried out [283]. The recommendations were formally voted on by office-holders who were eligible to vote (see section 1.9.2) during these processes.

In the guideline, all evidence-based statements and recommendations are given the evidence level of the studies on which they are based, and in the case of recommendations the strength of the recommendation (recommendation grade) is also given. With regard to the strength of the recommendation, this guideline distinguishes between three grades of recommendation (Table 21), which are also reflected in the way in which each recommendation is expressed.

The grades of recommendation express the degree of certainty with which the expected benefits of the intervention are likely to make up for the potential harm (net benefit) and the expected positive effects are likely to reach a relevant level for the patient. In the case of negative recommendations ("must not"), the certainty of an absence of benefit or possible harm is expressed correspondingly. The grades of recommendation take into account not only the results of the studies they are based on — the clinical relevance of the effect sizes investigated in the studies, the strengths of effect observed, and the consistency of the study results — but also the applicability of the study results to the patient target group, their feasibility in everyday clinical work, and ethical obligations, as well as patient preferences [284], [283].

Table 21: The grade of recommendation scheme

Grade of recommendation	Description	Expression
A	Strong recommendation	shall/shall not
B	Recommendation	should/should not
0	Recommendation open	may/can

The criteria used to decide on the grades of recommendation are explained in the guideline report for this guideline (see section 1.8).

13.3.3. Recommendations

Recommendations are topic-related core statements in the guideline that are intended to guide action. They are developed by the guideline group and are voted on in the framework of formal consensus procedures.

13.3.4. Statements

Presentations or explanations of specific matters or issues, without direct instructions for action, are described as "statements." They are decided on in

the same way as for recommendations, in the framework of a formal consensus procedure, and may be based either on study results or expert opinions.

13.3.5. Expert consensus (EC)

Recommendations for which systematic literature research was not carried out are described as expert consensus (EC). These recommendations usually refer to procedures involving good clinical practice, for which scientific studies are not necessary or cannot be expected. No symbols or letters have been used to grade the expert consensus; the strength of the consensus point is expressed by the form of expression used (must, should, or can/may) in accordance with the gradation given in Table 21.

14. List of illustrations

15. List of tables

16. References

1. Deutsches Institut für Medizinische Dokumentation und Information (DIMDI), *ICD-10-GM 2018 Systematisches Verzeichnis : Internationale statistische Klassifikation der Krankheiten und verwandter Gesundheitsprobleme* 1. Auflage ed. 2017, im Druck, Köln: Deutscher Ärzte-Verlag.
2. *Krebs in Deutschland 2011/2012*, Gemeinsame Veröffentlichung des Robert Koch-Instituts und der Gesellschaft der epidemiologischen Krebsregister in Deutschland e. V., Editor. 2015: Berlin.
3. Beral, V., D. Bull, and G. Reeves, *Endometrial cancer and hormone-replacement therapy in the Million Women Study.* Lancet, 2005. **365**(9470): p. 1543-51.
4. Nelson, H.D., et al., *Postmenopausal hormone replacement therapy: scientific review.* JAMA, 2002. **288**(7): p. 872-81.
5. Grady, D., et al., *Hormone replacement therapy and endometrial cancer risk: a meta-analysis.* Obstet Gynecol, 1995. **85**(2): p. 304-13.
6. Razavi, P., et al., *Long-term postmenopausal hormone therapy and endometrial cancer.* Cancer Epidemiol Biomarkers Prev, 2010. **19**(2): p. 475-83.
7. Lacey, J.V., Jr., et al., *Endometrial carcinoma risks among menopausal estrogen plus progestin and unopposed estrogen users in a cohort of postmenopausal women.* Cancer Epidemiol Biomarkers Prev, 2005. **14**(7): p. 1724-31.
8. Allen, N.E., et al., *Menopausal hormone therapy and risk of endometrial carcinoma among postmenopausal women in the European Prospective Investigation Into Cancer and Nutrition.* Am J Epidemiol, 2010. **172**(12): p. 1394-403.
9. Chlebowski, R.T., et al., *Continuous Combined Estrogen Plus Progestin and Endometrial Cancer: The Women's Health Initiative Randomized Trial.* J Natl Cancer Inst, 2015. **108**(3).
10. Manson, J.E., et al., *Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials.* JAMA, 2013. **310**(13): p. 1353-68.
11. Doherty, J.A., et al., *Long-term use of postmenopausal estrogen and progestin hormone therapies and the risk of endometrial cancer.* Am J Obstet Gynecol, 2007. **197**(2): p. 139 e1-7.
12. Fournier, A., et al., *Risks of endometrial cancer associated with different hormone replacement therapies in the E3N cohort, 1992-2008.* Am J Epidemiol, 2014. **180**(5): p. 508-17.
13. Crosbie, E.J., et al., *Body mass index, hormone replacement therapy, and endometrial cancer risk: a meta-analysis.* Cancer Epidemiol Biomarkers Prev, 2010. **19**(12): p. 3119-30.
14. Ettinger, B., et al., *Endometrial effects of tibolone in elderly, osteoporotic women.* Obstet Gynecol, 2008. **112**(3): p. 653-9.
15. Nelson, H.D., et al., *Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force.* Ann Intern Med, 2013. **158**(8): p. 604-14.
16. Braithwaite, R.S., et al., *Meta-analysis of vascular and neoplastic events associated with tamoxifen.* J Gen Intern Med, 2003. **18**(11): p. 937-47.
17. Al-Mubarak, M., et al., *Extended adjuvant tamoxifen for early breast cancer: a meta-analysis.* PLoS One, 2014. **9**(2): p. e88238.
18. DeMichele, A., et al., *Impact of raloxifene or tamoxifen use on endometrial cancer risk: a population-based case-control study.* J Clin Oncol, 2008. **26**(25): p. 4151-9.
19. Collaborative Group on Epidemiological Studies on Endometrial Cancer, *Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies.* Lancet Oncol, 2015. **16**(9): p. 1061-1070.
20. Gierisch, J.M., et al., *Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review* Cancer Epidemiology, Biomarkers and Prevention, 2013. **22**(11): p. 1931-1943.
21. Parazzini, F., et al., *Use of fertility drugs and risk of endometrial cancer in an Italian case-control study.* Eur J Cancer Prev, 2010. **19**(6): p. 428-30.
22. Siristatidis, C., et al., *Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer--a systematic review and meta-analysis* Human Reproduction Update, 2013. **19**(2): p. 105-123.

23. Setiawan, V.W., et al., *Age at last birth in relation to risk of endometrial cancer: pooled analysis in the epidemiology of endometrial cancer consortium.* Am J Epidemiol, 2012. **176**(4): p. 269-78.
24. Karageorgi, S., et al., *Reproductive factors and postmenopausal hormone use in relation to endometrial cancer risk in the Nurses' Health Study cohort 1976-2004.* Int J Cancer, 2010. **126**(1): p. 208-16.
25. Dossus, L., et al., *Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition.* Int J Cancer, 2010. **127**(2): p. 442-51.
26. Friberg, E., et al., *Diabetes mellitus and risk of endometrial cancer: a meta-analysis.* Diabetologia, 2007. **50**(7): p. 1365-74.
27. Barone, B.B., et al., *Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis.* JAMA, 2008. **300**(23): p. 2754-64.
28. Huang, Y., et al., *Prediabetes and the risk of cancer: a meta-analysis.* Diabetologia, 2014. **57**(11): p. 2261-9.
29. Zhang, Z.H., et al., *The role of preexisting diabetes mellitus on incidence and mortality of endometrial cancer: a meta-analysis of prospective cohort studies.* Int J Gynecol Cancer, 2013. **23**(2): p. 294-303.
30. Liao, C., et al., *Is diabetes mellitus associated with increased incidence and disease-specific mortality in endometrial cancer? A systematic review and meta-analysis of cohort studies.* Gynecol Oncol, 2014. **135**(1): p. 163-171.
31. Luo, J., et al., *Association between diabetes, diabetes treatment and risk of developing endometrial cancer.* Br J Cancer, 2014. **111**(7): p. 1432-9.
32. Gnagnarella, P., et al., *Glycemic index, glycemic load, and cancer risk: a meta-analysis.* Am J Clin Nutr, 2008. **87**(6): p. 1793-801.
33. Mulholland, H.G., et al., *Dietary glycaemic index, glycaemic load and endometrial and ovarian cancer risk: a systematic review and meta-analysis.* Br J Cancer, 2008. **99**(3): p. 434-41.
34. Choi, Y., E. Giovannucci, and J.E. Lee, *Glycaemic index and glycaemic load in relation to risk of diabetes-related cancers: a meta-analysis* British Journal of Nutrition, 2012. **108**(11): p. 1934-1947.
35. Nagle, C.M., et al., *Glycemic index, glycemic load and endometrial cancer risk: results from the Australian National Endometrial Cancer study and an updated systematic review and meta-analysis.* Eur J Nutr, 2013. **52**(2): p. 705-15.
36. Fearnley, E.J., et al., *Polycystic ovary syndrome increases the risk of endometrial cancer in women aged less than 50 years: an Australian case-control study.* Cancer Causes Control, 2010. **21**(12): p. 2303-8.
37. Gottschau, M., et al., *Risk of cancer among women with polycystic ovary syndrome: a Danish cohort study.* Gynecol Oncol, 2015. **136**(1): p. 99-103.
38. Chittenden, B.G., et al., *Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review.* Reprod Biomed Online, 2009. **19**(3): p. 398-405.
39. Haoula, Z., M. Salman, and W. Atiomo, *Evaluating the association between endometrial cancer and polycystic ovary syndrome.* Hum Reprod, 2012. **27**(5): p. 1327-31.
40. Barry, J.A., M.M. Azizia, and P.J. Hardiman, *Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis.* Hum Reprod Update, 2014. **20**(5): p. 748-58.
41. Ward, K.K., et al., *The risk of uterine malignancy is linearly associated with body mass index in a cohort of US women.* Am J Obstet Gynecol, 2013. **209**(6): p. 579 e1-5.
42. Renehan, A.G., et al., *Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies.* Lancet, 2008. **371**(9612): p. 569-78.
43. Dobbins, M., K. Decorby, and B.C. Choi, *The Association between Obesity and Cancer Risk: A Meta-Analysis of Observational Studies from 1985 to 2011.* ISRN Prev Med, 2013. **2013**: p. 680536.
44. Bergstrom, A., et al., *Overweight as an avoidable cause of cancer in Europe.* Int J Cancer, 2001. **91**(3): p. 421-30.
45. Reeves, K.W., et al., *Obesity in relation to endometrial cancer risk and disease characteristics in the Women's Health Initiative.* Gynecol Oncol, 2011. **121**(2): p. 376-82.
46. Win, A.K., J.C. Reece, and S. Ryan, *Family history and risk of endometrial cancer: a systematic review and meta-analysis.* Obstet Gynecol, 2015. **125**(1): p. 89-98.
47. Keum, N., et al., *Leisure-time physical activity and endometrial cancer risk: dose-response meta-analysis of epidemiological studies.* Int J Cancer, 2014. **135**(3): p. 682-94.

48. Gierach, G.L., et al., *Physical activity, sedentary behavior, and endometrial cancer risk in the NIH-AARP Diet and Health Study.* Int J Cancer, 2009. **124**(9): p. 2139-47.
49. Moore, S.C., et al., *Physical activity, sedentary behaviours, and the prevention of endometrial cancer.* Br J Cancer, 2010. **103**(7): p. 933-8.
50. Voskuil, D.W., et al., *Physical activity and endometrial cancer risk, a systematic review of current evidence.* Cancer Epidemiol Biomarkers Prev, 2007. **16**(4): p. 639-48.
51. Schmid, D. and M.F. Leitzmann, *Television viewing and time spent sedentary in relation to cancer risk: a meta-analysis.* J Natl Cancer Inst, 2014. **106**(7).
52. Soini, T., et al., *Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland.* Obstet Gynecol, 2014. **124**(2 Pt 1): p. 292-9.
53. Felix, A.S., et al., *Intrauterine devices and endometrial cancer risk: a pooled analysis of the Epidemiology of Endometrial Cancer Consortium.* Int J Cancer, 2015. **136**(5): p. E410-22.
54. Manchanda, R., et al., *Annual outpatient hysteroscopy and endometrial sampling (OHES) in HNPCC/Lynch syndrome (LS).* Arch Gynecol Obstet, 2012. **286**(6): p. 1555-62.
55. Helder-Woolderink, J.M., et al., *The additional value of endometrial sampling in the early detection of endometrial cancer in women with Lynch syndrome.* Gynecol Oncol, 2013. **131**(2): p. 304-8.
56. Saccardi, C., et al., *Endometrial surveillance in tamoxifen users: role, timing and accuracy of hysteroscopic investigation: observational longitudinal cohort study.* Endocr Relat Cancer, 2013. **20**(4): p. 455-62.
57. Gao, W.L., L.P. Zhang, and L.M. Feng, *Comparative study of transvaginal ultrasonographic and diagnostic hysteroscopic findings in postmenopausal breast cancer patients treated with tamoxifen.* Chin Med J (Engl), 2011. **124**(15): p. 2335-9.
58. Bertelli, G., et al., *Limited value of sonohysterography for endometrial screening in asymptomatic, postmenopausal patients treated with tamoxifen.* Gynecol Oncol, 2000. **78**(3 Pt 1): p. 275-7.
59. Gerber, B., et al., *Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound.* J Clin Oncol, 2000. **18**(20): p. 3464-70.
60. Fung, M.F., et al., *Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen.* Gynecol Oncol, 2003. **91**(1): p. 154-9.
61. Van den Bosch, T., et al., *Ultrasound assessment of endometrial thickness and endometrial polyps in women on hormonal replacement therapy.* Am J Obstet Gynecol, 2003. **188**(5): p. 1249-53.
62. Pennant, M.E., et al., *Premenopausal abnormal uterine bleeding and risk of endometrial cancer.* BJOG, 2017. **124**(3): p. 404-411.
63. Huang, G.S., et al., *Accuracy of preoperative endometrial sampling for the detection of high-grade endometrial tumors.* Am J Obstet Gynecol, 2007. **196**(3): p. 243 e1-5.
64. Leitao, M.M., Jr., et al., *Accuracy of preoperative endometrial sampling diagnosis of FIGO grade 1 endometrial adenocarcinoma.* Gynecol Oncol, 2008. **111**(2): p. 244-8.
65. Clark, T.J., et al., *Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review.* BJOG. An International Journal of Obstetrics and Gynaecology, 2002. **109**(3): p. 313-321.
66. Al-Azemi, M., et al., *Prevalence of endometrial proliferation in pipelle biopsies in tamoxifen-treated postmenopausal women with breast cancer in Kuwait.* Med Princ Pract, 2004. **13**(1): p. 30-4.
67. Timmermans, A., et al., *Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis.* Obstet Gynecol, 2010. **116**(1): p. 160-7.
68. Wong, A.S., et al., *Reappraisal of endometrial thickness for the detection of endometrial cancer in postmenopausal bleeding: a retrospective cohort study.* BJOG, 2016. **123**(3): p. 439-46.
69. (IKNL), I.K.N. *Endometriumcarcinoom. Versie: 3.0, 24.10.2011. Landelijke richtlijn.* 2011; Available from: http://www.oncoline.nl/endometriumcarcinoom.
70. Lalwani, N., et al., *ACR Appropriateness Criteria(®) pretreatment evaluation and follow-up of endometrial cancer.* Ultrasound Q, 2014. **30**(1): p. 21-8.
71. Amkreutz, L.C., et al., *The value of imaging of the lungs in the diagnostic workup of patients with endometrial cancer.* Gynecol Oncol, 2013. **131**(1): p. 147-50.
72. Savelli, L., et al., *Preoperative local staging of endometrial cancer: transvaginal sonography vs. magnetic resonance imaging.* Ultrasound Obstet Gynecol, 2008. **31**(5): p. 560-6.

73. Selman, T.J., et al., *A systematic review of tests for lymph node status in primary endometrial cancer.* BMC Womens Health, 2008. **8**: p. 8.
74. Chang, M.C., et al., *18F-FDG PET or PET/CT for detection of metastatic lymph nodes in patients with endometrial cancer: a systematic review and meta-analysis.* Eur J Radiol, 2012. **81**(11): p. 3511-7.
75. Kakhki, V.R., et al., *Diagnostic performance of fluorine 18 fluorodeoxyglucose positron emission tomography imaging for detection of primary lesion and staging of endometrial cancer patients: systematic review and meta-analysis of the literature* International Journal of Gynecological Cancer, 2013. **23**(9): p. 1536-1543.
76. Antonsen, S.L., et al., *MRI, PET/CT and ultrasound in the preoperative staging of endometrial cancer - a multicenter prospective comparative study.* Gynecol Oncol, 2013. **128**(2): p. 300-8.
77. Bokhman, J.V., *Two pathogenetic types of endometrial carcinoma.* Gynecol Oncol, 1983. **15**(1): p. 10-7.
78. Matias-Guiu, X., et al., *Molecular pathology of endometrial hyperplasia and carcinoma.* Hum Pathol, 2001. **32**(6): p. 569-77.
79. Geels, Y.P., et al., *Endometrioid endometrial carcinoma with atrophic endometrium and poor prognosis.* Obstet Gynecol, 2012. **120**(5): p. 1124-31.
80. Geels, Y.P., et al., *Immunohistochemical and genetic profiles of endometrioid endometrial carcinoma arising from atrophic endometrium.* Gynecol Oncol, 2015. **137**(2): p. 245-51.
81. Kuhn, E., et al., *Identification of molecular pathway aberrations in uterine serous carcinoma by genome-wide analyses.* J Natl Cancer Inst, 2012. **104**(19): p. 1503-13.
82. Zaino, R., S.G. Carinelli, and L.H. Ellenson, *Tumours of the uterine Corpus: epithelial Tumours and Precursors*, in *WHO Classification of Tumours of Female Reproductive Tract*, C.M. Kurman RJ, Herrington CS, Young RH (Eds.), Editor. 2014, IARC Press: Lyon. p. 125-126.
83. Kurman, R.J., P.F. Kaminski, and H.J. Norris, *The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients.* Cancer, 1985. **56**(2): p. 403-12.
84. Baak, J.P., et al., *Assessment of the risk on endometrial cancer in hyperplasia, by means of morphological and morphometrical features.* Pathol Res Pract, 1992. **188**(7): p. 856-9.
85. Horn, L.C., et al., *Risk of progression in complex and atypical endometrial hyperplasia: clinicopathologic analysis in cases with and without progestogen treatment.* Int J Gynecol Cancer, 2004. **14**(2): p. 348-53.
86. Mutter, G.L., et al., *Molecular identification of latent precancers in histologically normal endometrium.* Cancer Res, 2001. **61**(11): p. 4311-4.
87. Farooq, A., et al., *Cowden syndrome.* Cancer Treat Rev, 2010. **36**(8): p. 577-83.
88. Banno, K., et al., *Epigenetics and genetics in endometrial cancer: new carcinogenic mechanisms and relationship with clinical practice.* Epigenomics, 2012. **4**(2): p. 147-62.
89. Lacey, J.V., Jr. and V.M. Chia, *Endometrial hyperplasia and the risk of progression to carcinoma.* Maturitas, 2009. **63**(1): p. 39-44.
90. Soslow, R.A., *High-grade endometrial carcinomas - strategies for typing.* Histopathology, 2013. **62**(1): p. 89-110.
91. Clarke, B.A. and C.B. Gilks, *Endometrial carcinoma: controversies in histopathological assessment of grade and tumour cell type.* J Clin Pathol, 2010. **63**(5): p. 410-5.
92. McCluggage, W.G., et al., *Data set for reporting of endometrial carcinomas: recommendations from the International Collaboration on Cancer Reporting (ICCR) between United Kingdom, United States, Canada, and Australasia.* Int J Gynecol Pathol, 2013. **32**(1): p. 45-65.
93. Zheng, W. and P.E. Schwartz, *Serous EIC as an early form of uterine papillary serous carcinoma: recent progress in understanding its pathogenesis and current opinions regarding pathologic and clinical management.* Gynecol Oncol, 2005. **96**(3): p. 579-82.
94. Kurman, R.J., et al., *WHO classification of tumours of female reproductive organs*. World Health Organization classification of tumours, 4th edition ed. W.H.O. International Agency for Research on Cancer. 2014, Lyon: IARC Press.
95. Deutsches Institut für Medizinische Dokumentation und Information (DIMDI), *Internationale Klassifikation der Krankheiten für die Onkologie*. 2014: Köln.
96. Deutsche Gesellschaft für Gynäkologie und Geburtshilfe, AWMF. *Uterine Sarkome, Version 1.0 2015, AWMF-Registernummer: 015-074*. 2015 [cited 2017 25.10.2017]; Available from: http://www.awmf.org/leitlinien/detail/ll/015-074.html.

97. Fujii, H., et al., *Frequent genetic heterogeneity in the clonal evolution of gynecological carcinosarcoma and its influence on phenotypic diversity.* Cancer Res, 2000. **60**(1): p. 114-20.
98. Lopez-Garcia, M.A. and J. Palacios, *Pathologic and molecular features of uterine carcinosarcomas.* Semin Diagn Pathol, 2010. **27**(4): p. 274-86.
99. Horn, L.C., M. Dallacker, and K. Bilek, *[Carcinosarcomas (malignant mixed Mullerian tumors) of the uterus. Morphology, pathogenetic aspects and prognostic factors].* Pathologe, 2009. **30**(4): p. 292-301.
100. *TNM-Klassifikation maligner Tumoren. Endometriumkarzinom*. 7th ed. TNM-Klassifikation maligner Tumoren, ed. Wittekind C. and H.J. Meyer. 2010, Weinheim: Wiley-VCH.
101. Denschlag, D., et al., *Sarcoma of the Uterus. Guideline of the DGGG (S2k-Level, AWMF Registry No. 015/074, August 2015).* Geburtshilfe Frauenheilkd, 2015. **75**(10): p. 1028-1042.
102. Colgan TJ, H.L., Kim I, McCluggage WG, *Neuroendocrine Tumours of the uterine cervix*, in *WHO Classification of Tumours of Female Reproductive Tract*, C.M. Kurman RJ, Herrington CS, Young RH (Eds.), Editor. 2014, IARC Press: Lyon. p. 196-198.
103. Robboy SJ, M.G., Shako-Levy R, Bean SM, Prat J, Bentley, Russel P. , *Cutup – gross description and processing of specimens*, in *Robboy´s Pathology of the Female Reproductive Tract*, M.G. Robboy SJ, Prat J, Bentley RC, Russel P, Anderson MC (Eds.) Editor. 2009, Elsevier: Edinburgh, London, New York, Oxford, Philadelphia, St. Louis, Sydney, Toronto.
104. Ali, A., D. Black, and R.A. Soslow, *Difficulties in assessing the depth of myometrial invasion in endometrial carcinoma.* Int J Gynecol Pathol, 2007. **26**(2): p. 115-23.
105. Hirschowitz, L., M. Nucci, and R.J. Zaino, *Problematic issues in the staging of endometrial, cervical and vulval carcinomas.* Histopathology, 2013. **62**(1): p. 176-202.
106. Argani, P. and A. Cimino-Mathews, *Intraoperative Frozen Sections. Diagnostic Pitfalls*. Consultant Pathology, ed. D.E. Elder. Vol. 5. 2014, New York: Demos Medical Publishing.
107. Williams, J.W. and L. Hirschowitz, *Assessment of uterine wall thickness and position of the vascular plexus in the deep myometrium: implications for the measurement of depth of myometrial invasion of endometrial carcinomas.* Int J Gynecol Pathol, 2006. **25**(1): p. 59-64.
108. Dunn, M., M.B. Morgan, and T.W. Beer, *Perineural invasion: identification, significance, and a standardized definition.* Dermatol Surg, 2009. **35**(2): p. 214-21.
109. Liebig, C., et al., *Perineural invasion in cancer: a review of the literature.* Cancer, 2009. **115**(15): p. 3379-91.
110. *TNM-Supplement. A Commentary on uniform use*. 4th ed, ed. Wittekind C., et al. 2012, Oxford (UK), Chichester (UK), Hoboken (USA): Wiley-Blackwell.
111. Zaino, R.J., *Unusual patterns of endometrial carcinoma including MELF and its relation to epithelial mesenchymal transition.* Int J Gynecol Pathol, 2014. **33**(4): p. 357-64.
112. Horn, L.C., M. Trost, and K. Bilek, *Staging of endometrial carcinoma: aspects of ovarian and cervical involvement.* Int J Gynecol Pathol, 2010. **29**(1): p. 63-6.
113. Movahedi-Lankarani, S., et al. *Protocol for the Examination of Specimens from Patients with Carcinoma of the Endometrium*. 2011; Available from: http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2011/Endometrium_11protocol.doc.
114. Burke, W.M., et al., *Endometrial cancer: a review and current management strategies: part I.* Gynecol Oncol, 2014. **134**(2): p. 385-92.
115. Burke, W.M., et al., *Endometrial cancer: a review and current management strategies: part II.* Gynecol Oncol, 2014. **134**(2): p. 393-402.
116. Syed, S., N. Reed, and D. Millan, *Adequacy of cervical sampling in hysterectomy specimens for endometrial cancer.* Ann Diagn Pathol, 2015. **19**(2): p. 43-4.
117. Ahmed, Q.F., et al., *Vanishing endometrial cancer in hysterectomy specimens: a myth or a fact.* Am J Surg Pathol, 2015. **39**(2): p. 221-6.
118. Quddus, M.R., et al., *Minor serous and clear cell components adversely affect prognosis in "mixed-type" endometrial carcinomas: a clinicopathologic study of 36 stage-I cases.* Reprod Sci, 2010. **17**(7): p. 673-8.
119. Kalyanasundaram, K., et al., *Diffusely infiltrating endometrial carcinomas with no stromal response: report of a series, including cases with cervical and ovarian involvement and emphasis on the potential for misdiagnosis.* Int J Surg Pathol, 2010. **18**(2): p. 138-43.

120. Euscher, E., et al., *The pattern of myometrial invasion as a predictor of lymph node metastasis or extrauterine disease in low-grade endometrial carcinoma.* Am J Surg Pathol, 2013. **37**(11): p. 1728-36.
121. Han, G., et al., *Histological features associated with occult lymph node metastasis in FIGO clinical stage I, grade I endometrioid carcinoma.* Histopathology, 2014. **64**(3): p. 389-98.
122. Jorge, S., et al., *Magnitude of risk for nodal metastasis associated with lymphvascular space invasion for endometrial cancer.* Gynecol Oncol, 2016. **140**(3): p. 387-93.
123. Zaino, R.J., *FIGO staging of endometrial adenocarcinoma: a critical review and proposal.* Int J Gynecol Pathol, 2009. **28**(1): p. 1-9.
124. Stewart, C.J., Y.C. Leung, and A. Whitehouse, *Fallopian tube metastases of non-gynaecological origin: a series of 20 cases emphasizing patterns of involvement including intra-epithelial spread.* Histopathology, 2012. **60**(6B): p. E106-14.
125. Medeiros, F., et al., *The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome.* Am J Surg Pathol, 2006. **30**(2): p. 230-6.
126. Society of Gynecologic Oncologists (SGO), *Society of Gynecologic Oncologists Clinical Practice Committee Statement on Prophylactic Salpingo-oophorectomy.* Gynecol Oncol, 2005. **98**(2): p. 179-81.
127. Shaw, P.A. and B.A. Clarke, *Prophylactic Gynecologic Specimens from Hereditary Cancer Carriers.* Surg Pathol Clin, 2016. **9**(2): p. 307-28.
128. Colombo, N., et al., *ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up.* Int J Gynecol Cancer, 2016. **26**(1): p. 2-30.
129. Bendifallah, S., et al., *A risk scoring system to determine recurrence in early-stage type 1 endometrial cancer: a French multicentre study.* Ann Surg Oncol, 2014. **21**(13): p. 4239-45.
130. Antonsen, S.L., L. Ulrich, and C. Hogdall, *Patients with atypical hyperplasia of the endometrium should be treated in oncological centers.* Gynecol Oncol, 2012. **125**(1): p. 124-8.
131. Gunderson, C.C., et al., *Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review.* Gynecol Oncol, 2012. **125**(2): p. 477-82.
132. Luo, L., et al., *Levonorgestrel-releasing intrauterine system for atypical endometrial hyperplasia.* Cochrane Database Syst Rev, 2013. **6**: p. CD009458.
133. Gallos, I.D., et al., *Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis.* Am J Obstet Gynecol, 2012. **207**(4): p. 266 e1-12.
134. Baker, J., et al., *Efficacy of oral or intrauterine device-delivered progestin in patients with complex endometrial hyperplasia with atypia or early endometrial adenocarcinoma: a meta-analysis and systematic review of the literature.* Gynecol Oncol, 2012. **125**(1): p. 263-70.
135. Koskas, M., et al., *Prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma: systematic review and meta-analysis.* Fertil Steril, 2014. **101**(3): p. 785-94.
136. Chan, J.K., et al., *The outcomes of 27,063 women with unstaged endometrioid uterine cancer.* Gynecol Oncol, 2007. **106**(2): p. 282-8.
137. Williams, M.G., et al., *Synchronous primary ovarian and endometrial cancers: a population-based assessment of survival.* Obstet Gynecol, 2009. **113**(4): p. 783-9.
138. Oranratanaphan, S., T. Manchana, and N. Sirisabya, *Clinicopathologic variables and survival comparison of patients with synchronous endometrial and ovarian cancers versus primary endometrial cancer with ovarian metastasis.* Asian Pac J Cancer Prev, 2008. **9**(3): p. 403-7.
139. Akbayir, O., et al., *Coexisting ovarian malignancy in patients with clinical stage I endometrial carcinoma.* Arch Gynecol Obstet, 2012. **286**(5): p. 1241-5.
140. Duska, L.R., et al., *Endometrial cancer in women 40 years old or younger.* Gynecol Oncol, 2001. **83**(2): p. 388-93.
141. Walsh, C., et al., *Coexisting ovarian malignancy in young women with endometrial cancer.* Obstet Gynecol, 2005. **106**(4): p. 693-9.
142. Dogan, A., et al., *Synchronous Endometrial and Ovarian Cancer in Young Women: Case Report and Review of the Literature.* Anticancer Res, 2017. **37**(3): p. 969-978.
143. Anglesio, M.S., et al., *Synchronous Endometrial and Ovarian Carcinomas: Evidence of Clonality.* J Natl Cancer Inst, 2016. **108**(6): p. djv428.

144. Goyal, A., R.P. Masand, and A.A. Roma, *Value of PAX-8 and SF-1 Immunohistochemistry in the Distinction Between Female Adnexal Tumor of Probable Wolffian Origin and its Mimics.* Int J Gynecol Pathol, 2016. **35**(2): p. 167-75.
145. Batte, B.A., et al., *Consequences of universal MSI/IHC in screening ENDOMETRIAL cancer patients for Lynch syndrome.* Gynecol Oncol, 2014. **134**(2): p. 319-25.
146. Takano, M., et al., *Surgery for endometrial cancers with suspected cervical involvement: is radical hysterectomy needed (a GOTIC study)?* Br J Cancer, 2013. **109**(7): p. 1760-5.
147. Frost, J.A., et al., *Lymphadenectomy for the management of endometrial cancer.* Cochrane Database Syst Rev, 2015. **9**: p. CD007585.
148. Todo, Y., et al., *Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis.* Lancet, 2010. **375**(9721): p. 1165-72.
149. Kim, H.S., et al., *Systematic lymphadenectomy for survival in patients with endometrial cancer: a meta-analysis.* Jpn J Clin Oncol, 2012. **42**(5): p. 405-12.
150. Nemani, D., et al., *Assessing the effects of lymphadenectomy and radiation therapy in patients with uterine carcinosarcoma: a SEER analysis.* Gynecol Oncol, 2008. **111**(1): p. 82-8.
151. Odagiri, T., et al., *Distribution of lymph node metastasis sites in endometrial cancer undergoing systematic pelvic and para-aortic lymphadenectomy: a proposal of optimal lymphadenectomy for future clinical trials.* Ann Surg Oncol, 2014. **21**(8): p. 2755-61.
152. Alay, I., et al., *Lymphadenectomy should be performed up to the renal vein in patients with intermediate-high risk endometrial cancer.* Pathol Oncol Res, 2015. **21**(3): p. 803-10.
153. Galaal, K., et al., *Laparoscopy versus laparotomy for the management of early stage endometrial cancer.* Cochrane Database Syst Rev, 2012. **9**: p. CD006655.
154. Tanner, E.J., et al., *The role of cytoreductive surgery for newly diagnosed advanced-stage uterine carcinosarcoma.* Gynecol Oncol, 2011. **123**(3): p. 548-52.
155. Barlin, J.N., I. Puri, and R.E. Bristow, *Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis.* Gynecol Oncol, 2010. **118**(1): p. 14-8.
156. Klopp, A., et al., *The role of postoperative radiation therapy for endometrial cancer: Executive summary of an American Society for Radiation Oncology evidence-based guideline.* Pract Radiat Oncol, 2014. **4**(3): p. 137-44.
157. Kong, A., et al., *Adjuvant radiotherapy for stage I endometrial cancer: an updated Cochrane systematic review and meta-analysis.* J Natl Cancer Inst, 2012. **104**(21): p. 1625-34.
158. Sorbe, B., et al., *Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer: a controlled randomized study.* Int J Gynecol Cancer, 2009. **19**(5): p. 873-8.
159. Ortoft, G., E.S. Hansen, and K. Bertelsen, *Omitting adjuvant radiotherapy in endometrial cancer increases the rate of locoregional recurrences but has no effect on long-term survival: the Danish Endometrial Cancer Study.* Int J Gynecol Cancer, 2013. **23**(8): p. 1429-37.
160. Nout, R.A., et al., *Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial.* J Clin Oncol, 2009. **27**(21): p. 3547-56.
161. Nout, R.A., et al., *Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial.* Lancet, 2010. **375**(9717): p. 816-23.
162. Nout, R.A., et al., *Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial.* J Clin Oncol, 2011. **29**(13): p. 1692-700.
163. van der Steen-Banasik, E., et al., *Systemic review: Radiation therapy alone in medical non-operable endometrial carcinoma.* Eur J Cancer, 2016. **65**: p. 172-81.
164. Reed, N.S., et al., *Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874).* Eur J Cancer, 2008. **44**(6): p. 808-18.
165. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). *S3-Leitlinie Supportive Therapie bei onkologischen PatientInnen, Langversion 1.1 – April 2017, AWMF-Registernummer: 032/054OL.* 2017; Available from: http://www.leitlinienprogramm-onkologie.de/leitlinien/supportive-therapie/.
166. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). *S3-Leitlinie Diagnostik, Therapie und Nachsorge der Patientin mit Zervixkarzinom, Version 1.0, September 2014, AWMF-Registernummer: 032/033OL.*

2014; Available from: http://www.leitlinienprogramm-onkologie.de/leitlinien/zervixkarzinom/.
167. European Medicines Agency (EMEA) *PUBLIC SUMMARY OF POSITIVE OPINION FOR ORPHAN DESIGNATION OF sodium butyrate (rectal use) for the prevention of radiation proctitis*. 2005.
168. Hensley, M.L., et al., *American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants.* J Clin Oncol, 2009. **27**(1): p. 127-45.
169. Martin-Hirsch, P.P.L., et al. *Adjuvant progestagens for endometrial cancer*. Cochrane Database of Systematic Reviews, 2011. DOI: 10.1002/14651858.CD001040.pub2.
170. Johnson, N., et al., *Adjuvant chemotherapy for endometrial cancer after hysterectomy.* Cochrane Database Syst Rev, 2011(10): p. CD003175.
171. Galaal, K., et al., *Adjuvant chemotherapy for advanced endometrial cancer.* Cochrane Database Syst Rev, 2014. **5**: p. CD010681.
172. Cantrell, L.A., et al., *A multi-institutional cohort study of adjuvant therapy in stage I-II uterine carcinosarcoma.* Gynecol Oncol, 2012. **127**(1): p. 22-6.
173. Galaal, K., et al., *Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma.* Cochrane Database Syst Rev, 2013. **2**: p. CD006812.
174. Sutton, G., et al., *A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: A Gynecologic Oncology Group Study.* Gynecol Oncol, 2000. **79**(2): p. 147-53.
175. Homesley, H.D., et al., *Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study.* J Clin Oncol, 2007. **25**(5): p. 526-31.
176. Stein, A., W. Voigt, and K. Jordan, *Chemotherapy-induced diarrhea: pathophysiology, frequency and guideline-based management.* Ther Adv Med Oncol, 2010. **2**(1): p. 51-63.
177. Benson, A.B., 3rd, et al., *Recommended guidelines for the treatment of cancer treatment-induced diarrhea.* J Clin Oncol, 2004. **22**(14): p. 2918-26.
178. Cascinu, S., et al., *Octreotide versus loperamide in the treatment of fluorouracil-induced diarrhea: a randomized trial.* J Clin Oncol, 1993. **11**(1): p. 148-51.
179. Zidan, J., et al., *Octreotide in the treatment of severe chemotherapy-induced diarrhea.* Ann Oncol, 2001. **12**(2): p. 227-9.
180. Rizzo, J.D., et al., *American society of clinical oncology/american society of hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer.* J Oncol Pract, 2010. **6**(6): p. 317-20.
181. Smith, T.J., et al., *2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline.* J Clin Oncol, 2006. **24**(19): p. 3187-205.
182. Aapro, M.S., et al., *2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours.* Eur J Cancer, 2011. **47**(1): p. 8-32.
183. Fung-Kee-Fung, M., et al., *Follow-up after primary therapy for endometrial cancer: a systematic review.* Gynecol Oncol, 2006. **101**(3): p. 520-9.
184. Gadducci, A., et al., *An intensive follow-up does not change survival of patients with clinical stage I endometrial cancer.* Anticancer Res, 2000. **20**(3B): p. 1977-84.
185. Sartori, E., et al., *Pattern of failure and value of follow-up procedures in endometrial and cervical cancer patients.* Gynecol Oncol, 2007. **107**(1 Suppl 1): p. S241-7.
186. Smith, C.J., et al., *Efficacy of routine follow-up in patients with recurrent uterine cancer.* Gynecol Oncol, 2007. **107**(1): p. 124-9.
187. Carrara, L., et al., *Could different follow-up modalities play a role in the diagnosis of asymptomatic endometrial cancer relapses?: an Italian multicentric retrospective analysis.* Int J Gynecol Cancer, 2012. **22**(6): p. 1013-9.
188. Creutzberg, C.L., et al., *Survival after relapse in patients with endometrial cancer: results from a randomized trial.* Gynecol Oncol, 2003. **89**(2): p. 201-9.
189. Reddoch, J.M., et al., *Surveillance for recurrent endometrial carcinoma: development of a follow-up scheme.* Gynecol Oncol, 1995. **59**(2): p. 221-5.
190. Bristow, R.E., et al., *Cost-effectiveness of routine vaginal cytology for endometrial cancer surveillance* Gynecologic Oncology, 2006. **103**(2): p. 709-713.
191. Salani, R., et al., *Recurrence patterns and surveillance for patients with early stage endometrial cancer.* Gynecol Oncol, 2011. **123**(2): p. 205-7.
192. Kadkhodayan, S., et al., *Accuracy of 18-F-FDG PET imaging in the follow up of endometrial cancer patients: systematic review and meta-analysis of the literature.* Gynecol Oncol, 2013. **128**(2): p. 397-404.

193. Kokka, F., et al., *Hormonal therapy in advanced or recurrent endometrial cancer.* Cochrane Database Syst Rev, 2010(12): p. CD007926.
194. Thigpen, J.T., et al., *Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group.* J Clin Oncol, 1999. **17**(6): p. 1736-44.
195. Covens, A.L., et al., *Phase II study of fulvestrant in recurrent/metastatic endometrial carcinoma: a Gynecologic Oncology Group study.* Gynecol Oncol, 2011. **120**(2): p. 185-8.
196. Vale, C.L., et al., *Chemotherapy for advanced, recurrent or metastatic endometrial carcinoma.* Cochrane Database Syst Rev, 2012. **8**: p. CD003915.
197. Lee, Y.K., et al., *Vaginal pH-balanced gel for the control of atrophic vaginitis among breast cancer survivors: a randomized controlled trial.* Obstet Gynecol, 2011. **117**(4): p. 922-7.
198. ten Broeke, S.W., et al., *Lynch syndrome caused by germline PMS2 mutations: delineating the cancer risk.* J Clin Oncol, 2015. **33**(4): p. 319-25.
199. Buchanan, D.D., et al., *Tumor mismatch repair immunohistochemistry and DNA MLH1 methylation testing of patients with endometrial cancer diagnosed at age younger than 60 years optimizes triage for population-level germline mismatch repair gene mutation testing.* J Clin Oncol, 2014. **32**(2): p. 90-100.
200. Carcangiu, M.L., et al., *Lynch syndrome--related endometrial carcinomas show a high frequency of nonendometrioid types and of high FIGO grade endometrioid types.* Int J Surg Pathol, 2010. **18**(1): p. 21-6.
201. Dowty, J.G., et al., *Cancer risks for MLH1 and MSH2 mutation carriers.* Hum Mutat, 2013. **34**(3): p. 490-7.
202. Egoavil, C., et al., *Prevalence of Lynch syndrome among patients with newly diagnosed endometrial cancers.* PLoS One, 2013. **8**(11): p. e79737.
203. Hampel, H., et al., *Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients.* Cancer Res, 2006. **66**(15): p. 7810-7.
204. Leenen, C.H., et al., *Prospective evaluation of molecular screening for Lynch syndrome in patients with endometrial cancer </= 70 years.* Gynecol Oncol, 2012. **125**(2): p. 414-20.
205. Lu, K.H., et al., *Prospective determination of prevalence of lynch syndrome in young women with endometrial cancer.* J Clin Oncol, 2007. **25**(33): p. 5158-64.
206. Westin, S.N., et al., *Carcinoma of the lower uterine segment: a newly described association with Lynch syndrome.* J Clin Oncol, 2008. **26**(36): p. 5965-71.
207. Win, A.K., et al., *Risks of colorectal and other cancers after endometrial cancer for women with Lynch syndrome.* J Natl Cancer Inst, 2013. **105**(4): p. 274-9.
208. Nelen, M.R., et al., *Novel PTEN mutations in patients with Cowden disease: absence of clear genotype-phenotype correlations.* Eur J Hum Genet, 1999. **7**(3): p. 267-73.
209. Daniels, M.S., *Genetic testing by cancer site: uterus.* Cancer J, 2012. **18**(4): p. 338-42.
210. Barrow, E., J. Hill, and D.G. Evans, *Cancer risk in Lynch Syndrome.* Fam Cancer, 2013. **12**(2): p. 229-40.
211. Senter, L., et al., *The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations.* Gastroenterology, 2008. **135**(2): p. 419-28.
212. Kempers, M.J., et al., *Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: a cohort study.* Lancet Oncol, 2011. **12**(1): p. 49-55.
213. Lynch, H.T., et al., *Lynch syndrome-associated extracolonic tumors are rare in two extended families with the same EPCAM deletion.* Am J Gastroenterol, 2011. **106**(10): p. 1829-36.
214. Riegert-Johnson, D.L., et al., *Cancer and Lhermitte-Duclos disease are common in Cowden syndrome patients.* Hered Cancer Clin Pract, 2010. **8**(1): p. 6.
215. Tan, M.H., et al., *Lifetime cancer risks in individuals with germline PTEN mutations.* Clin Cancer Res, 2012. **18**(2): p. 400-7.
216. Ferguson, S.E., et al., *Performance characteristics of screening strategies for Lynch syndrome in unselected women with newly diagnosed endometrial cancer who have undergone universal germline mutation testing.* Cancer, 2014. **120**(24): p. 3932-9.
217. Bubien, V., et al., *High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome.* J Med Genet, 2013. **50**(4): p. 255-63.
218. Mahdi, H., et al., *Germline PTEN, SDHB-D, and KLLN alterations in endometrial cancer patients with Cowden and Cowden-like syndromes: an international, multicenter, prospective study.* Cancer, 2015. **121**(5): p. 688-96.
219. Clarke, B.A. and K. Cooper, *Identifying Lynch syndrome in patients with endometrial carcinoma: shortcomings of morphologic and clinical schemas.* Adv Anat Pathol, 2012. **19**(4): p. 231-8.

220. Snowsill, T., et al., *A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome.* Health Technol Assess, 2014. **18**(58): p. 1-406.
221. Auranen, A. and T. Joutsiniemi, *A systematic review of gynecological cancer surveillance in women belonging to hereditary nonpolyposis colorectal cancer (Lynch syndrome) families.* Acta Obstet Gynecol Scand, 2011. **90**(5): p. 437-44.
222. Lecuru, F., et al., *Performance of office hysteroscopy and endometrial biopsy for detecting endometrial disease in women at risk of human non-polyposis colon cancer: a prospective study.* Int J Gynecol Cancer, 2008. **18**(6): p. 1326-31.
223. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). *S3-Leitlinie Psychoonkologische Diagnostik, Beratung und Behandlung von erwachsenen Krebspatienten, Version 1.1, Januar 2014, AWMF-Registernummer: 032/051OL.* 2014; Available from: http://www.leitlinienprogramm-onkologie.de/leitlinien/psychoonkologie/.
224. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). *Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Langversion 3.0, Aktualisierung 2012, AWMF-Registernummer: 032 – 045OL.* 2012; Available from: http://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/.
225. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, D.K., AWMF). *S3-Leitlinie Diagnostik, Therapie und Nachsorge maligner Ovarialtumoren, Version 2.0, Oktober 2016, AWMF-Registernummer: 032/035OL.* 2016; Available from: http://www.leitlinienprogramm-onkologie.de/leitlinien/ovarialkarzinom/.
226. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). *Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms, Langversion 4.0, Dezember 2016, AWMF-Registernummer: 043/022OL.* 2016; Available from: http://www.leitlinienprogramm-onkologie.de/leitlinien/prostatakarzinom/.
227. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). *Palliativmedizin für Patienten mit einer nicht heilbaren Krebserkrankung, Langversion 1.0, 2015, AWMF-Registernummer: 128/001OL.* 2015; Available from: http://leitlinienprogramm-onkologie.de/Palliativmedizin.80.0.html.
228. Temel, J.S., et al., *Early palliative care for patients with metastatic non-small-cell lung cancer.* N Engl J Med, 2010. **363**(8): p. 733-42.
229. Brumley, R., et al., *Increased satisfaction with care and lower costs: results of a randomized trial of in-home palliative care.* J Am Geriatr Soc, 2007. **55**(7): p. 993-1000.
230. Pantilat, S.Z., et al., *Hospital-based palliative medicine consultation: a randomized controlled trial.* Arch Intern Med, 2010. **170**(22): p. 2038-40.
231. Bakitas, M.A., et al., *Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial.* J Clin Oncol, 2015. **33**(13): p. 1438-45.
232. Zimmermann, C., et al., *Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial.* The Lancet, 2014. **383**(9930): p. 1721-1730.
233. Rugno, F.C., B.S. Paiva, and C.E. Paiva, *Early integration of palliative care facilitates the discontinuation of anticancer treatment in women with advanced breast or gynecologic cancers.* Gynecol Oncol, 2014. **135**(2): p. 249-54.
234. Maltoni, M., et al., *Systematic versus on-demand early palliative care: results from a multicentre, randomised clinical trial.* Eur J Cancer, 2016. **65**: p. 61-8.
235. Temel, J.S., et al., *Effects of Early Integrated Palliative Care in Patients With Lung and GI Cancer: A Randomized Clinical Trial.* J Clin Oncol, 2016: p. JCO2016705046.
236. Kavalieratos, D., et al., *Association Between Palliative Care and Patient and Caregiver Outcomes: A Systematic Review and Meta-analysis.* JAMA, 2016. **316**(20): p. 2104-2114.
237. Bundesministerium der Justiz und für Verbraucherschutz, *Sozialgesetzbuch (SGB) Neuntes Buch (IX) - Rehabilitation und Teilhabe behinderter Menschen - (Artikel 1 des Gesetzes v. 19.6.2001, BGBl. I S. 1046).* Artikel 1 des Gesetzes vom 19. Juni 2001, BGBl. I S. 1046, 1047, das durch Artikel 2 des Gesetzes vom 23. Dezember 2016 geändert worden ist.
238. Arbeitsgemeinschaft für Urogynäkologie und Plastische Beckenbodenrekonstruktion, AWMF. *Interdisziplinäre S2e-Leitlinie für die Diagnostik und Therapie der Belastungsinkontinenz der Frau, AWMF-Registernummer: 015/005.* 2013; Available from: http://www.awmf.org/leitlinien/detail/ll/015-005.html.
239. Adamsen, L., et al., *Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial.* BMJ, 2009. **339**: p. b3410.

240. Bourke, L., et al., *Pragmatic lifestyle intervention in patients recovering from colon cancer: a randomized controlled pilot study.* Arch Phys Med Rehabil, 2011. **92**(5): p. 749-55.
241. Brown, J.C., et al., *Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis.* Cancer Epidemiol Biomarkers Prev, 2011. **20**(1): p. 123-33.
242. Cantarero-Villanueva, I., et al., *Effectiveness of core stability exercises and recovery myofascial release massage on fatigue in breast cancer survivors: a randomized controlled clinical trial.* Evid Based Complement Alternat Med, 2012. **2012**: p. 620619.
243. Chandwani, K.D., et al., *Yoga improves quality of life and benefit finding in women undergoing radiotherapy for breast cancer.* J Soc Integr Oncol, 2010. **8**(2): p. 43-55.
244. Courneya, K.S., et al., *Three independent factors predicted adherence in a randomized controlled trial of resistance exercise training among prostate cancer survivors.* J Clin Epidemiol, 2004. **57**(6): p. 571-9.
245. Cramp, F. and J. Byron-Daniel, *Exercise for the management of cancer-related fatigue in adults.* Cochrane Database Syst Rev, 2012. **11**: p. CD006145.
246. Danhauer, S.C., et al., *Restorative yoga for women with breast cancer: findings from a randomized pilot study.* Psychooncology, 2009. **18**(4): p. 360-8.
247. Donnelly, C.M., et al., *A randomised controlled trial testing the feasibility and efficacy of a physical activity behavioural change intervention in managing fatigue with gynaecological cancer survivors.* Gynecol Oncol, 2011. **122**(3): p. 618-24.
248. Fillion, L., et al., *A brief intervention for fatigue management in breast cancer survivors.* Cancer Nurs, 2008. **31**(2): p. 145-59.
249. Heim, M.E., M.L. v d Malsburg, and A. Niklas, *Randomized controlled trial of a structured training program in breast cancer patients with tumor-related chronic fatigue.* Onkologie, 2007. **30**(8-9): p. 429-34.
250. Littman, A.J., et al., *Randomized controlled pilot trial of yoga in overweight and obese breast cancer survivors: effects on quality of life and anthropometric measures.* Support Care Cancer, 2012. **20**(2): p. 267-77.
251. Moadel, A.B., et al., *Randomized controlled trial of yoga among a multiethnic sample of breast cancer patients: effects on quality of life.* J Clin Oncol, 2007. **25**(28): p. 4387-95.
252. Mustian, K.M., et al., *A 4-week home-based aerobic and resistance exercise program during radiation therapy: a pilot randomized clinical trial.* J Support Oncol, 2009. **7**(5): p. 158-67.
253. Pinto, B.M., et al., *Maintenance of effects of a home-based physical activity program among breast cancer survivors.* Support Care Cancer, 2008. **16**(11): p. 1279-89.
254. Rogers, L.Q., et al., *Physical activity and health outcomes three months after completing a physical activity behavior change intervention: persistent and delayed effects.* Cancer Epidemiol Biomarkers Prev, 2009. **18**(5): p. 1410-8.
255. Velthuis, M.J., et al., *The effect of physical exercise on cancer-related fatigue during cancer treatment: a meta-analysis of randomised controlled trials.* Clin Oncol (R Coll Radiol), 2010. **22**(3): p. 208-21.
256. van Weert, E., et al., *Cancer-related fatigue and rehabilitation: a randomized controlled multicenter trial comparing physical training combined with cognitive-behavioral therapy with physical training only and with no intervention.* Phys Ther, 2010. **90**(10): p. 1413-25.
257. *Krebs in Deutschland 2005/2006, Häufigkeiten und Trends*, Gemeinsame Veröffentlichung des Robert Koch-Instituts und der Gesellschaft der epidemiologischen Krebsregister in Deutschland e. V., Editor. 2010. p. 64-67.
258. Bristow, R.E., et al., *Centralization of care for patients with advanced-stage ovarian cancer: a cost-effectiveness analysis.* Cancer, 2007. **109**(8): p. 1513-22.
259. du Bois, A., et al., *Variations in institutional infrastructure, physician specialization and experience, and outcome in ovarian cancer: a systematic review.* Gynecol Oncol, 2009. **112**(2): p. 422-36.
260. Beckmann, M.W., Jud, S.M., *Gynäkologische Krebszentren – Kompetenzbündelung zur Qualitätsverbesserung.* Frauenheilkunde up2date, 2009. **3**(2): p. 71-74.
261. Wesselmann, S., M.W. Beckmann, and A. Winter, *The concept of the certification system of the German Cancer Society and its impact on gynecological cancer care.* Arch Gynecol Obstet, 2014. **289**(1): p. 7-12.
262. Kowalski, C., et al., *Zertifizierte Brustkrebszentren aus Sicht der Zentrumsleitungen: Ergebnisse einer Schlüsselpersonenbefragung.* Geburtsh Frauenheilk, 2012. **72**: p. 235-242.
263. Huthmann, D., et al., *Zertifizierte Darmkrebszentren aus Sicht der Zentrumsleitungen: Ergebnisse einer Schlüsselpersonenbefragung.* Gastroenterol, 2012. **50**(8): p. 753-759.

264. Kowalski, C., et al., *Zertifizierte Brustkrebszentren aus Sicht der Patientinnen: Stärken und Verbesserungspotenziale.* Geburtsh Frauenheilk, 2012. **71**: p. 137-143.
265. Thiel, F.C., et al., *Financing of certified centers: a willingness-to-pay analysis.* Arch Gynecol Obstet, 2013. **287**(3): p. 495-509.
266. Lux, M.P., et al., *Marketing von Brust- und Perinatalzentren – Sind Patientinnen mit dem Produkt „zertifiziertes Zentrum" vertraut?* Geburtsh Frauenheilk, 2009. **69**: p. 321-327.
267. Wesselmann, S., et al., *Documented quality of care in certified colorectal cancer centers in Germany: German Cancer Society benchmarking report for 2013.* Int J Colorectal Dis, 2014. **29**(4): p. 511-8.
268. Beckmann, M.W., et al., *Dreistufenmodell optimiert Behandlung unter Kostendeckung Wie die künftigen Strukturen der onkologischen Versorgung in Deutschland aussehen sollten.* Dtsch Arztebl, 2007. **104**(44): p. 3004-3009.
269. Deutsche Krebsgesellschaft (DKG) *Jahresbericht der zertifizierten Gynäkologischen Krebszentren: Auditjahr 2015, Kennzahlenjahr 2014, Version e-A2.de, Stand 21.07.2016.* 2016.
270. Roland, P.Y., et al., *The benefits of a gynecologic oncologist: a pattern of care study for endometrial cancer treatment.* Gynecol Oncol, 2004. **93**(1): p. 125-30.
271. Macdonald, O.K., et al., *Does oncologic specialization influence outcomes following surgery in early stage adenocarcinoma of the endometrium?* Gynecol Oncol, 2005. **99**(3): p. 730-5.
272. Chan, J.K., et al., *Influence of gynecologic oncologists on the survival of patients with endometrial cancer.* J Clin Oncol, 2011. **29**(7): p. 832-8.
273. Beckmann, M.W.e.a., *Der neue Schwerpunkt Gynäkologische Onkologie: nationale und internationale Chance?* Geburtsh Frauenheilk, 2006. **66**(02): p. 123-127.
274. Ioka, A., et al., *Influence of hospital procedure volume on uterine cancer survival in Osaka, Japan.* Cancer Sci, 2005. **96**(10): p. 689-94.
275. Diaz-Montes, T.P., et al., *Uterine cancer in Maryland: impact of surgeon case volume and other prognostic factors on short-term mortality.* Gynecol Oncol, 2006. **103**(3): p. 1043-7.
276. Elit, L.M., et al., *Impact of wait times on survival for women with uterine cancer.* J Clin Oncol, 2014. **32**(1): p. 27-33.
277. Beckmann, M.W., *Frauenarzt/-ärztin der Zukunft: müssen die Kliniken neu strukturiert werden?* Der Gynäkologe, 2010. **43**(9): p. 748-756.
278. Bundesministerium für Gesundheit (BMG). *Querschnitts-AG Dokumentation: Datensparsame einheitliche Tumordokumentation*. 2011 24.08.2017]; Available from: https://www.bundesgesundheitsministerium.de/themen/praevention/nationaler-krebsplan/oeffentlichkeitsarbeit/handlungsfelder/datensparsame-einheitliche-tumordokumentation.html.
279. Zentralstelle der Deutschen Ärzteschaft zur Qualitätssicherung in der Medizin. *Versorgungsleitlinien. Programm für nationale Versorgungsleitlinien von BÄK, KBV und AWMF: Qualitätsindikatoren. Manual für Autoren*. 2009 [cited 2017 23.11.2017]; Available from: http://www.aezq.de/mdb/edocs/pdf/schriftenreihe/schriftenreihe36.pdf.
280. Vasen, H.F., et al., *New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC.* Gastroenterology, 1999. **116**(6): p. 1453-6.
281. Umar, A., et al., *Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability.* J Natl Cancer Inst, 2004. **96**(4): p. 261-8.
282. Howick, J., et al. *The 2011 Oxford CEBM Evidence Levels of Evidence (Introductory Document).* 2011; Available from: http://www.cebm.net/index.aspx?o=5653.
283. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Ständige Kommission Leitlinien. *AWMF-Regelwerk „Leitlinien"*. 2012 06.07.2017; 1. Aufl. 2012:[Available from: http://www.awmf.org/leitlinien/awmf-regelwerk.html.
284. Atkins, D., et al., *Grading quality of evidence and strength of recommendations.* BMJ, 2004. **328**(7454): p. 1490.