

## Interdisciplinary Diagnosis, Therapy and Follow-up of Patients with Endometrial Cancer. Guideline (S3-Level, AWMF Registry Number 032/034-OL, April 2018) – Part 2 with Recommendations on the Therapy and Follow-up of Endometrial Cancer, Palliative Care, Psycho-oncological/Psychosocial Care/Rehabilitation/Patient Information and Healthcare Facilities

### Interdisziplinäre Diagnostik, Therapie und Nachsorge der Patientinnen mit Endometriumkarzinom. Leitlinie (S3-Level, AWMF-Register-Nummer 032/034-OL, April 2018) – Teil 2 mit Empfehlungen zur Therapie, Nachsorge des Endometriumkarzinoms, Palliativmedizin, Psychoonkologie/psychosozialen Betreuung/Rehabilitation/Patientinnenaufklärung und Versorgungsstrukturen



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#### Key words

endometrial cancer, guideline, precancers, therapy, follow up

#### Schlüsselwörter

Endometriumkarzinom, Leitlinie, Präkanzerosen, Therapie, Nachsorge

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## ABSTRACT

**Summary** The first German interdisciplinary S3-guideline on the diagnosis, therapy and follow-up of patients with endometrial cancer was published in April 2018. Funded by German Cancer Aid as part of an Oncology Guidelines Program, the lead coordinators of the guideline were the German Society of Gynecology and Obstetrics (DGGG) and the Gynecological Oncology Working Group (AGO) of the German Cancer Society (DKG).

**Purpose** Using evidence-based, risk-adapted therapy to treat low-risk women with endometrial cancer avoids unnecessarily radical surgery and non-useful adjuvant radiotherapy and/or chemotherapy. This can significantly reduce therapy-induced morbidity and improve the patient's quality of life as well as avoiding unnecessary costs. For women with endometrial cancer and a high risk of recurrence, the guideline defines the optimal extent of surgical radicality together with the appropriate chemotherapy and/or adjuvant radiotherapy if required. An evidence-based optimal use of different therapeutic modalities should improve the survival rates and quality of life of these patients. This S3-guideline on endometrial cancer is intended as a basis for certified gynecological cancer centers. The aim is that the quality indicators established in this guideline will be incorporated in the certification processes of these centers.

**Methods** The guideline was compiled in accordance with the requirements for S3-level guidelines. This includes, in the first instance, the adaptation of source guidelines selected using the DELBI instrument for appraising guidelines. Other consulted sources included reviews of evidence, which were compiled from literature selected during systematic searches of literature databases using the PICO scheme. In addition, an external biostatistics institute was commissioned to carry out a systematic search and assessment of the literature for one part of the guideline. Identified materials were used by the interdisciplinary working groups to develop suggestions for Recommendations and Statements, which were then subsequently modified during structured consensus conferences and/or additionally amended online using the DELPHI method, with consent between members achieved online. The guideline report is freely available online.

**Recommendations** Part 2 of this short version of the guideline presents recommendations for the therapy of endometrial cancer including precancers and early endometrial cancer as well as recommendations on palliative medicine, psycho-oncology, rehabilitation, patient information and healthcare facilities to treat endometrial cancer. The management of precancers of early endometrial precancerous conditions including fertility-preserving strategies is presented. The concept used for surgical primary therapy of endometrial cancer is described. Radiotherapy and adjuvant medical therapy to treat endometrial cancer and uterine carcinosarcomas are described. Recommendations are given for the follow-up care of

endometrial cancer, recurrence and metastasis. Palliative medicine, psycho-oncology including psychosocial care, and patient information and rehabilitation are presented. Finally, the care algorithm and quality assurance steps for the diagnosis, therapy and follow-up of patients with endometrial cancer are outlined.

## ZUSAMMENFASSUNG

**Zusammenfassung** Im April 2018 erschien die erste deutsche interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge der Patientinnen mit Endometriumkarzinom. Von der Deutschen Krebshilfe im Rahmen des Leitlinienprogramms Onkologie gefördert, wurde sie von der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) und der Arbeitsgemeinschaft Onkologische Gynäkologie (AGO) der Deutschen Krebsgesellschaft (DKG) federführend koordiniert.

**Ziele** Durch eine evidenzbasierte risikoadaptierte Therapie können bei den Frauen mit Endometriumkarzinom mit geringem Risiko eine unnötige Radikalität bei der Operation und nicht sinnvolle adjuvante Strahlen- und/oder Chemotherapie vermieden werden. Dies reduziert zum einen deutlich die therapieinduzierte Morbidität und erhöht die Lebensqualität der Patientinnen. Auf der anderen Seite werden unnötige Kosten vermieden. Für die Frauen mit einem Endometriumkarzinom mit hohem Rezidivrisiko definiert die Leitlinie die optimale operative Radikalität sowie die ggf. erforderliche Chemotherapie und/oder adjuvante Strahlentherapie. Durch den evidenzbasierten optimalen Einsatz der verschiedenen Therapiemodalitäten sollten Überleben und Lebensqualität dieser Patientinnen verbessert werden. Die S3-Leitlinie zum Endometriumkarzinom soll eine Grundlage für die Arbeit der zertifizierten gynäkologischen Krebszentren sein. Die auf dieser Leitlinie basierenden Qualitätsindikatoren sollen in den Zertifizierungsprozess dieser Zentren einfließen.

**Methoden** Die Leitlinie wurde gemäß den Anforderungen eines S3-Niveaus erarbeitet. Dies umfasst zum einen die Adaptation der mittels des DELBI-Instruments selektierten Quellleitlinien. Zum anderen Evidenzübersichten, die anhand der in systematische Recherchen nach dem PICO-Schema in ausgewählten Literaturdatenbanken selektierten Literatur erstellt wurden. Ergänzend wurde ein externes Biostatistik-Institut mit der systematischen Literaturrecherche und -Bewertung eines Teilbereichs beauftragt. Diese Ergebnisse dienten den interdisziplinären Arbeitsgruppen als Basis für die Erarbeitung von Vorschlägen für Empfehlungen und Statements, welche in strukturierten Konsensuskonferenzen und/oder ergänzend im DELPHI-Verfahren auch online modifiziert und konsentiert wurden. Der Leitlinienreport ist online frei verfügbar.

**Empfehlungen** Der Teil 2 dieser Kurzversion der Leitlinie zeigt Empfehlungen zur Therapie des Endometriumkarzinoms, inklusive der Präkanzerosen und des frühen Endometriumkarzinoms, zur Palliativmedizin, Psychoonkologie, Rehabilitation und Patientinnenaufklärung und zu den Versorgungsstrukturen des Endometriumkarzinoms: Das Management von Präkanzerosen und frühen Endometriumkarzinomen, in-

klusive fertilitätserhaltender Strategien, wird dargestellt. Das Konzept der operativen Primärtherapie des Endometriumkarzinoms wird behandelt. Weiterhin werden die Strahlentherapie und die adjuvante medikamentöse Therapie des Endometriumkarzinoms und der uterinen Karzinosarkome abgebildet. Es werden Empfehlungen zur Nachsorge des Endometriumkarzinoms, zum Rezidiv und zur metastasierten Situation ge-

geben. Die Bereiche Palliativmedizin, Psychoonkologie, einschließlich psychosozialer Betreuung und Patientinnenaufklärung, und Rehabilitation werden dargelegt. Abschließend werden der Versorgungsalgorithmus und die Qualitätssicherungsschritte für die Diagnostik, die Therapie und die Nachsorge der Patientinnen mit Endometriumkarzinom vorgestellt.

## I Guideline Information

### Editors

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

### Lead professional organizations

The German Society of Gynecology and Obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe, DGGG); the German Cancer Society (Deutsche Krebsgesellschaft, DKG) represented by the Gynecological Oncology Working Group (Arbeitsgemeinschaft Gynäkologische Onkologie, AGO).

This guideline was developed in cooperation with the Guideline Program of the DGGG, OEGGG and SGGG. For further information see bottom of this article.

### Funding

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### Citation format

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### Guideline documents

The complete long version including a list of all conflicts of interest of all authors, a short version, the guideline report and the external literature search are available in German on the homepage of the Oncology Guidelines Program under: <https://www.leitlinienprogramm-onkologie.de/leitlinien/endometriumkarzinom/>, accessed on 13.08.2018.

### Guideline authors

The working groups who contributed to this guideline consisted of members of the guideline steering committee (► **Table 1**) and specialists and experts (► **Table 3**) nominated by participating professional societies and organizations (► **Table 2**), and they are the authors of the guideline. Only mandate holders nominated by participating professional societies and organizations were eligible to vote on a chapter-by-chapter basis during the voting process (consensus process) after they had disclosed and excluded any conflicts of interest [1]. The guideline was compiled with the direct participation of two patient representatives.

Physicians of the Competence Oncology Center of the National Association of Statutory Health Insurance Funds (Kompetenz Centrum Onkologie des GKV-Spitzenverbandes) and the Medical Service of German Health Funds (MDK-Gemeinschaft) were involved in an advisory capacity during the formulation of specific aspects of this S3-guideline which were relevant for social medicine.

They did not participate in the voting on individual recommendations and are not responsible for the contents of this guideline.

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	Name	City
1.	Prof. Dr. med. Günter Emons (guideline coordinator)	Göttingen
2.	Prof. Dr. med. Eric Steiner (deputy guideline coordinator)	Rüsselsheim
3.	Dr. med. Nina Bock (editor)	Göttingen
4.	Kerstin Paradies	Hamburg
5.	Dr. med. Christoph Uleer	Hildesheim
6.	Prof. Dr. med. Dirk Vordermark	Halle/Saale

► **Table 2** Participating professional societies and organizations.

Participating professional societies and organizations	Mandate holder	Deputy
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AET (DKG Working Group for Hereditary Tumor Disease [AG Erbliche Tumorerkrankungen der DKG])	Prof. Dr. med. Stefan Aretz, Bonn	Prof. Dr. med. Rita Katharina Schmutzler, Cologne Prof. Dr. med. Alfons Meindl, Munich (only once in 06/2015)
AGO (Gynecological Oncology Working Group of the DGGG and DKG [Arbeitsgemeinschaft Gynäkologische Onkologie in der DGGG und DKG])	Prof. Dr. med. Peter Mallmann, Cologne	
AGO Study Group (Arbeitsgemeinschaft Gynäkologische Onkologie [AGO] Studiengruppe)	PD Dr. med. Christian Kurzeder, Basel	Prof. Dr. med. Felix Hilpert, Hamburg
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Continued next page

► **Table 2** Participating professional societies and organizations. (continued)

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OEGGG (Austrian Society of Gynecology and Obstetrics [Österreichische Gesellschaft für Gynäkologie und Geburtshilfe])	Prof. Dr. med. Alain-Gustave Zeimet, Innsbruck	Prof. Dr. med. Edgar Petru, Graz
PRIO (Prevention and Integrative Oncology Working Group of the DKG [Arbeitsgemeinschaft der DKG Prävention und integrative Medizin in der Onkologie])	Prof. Dr. med. Volker Hanf, Fürth	Prof. Dr. med. Jutta Hübner, Jena
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► **Table 3** Experts who contributed in an advisory capacity, methodological advisors and other contributors.

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## Abbreviations used in this guideline

AEH	atypical endometrial hyperplasia
AG	working group (Arbeitsgruppe)
AUC	area under the curve
AWMF	Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.)
BSO	bilateral salpingo-oophorectomy
CEB	Basel Institute for Clinical Epidemiology & Biostatistics of the University of Basel
DELBI	German Guideline Assessment Instrument
DELPHI	multistage survey method
DKG	German Cancer Society (Deutsche Krebsgesellschaft e.V.)
DKH	German Cancer Aid (Deutsche Krebshilfe e.V.)
EC	expert consensus
FIGO	International Federation of Gynecology and Obstetrics
GGPO	German Guideline Program in Oncology
GoR	Grade of Recommendation
HT/HRT	hormone replacement therapy
ICD-10	International Statistical Classification of Diseases and Related Health Problems (10th edition)
ICD-O-3	International Classification of Diseases for Oncology (3rd edition, 1st revision)
IUD	intrauterine device
LN	lymph node
LNG-IUD	levonorgestrel-releasing intrauterine device
LNE	lymphadenectomy
LoE	level of evidence
LVSI	lymphovascular space invasion
MGA	megestrol acetate
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
s/p	status post
ST	statement

## II Guideline Application

### Purpose and objectives

The most important reason to compile this interdisciplinary guideline is the high epidemiological significance of endometrial cancer and its associated burden of disease. The use of evidence-based risk-adapted therapy to treat low-risk women with endometrial cancer can avoid unnecessarily radical surgery and non-useful adjuvant radiotherapy and/or chemotherapy. This reduces therapy-induced morbidity, improves patients' quality of life, and avoids unnecessary costs. For women with endometrial cancer and a high risk of recurrence, the guideline defines the optimal surgical radicality and the appropriate adjuvant chemotherapy and/or adjuvant radiotherapy. The optimal evidence-based use of different therapy modalities should improve survival rates and the quality of life of patients.

### Targeted areas of patient care

The guideline covers outpatient and inpatient care.

### Target patient groups

The recommendations of the guideline are aimed at all women with endometrial cancer and their relatives.

### Target user groups

The recommendations of the guideline are addressed to all physicians and professionals who provide care to patients with endometrial cancer. In the first instance, this group consists of gynecologists, general practitioners, radiologists, pathologists, radio-oncologists, hematologists/oncologists, psycho-oncologists, palliative care professionals and nursing staff.

Other target groups are:

- Scientific medical societies and professional organizations;
- Advocacy groups for affected women (women's health organizations, patient and self-help organizations);
- Quality assurance institutions and projects at federal and *Länder* levels (AQUA, the Institute for Applied Quality Improvement and Research in Healthcare, the Association of German Tumor Centers, etc.);
- Health policy institutions and decision-makers at federal and *Länder* levels;
- Funding agencies.

### Period of validity and update procedure

This guideline is valid from 1 April 2018 through to 1 April 2023. Regular updates are planned; if changes are urgently required, amendments will be developed which will be published in the latest version of the guideline. The current aim is to update the guideline every two years.

## III Methodology of the Guideline

### Basic principles

The method used to prepare this guideline was determined by the class to which this guideline was assigned. The AWMF Guidance Manual (version 1.1, <https://www.awmf.org/leitlinien/awmf-regelwerk/awmf-regelwerk-offline.html>, last accessed on 13.08.2018) differentiates between the lowest (S1), the intermediate (S2) and the highest (S3) class of guidelines [4]. The lowest category is defined as a set of recommendations for action compiled by a non-representative group of experts. In 2004, the S2 class was subdivided into two subclasses: a systematic evidence-based subclass (S2e) and a structural consensus-based subclass (S2k). The highest class (S3) combines both approaches. This guideline is classified as: S3.

### Grading of evidence

Identified trials used in this guideline were assessed using the 2011 version of the system developed by the Oxford Centre for Evidence-based Medicine. This system classifies studies according to various clinical questions (benefit of therapy, prognostic value, diagnostic validity). Further information is available online at: <http://www.cebm.net/index.aspx?o=5653>, last accessed on 13.08.2018.

## Grading of recommendations

The level of recommendation expresses the degree of certainty that the expected benefit of the intervention will outweigh the possible damage caused (net benefit) and that the expected positive effects will be big enough to make a relevant difference to the patient. Negative recommendations (must not) indicate the certainty that there will be no benefit or that the result may even be damaging (► **Table 4**). The grading of recommendations incorporates the results of evaluated trials, the applicability of study results to target patient groups, the feasibility in daily clinical practice, ethical obligations, and patient preferences [2, 3].

► **Table 4** Grading of recommendations.

Level of recommendation	Description	Syntax
A	Strong recommendation	must/must not
B	Recommendation	should/should not
0	Recommendation open	may/can

## Recommendations

Recommendations are thematically grouped key sentences with a recommendation for action, which were developed by the guideline group and voted on in a formal consensus procedure.

## Statements

Statements are expositions or explanations of specific facts, circumstances, or problems, with no direct recommendations for action. Statements are adopted after a formal consensus process using the same approach as that used when formulating recommendations and can be based either on study results or expert opinions.

## Expert consensus (EC)

Recommendations for which no systematic search of the literature was carried out are referred to as expert consensus (EC). As a rule, these recommendations cover approaches considered to be good clinical practice where no scientific studies are necessary or could be expected.

## IV Guideline

### 1 Management of endometrial precancers and early endometrial cancer

#### 1.1 Endometrial hyperplasias

##### 1.1.1 Endometrial hyperplasia without atypia

No.	Recommendation	GoR	LoE	Sources
5.1	Hysterectomy should not be used to treat endometrial hyperplasia without atypia.	A	3	[5]

##### 1.1.2 Atypical endometrial hyperplasia (AEH)

##### 1.1.2.1 Management of 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	[5, 6]

##### 1.1.2.2 Management of 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		



### 1.1.2.3 Fertility preservation in women with AEH

No.	Recommendation	GoR	LoE	Sources
5.4	If a patient with atypical endometrial hyperplasia wishes to preserve her uterus, the uterus and adnexa may be preserved if the patient is informed that the standard treatment, which is almost always curative, is total hysterectomy; the patient agrees to close and regular monitoring; and the patient is informed that total hysterectomy will be necessary after she has either fulfilled her wish to have children or decided not to have children.	EC		
5.5	If a patient with atypical endometrial hyperplasia wishes to preserve her uterus, the uterus and adnexa may be preserved if hysteroscopy with targeted biopsy or curettage is performed to confirm the diagnosis, and the diagnosis of "atypical hyperplasia" was either made or confirmed by a pathologist with a lot of experience in gynecological pathology.	EC		
5.6	If a patient with atypical endometrial hyperplasia wishes to preserve her uterus, the uterus and adnexa may be preserved if laparoscopy combined with vaginal ultrasound or MRI is carried out to best assess the risk of adnexal involvement/myometrial infiltration.	EC		
5.7	If AEH is in complete remission after 6 months of conservative treatment, the patient should try for the planned pregnancy she wants.	EC		
5.8	If the patient does not want to have children at present, she must be given maintenance therapy. An endometrial biopsy must be carried out 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	[7–11]

## 1.2 Early endometrial cancer

### 1.2.1 Management of early endometrial cancer

No.	Recommendation	GoR	LoE	Sources
5.10	Patients with early endometrial cancer must have a hysterectomy with bilateral salpingo-oophorectomy.	A	3	[12]
5.11	When carrying out a hysterectomy with bilateral salpingectomy in premenopausal patients with endometrioid endometrial cancer (G1/G2, pT1a), the ovaries may be preserved as long as there are no indications that the patient has a hereditary predisposition to develop ovarian cancer (e.g., BRCA mutation or Lynch syndrome) and the patient has been informed about the risk involved.	EC		

### 1.2.2 Fertility preservation in women with early endometrial cancer

No.	Recommendation	GoR	LoE	Sources
5.12	The uterus and adnexa may be preserved in women with endometrial cancer who want to have (further) children and wish to preserve their fertility if the patient is informed that the standard treatment, which is almost always curative, is total hysterectomy; the patient temporarily eschews curative treatment of the malignancy at her own responsibility and is fully aware of the potentially fatal consequences (disease progression, metastasis) even if a pregnancy is carried to term.	EC		
5.13	The uterus and adnexa may be preserved in women with early endometrial cancer who wish to preserve their uterus if the patient is given the recommendation to consult a specialist for reproductive medicine to assess her likelihood of being able to conceive and bear a child.	EC		
5.14	The uterus and adnexa may be preserved in women with early endometrial cancer who wish to preserve their uterus if the patient agrees to regular close monitoring and the patient has been informed of the necessity of having a hysterectomy after she has either fulfilled or given up her wish to have a child.	EC		
5.15	The uterus and adnexa may be preserved in women with early endometrial cancer who wish to preserve their fertility if hysteroscopy with targeted biopsy or curettage and evaluation of the specimen by a pathologist with a lot of experience in gynecological pathology results in a diagnosis of a well-differentiated (G1) endometrioid endometrial cancer which expresses progesterone receptors.	EC		
5.16	The uterus and adnexa may be preserved in women with early endometrial cancer (pT1a, G1) who wish to preserve their fertility if adnexal involvement or myometrial infiltration is excluded, as far as possible, by laparoscopy combined with vaginal ultrasound or MRI.	EC		
5.17	The uterus and adnexa may be preserved in women with early endometrial cancer who wish to preserve their fertility if the patient then receives adequate medical treatment with medroxyprogesterone acetate or megestrol acetate or a levonorgestrel-releasing IUD.	EC		

No.	Recommendation	GoR	LoE	Sources
5.18	If the endometrial cancer is in complete remission after 6 months of conservative treatment, the patient should try for the planned pregnancy she wants, if necessary after consultation with a specialist for reproductive medicine.	EC		
5.19	Patients with endometrial cancer (pT1a without myometrial infiltration, G1) who do not want to have children at that point in time should receive maintenance therapy (levonorgestrel-releasing IUD, oral contraceptives, cyclical progestogens) and should have an endometrial biopsy every 6 months.	EC		
5.20	A hysterectomy should be carried out if the cancer does not respond to 6 months of conservative treatment.	EC		
5.21	The uterus and adnexa may be preserved in women with endometrioid adenocarcinoma of the endometrium (cT1A, G1) with no evidence of myometrial infiltration and with progesterone receptor expression who wish to preserve their uterus if the following conditions are met: <ul style="list-style-type: none"> <li>▪ The patient is fully informed of the fact that the standard procedure is total hysterectomy and that this procedure is almost always curative,</li> <li>▪ The patient consents to regular close monitoring and follow-up,</li> <li>▪ The patient is informed that a hysterectomy will be necessary after she has either fulfilled her wish to have children or decided not to have children,</li> <li>▪ A hysteroscopy with targeted biopsy or curettage is carried out to confirm the diagnosis,</li> <li>▪ Laparoscopy combined with vaginal ultrasound or MRI is performed to exclude adnexal involvement or myometrial infiltration,</li> <li>▪ The diagnosis is made or confirmed by a pathologist with a lot of experience of gynecological pathology,</li> <li>▪ The patient is treated with MPA or MGA or an LNG-IUD,</li> <li>▪ The patient undergoes hysteroscopy with curettage and imaging after 6 months. A hysterectomy must be carried out if the cancer has not responded to conservative treatment,</li> <li>▪ If the patient is in complete remission, she can try to become pregnant (consult with a specialist for reproductive medicine),</li> <li>▪ If the patient does not want to have children at that point in time: maintenance therapy and endometrial biopsy every 6 months,</li> <li>▪ Once the patient has had children or no longer wishes to have children: total hysterectomy and bilateral salpingo-oophorectomy should be recommended.</li> </ul>	EC		

## 2 Surgical therapy of endometrial cancer

### 2.1 Basic surgical therapy

Surgical treatment for endometrial carcinoma is based on total hysterectomy and bilateral salpingo-oophorectomy (BSO) (s. Chapter 5 “Management of endometrial precancers and early endometrial cancer” in the long version of the S3-Guideline) [32]. In exceptional cases, surgical removal of the ovaries may not be necessary (in this article s. Chapter 1; Recommendations 5.11–5.17 and 5.21).

### 2.2 Parametrial resection

No.	Recommendation	GoR	LoE	Sources
6.1	Radical hysterectomy (parametrial resection) must not be carried out in cases with cT2 or pT2 endometrial cancer (with histological confirmation of involvement of the cervical stroma) but no clinical suspicion of parametrial infiltration.	A	3	[13]

### 2.3 Lymphadenectomy

No.	Recommendation	GoR	LoE	Sources
6.2	All suspicious lymph nodes or lymph nodes which are found to be enlarged on palpation or macroscopic examination must be resected.	EC		

No.	Recommendation	GoR	LoE	Sources
6.3	No lymph node sampling must be done of unsuspecting lymph nodes.	EC		
6.4	Systematic lymphadenectomy of clinically unsuspecting LNs must not be done in patients with pT1a, G1/2 endometrial cancer (type I) (ICD-0: 8380/3, 8570/3, 8263/3, 8382/3, 8480/3).	A	1	[14]
6.5	Systematic lymphadenectomy may be carried out in patients with pT1a, G3, pT1b, G1/2 endometrial cancer (type I).	0	4	[15, 16]
6.6	Systematic lymphadenectomy should be carried out in patients with pT1b, G3 endometrial cancer (type I).	B	4	[15, 16]
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	[15, 16]
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 LNE should be carried out in patients with carcinosarcoma of the uterus.	B	4	[17]
6.10	If there is lymphovascular space invasion, lymphadenectomy may be carried out in patients with endometrial carcinoma even if no other risk factors are present.	EC		
6.11	If systematic LNE is indicated, full pelvic and infrarenal-paraortic lymphadenectomy should be carried out.	B	4	[15, 18, 19]
6.12	Sentinel lymph-node biopsy alone in patients with endometrial cancer must only be carried out in the framework of controlled studies.	EC		

## 2.4 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	[20]

## 2.5 Robot-assisted surgery

No.	Recommendation	GoR	LoE	Sources
6.14	Robot-assisted laparoscopic procedures may be used to treat patients with endometrial cancer in the same way as conventional laparoscopy is used during surgery for endometrial cancer.	EC		

## 2.6 Tumor reduction in advanced endometrial cancer

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	[21, 22]

## 3 Radiotherapy for endometrial cancer

### 3.1 Postoperative external radiotherapy of the pelvis for type I, stage I–II endometrial cancer

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	[23–25]

### 3.2 Postoperative vaginal brachytherapy for type I, stage I–II endometrial cancer

No.	Recommendation	GoR	LoE	Sources
7.2	Patients with type I (stage pT1a, pNX/0 without involvement of the myometrium, G3) endometrioid endometrial cancer may be treated with vaginal brachytherapy to reduce the risk of vaginal recurrence.	0	4	[23, 26]
7.3	Patients with type I (stage pT1b, G1 or G2 pNX/0 and stage pT1a with myometrial involvement, G3 pNX/0) endometrioid endometrial cancer should be given only vaginal brachytherapy postoperatively to reduce the risk of vaginal recurrence.	B	2	[27–29]
7.4	Patients with type I (stage pT1b pNX G3 or stage pT2 pNX) endometrioid endometrial cancer should be given vaginal brachytherapy; alternatively they may be treated with percutaneous radiotherapy.	EC		
7.5	Patients who have had systematic LNE for stage pT1b pN0 G3 or stage pT2 pN0 type I endometrioid endometrial cancer should be given vaginal brachytherapy. They must not be treated with percutaneous radiotherapy.	EC		
7.6	Patients with stage pT1 pNX (all grades) endometrial cancer with “substantial LVSI” (the highest stage of the three-stage grading system for lymph node invasion) may be treated with percutaneous pelvic radiotherapy instead of vaginal brachytherapy.	EC		

### 3.3 Postoperative radiotherapy for type I, stage III–IVA endometrial cancer

No.	Recommendation	GoR	LoE	Sources
7.7	In addition to chemotherapy, patients with type I endometrioid endometrial cancer and positive LNs and involvement of the uterine serosa, the adnexa, the vagina, the bladder or the rectum (all stages from III to IVA) may be given external pelvic radiation postoperatively to improve local control of disease.	EC		

### 3.4 Vaginal brachytherapy as a boost after postoperative percutaneous pelvic radiotherapy

No.	Recommendation	GoR	LoE	Sources
7.8	If the patient has particular risk factors for vaginal recurrence (stage II or stage IIIB-vaginal, with very small or positive resection margins), additional vaginal brachytherapy may be administered as a boost after postoperative external pelvic radiotherapy following hysterectomy for endometrioid endometrial cancer.	EC		

### 3.5 Postoperative radiotherapy for type II endometrial cancer

No.	Recommendation	GoR	LoE	Sources
7.9	The decision whether postoperative vaginal brachytherapy or external pelvic radiotherapy is indicated to treat type II carcinoma (serous or clear-cell) should be based on the recommendations on how to treat type I grade G3 (endometrioid) carcinoma with the same staging.	EC		

### 3.6 Primary radiotherapy alone for inoperable disease

For patients with inoperable endometrial cancer, radiotherapy alone is a treatment approach with curative intent.

Because no randomized studies exist, the Gynecological Cancer Group of the European Organization for Research and Treatment of Cancer has recently compiled a systematic review which describes the uses of radiotherapy for this indication and the outcomes [30].

A total of 2694 patients from 25 case series were reviewed. These patients were treated either with brachytherapy alone (51%) or a combination of brachytherapy plus percutaneous radiotherapy (47%). After five years, the disease-specific survival

rate was 78.5%, the rate of local control was 79.9% and the overall survival rate, which reflects preexisting comorbidities, was 53.2%. The risk of long-term significant (higher grade) sequelae was 2.8% (brachytherapy alone) and 3.7% (combination), respectively. Based on these data, when the patient presents with inoperable cancer, the use of brachytherapy alone is only recommended for stage I grade 1 cancers; all other stage I cancers and all stage II to IV cancers should be treated with a combination of percutaneous radiation therapy and brachytherapy.

### 3.7 Radiotherapy for carcinosarcoma

No.	Recommendation	GoR	LoE	Sources
7.10	Radiotherapy should be administered postoperatively for FIGO stage I or II carcinosarcomas to improve local control.	B	3	[31]

### 3.8 Supportive therapy

When providing radiotherapeutic treatment, the recommendations of the S3-guideline on supportive care (currently only available in German) “Supportive Therapie bei onkologischen PatientInnen” (long version 1.1, April 2017, AWMF registry number: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html>) should be taken into consideration [40]. See also the detailed text on this issue in the long version of the S3-guideline on endometrial cancer (an english version will be available soon) [32].

## 4 Adjuvant medical therapy for endometrial cancer

### 4.1 Adjuvant medical therapy for endometrial cancer

#### 4.1.1 Adjuvant progestogen therapy

No.	Recommendation	GoR	LoE	Sources
8.1	Adjuvant progestogen therapy must not be administered after surgery for endometrial cancer.	A	1	[33]

#### 4.1.2 Adjuvant chemotherapy

No.	Recommendation	GoR	LoE	Sources
8.2	Patients with endometrioid or another type I stage pT1a/b G1 and G2 cN0/pN0 endometrial cancer (ICD-0: 8380/3, 8570/3, 8263/3, 8382/3, 8480/3) must not be given adjuvant chemotherapy.	EC		
8.3	There is currently not enough data to state whether patients with endometrioid or another type I stage pT1a G3 cN0 or pN0 endometrial cancer benefit from adjuvant chemotherapy or not.	ST	2	[34]

No.	Recommendation	GoR	LoE	Sources
8.4	Adjuvant chemotherapy may be administered to patients with type II and patients with type I G3 pT1b and stage pT2 (both pN0) endometrial cancer. <sup>1</sup>	0	2	[34, 35]
8.5	Patients with stage pT3 and/or pN1 endometrial cancer should be given adjuvant chemotherapy. <sup>1</sup>	B	1	[34, 35]
8.6	Patients with stage pT4a or M1 endometrial cancer who have had surgery and have no evidence of residual macroscopic tumor or who have a residual tumor with a maximum diameter of less than 2 cm should be given adjuvant chemotherapy. <sup>1</sup>	B	1	[34, 35]
8.7	Adjuvant chemotherapy for endometrial cancer should consist of carboplatin and paclitaxel. <sup>1</sup>	EC		

<sup>1</sup> It is important to note that these chemotherapies have not been approved as adjuvant therapies for endometrial cancer and that their use to treat these indications constitutes an off-label use.

#### 4.2 Adjuvant medical therapy for carcinosarcoma

No.	Recommendation	GoR	LoE	Sources
8.8	Patients with FIGO stage I or II carcinosarcoma may be given adjuvant chemotherapy with cisplatin/ifosfamide at a dose of ifosfamide 1.6 g/m <sup>2</sup> i. v. on Days 1–4 and cisplatin 20 mg/m <sup>2</sup> i. v. on Days 1–4 or carboplatin/paclitaxel at a dose of paclitaxel 175 mg/m <sup>2</sup> on Day 1 and carboplatin AUC5. <sup>1</sup>	0	4	[36]
8.9	A significant survival benefit has been reported for adjuvant chemotherapy with ifosfamide/paclitaxel or ifosfamide/cisplatin compared to monotherapy with ifosfamide alone when administered to patients with FIGO stage III or IV carcinosarcoma.	ST	1	[37–39]
8.10	Because of the high toxicity of ifosfamide-containing combinations, adjuvant chemotherapy given to patients with carcinosarcoma may also consist of a combination of carboplatin and paclitaxel.	EC		

<sup>1</sup> It is important to note that these chemotherapies have not been approved for the adjuvant therapy of endometrial cancer and that using them to treat these indications constitutes an off-label use.

#### 4.3 Supportive therapy

When administering systemic therapy, all the necessary supportive measures described in the S3-guideline “Supportive Therapie bei onkologischen PatientInnen” (long version 1.1 [currently only available in German], April 2017, AWMF registry number: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html>) [40] must be implemented. A detailed description is also available in the long version of the S3-guideline on endometrial cancer (an english version will be available soon) [32].

### 5 Follow-up/recurrence/metastasis of endometrial cancer

#### 5.1 Follow-up

No.	Recommendation	GoR	LoE	Sources
9.1	There is no evidence that follow-up examinations of women with endometrial cancer prolong survival.	ST	4	[41–50]
9.2	Careful questioning of the patient to obtain her medical history, carefully targeted inquiries about symptoms, and a clinical gynecologic exam using a speculum and including rectovaginal palpation should be carried out every 3 to 6 months in the first 3 years after completing primary therapy and every 6 months in the 4th and 5th years.	EC		
9.3	Imaging examinations and the determination of tumor markers should not be carried out for asymptomatic patients.	B	4	[41–43, 48]

#### 5.2 Management of recurrence

No.	Recommendation	GoR	LoE	Sources
9.4	Histological confirmation must be sought if there is a suspicion of local recurrence in the vaginal area or the area of the lower pelvis or if there is a suspicion of distant metastasis.	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	[41, 51, 52]

### 5.2.1 Isolated vaginal or vaginal stump recurrence

No.	Recommendation	GoR	LoE	Sources
9.6	Women with isolated vaginal or vaginal stump recurrence after endometrial cancer who did not previously receive radiation treatment during primary therapy should be given radiotherapy with curative intent, consisting of external pelvic radiotherapy and brachytherapy, with or without local tumor resection.	EC		
9.7	Women with isolated vaginal or vaginal stump recurrence after endometrial cancer who had adjuvant brachytherapy alone during primary therapy may be given radiotherapy with curative intent with or without local tumor resection.	EC		
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" (currently only available in German) [40]. <sup>1</sup>	EC		

<sup>1</sup> For this issue, see also Chapter 7.8. on supportive therapy in the long version of the guideline (an english version will be available soon) [32].

### 5.3 Surgical therapy for recurrence

No.	Recommendation	GoR	LoE	Sources
9.10	Surgical therapy may be carried out to treat recurrence of endometrial cancer if complete resection of the recurrent tumor seems achievable and tomography has not shown any evidence of distant metastasis.	EC		
9.11	There is no evidence that exenteration in women with recurrence of endometrial cancer improves survival times, survival rates or progression-free survival compared to other therapies or best supportive care.	EC		
9.12	Exenteration may be considered in individual cases in women with recurrent endometrial cancer.	EC		

### 5.4 Endocrine therapy for recurrence

No.	Recommendation	GoR	LoE	Sources
9.13	There are no data which demonstrate that the administration of endocrine therapy to women with recurrence of endometrial cancer leads to an improvement in survival times, survival rates or progression-free survival compared to other therapies or best supportive care.	EC		
9.14	Endocrine therapy with either MPA (200 mg/d) or MGA (160 mg/d) may be administered to women with recurrence of endometrial cancer.	0	3	[53, 54]
9.15	The response rates for endocrine therapy with MPA administered to women with recurrence of endometrial cancer are higher if there is evidence of progesterone receptor expression or estrogen receptor expression or the tumor is well-to-moderately differentiated (G1/G2).	ST	3	[54, 55]

### 5.5 Chemotherapy for recurrence

No.	Recommendation	GoR	LoE	Sources
9.16	Systemic chemotherapy may be administered to women with endometrial cancer recurrence which cannot be treated locally or with distant metastasis.	0	1	[41, 56]
9.17	There is currently no evidence that any specific chemotherapy regimen is superior when treating women with recurrence of endometrial cancer. Platinum salts, anthracyclines and taxanes are considered to be the most effective substances for the chemotherapeutic treatment of advanced or recurrent endometrial cancer. The established treatment consists of a combination of carboplatin with paclitaxel, which is relatively well tolerated and safe. <sup>1</sup>	ST	3	[56]

<sup>1</sup> Statements about off-label use must be considered carefully (see Chapter 8 on the adjuvant medical therapy of endometrial cancer in the long version of the guideline (an english version will be available soon) [32]. There can be no doubt, however, that this cases meets the criterion "life-threatening disease". Robust data from phase III studies is available for the administration of adriamycin/cisplatin, adriamycin/cisplatin/paclitaxel and carboplatin/paclitaxel in this context.

## 5.6 Post-actinic changes in the irradiated area

### 5.6.1 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	[57]

### 5.6.2 Topical administration of estrogen

No.	Recommendation	GoR	LoE	Sources
9.19	Topical application of estrogen after primary therapy for endometrial cancer may be considered if the results of treatment with an inert lubricant jelly or cream were unsatisfactory.	EC		

### 5.6.3 Treatment for and prophylaxis against vaginal stenosis

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		

## 5.7 Palliative radiotherapy

No.	Recommendation	GoR	LoE	Sources
9.21	A schedule of lower total dose radiotherapy may be administered as a palliative measure in cases with vaginal bleeding or pain caused by vaginal stump or pelvic wall recurrence, even if patients have previously had radiotherapy.	EC		

## 6 Palliative medicine, psycho-oncology, rehabilitation, psychosocial care, patient information

### 6.1 Psycho-oncological aspects

No.	Recommendation	GoR	LoE	Sources
11.1	Patients with endometrial cancer and their relatives may be facing many different physical, psychological, social and spiritual/religious stresses.	EC		

#### 6.1.1 Psychosocial support

No.	Recommendation	GoR	LoE	Sources
11.2	Cancer patients and their relatives must be informed as early as possible about the available options for psychosocial support, counseling and treatment; they must be informed during all stages of disease and must be helped to access these options based on their individual needs.	EC		

#### 6.1.2 Screening to determine extent of psychosocial stress

No.	Recommendation	GoR	LoE	Sources
11.3	All patients must be screened to determine the extent of their psychosocial stress. Psycho-oncological screening should be carried out as early as possible and then repeated at appropriate intervals throughout the course of disease when clinically indicated or if the disease status changes (e.g., recurrence or progression of disease).	EC		

#### 6.1.3 Indications for psycho-oncological intervention

No.	Recommendation	GoR	LoE	Sources
11.4	The indications for psycho-oncological interventions must be based on the patient's ascertained individual needs, the respective setting, and the stage of disease (primary diagnosis, surgery, adjuvant therapy, recurrence-free period, recurrence phase, palliative phase) and must take the wishes of the patient into account.	EC		

### 6.1.4 Sexuality and endometrial cancer

No.	Recommendation	GoR	LoE	Sources
11.5	The issue of sexuality must be actively addressed during the different stages of treatment and during the follow-up of patients with endometrial cancer to determine the patient's need for support and take the appropriate steps to provide assistance.	EC		

## 6.2 Patient education, information and patient education content

### 6.2.1 Information materials

No.	Recommendation	GoR	LoE	Sources
11.6	Patients must be provided with accurate and pertinent information materials (print or internet media) which were compiled in accordance with defined quality criteria for healthcare information. Providing generally intelligible data about associated risks (e.g., information on the reduction of risk in absolute figures) supports the patient and allows her to make an independent decision for or against medical measures.	EC		

### 6.2.2 Conveying the diagnosis

No.	Recommendation	GoR	LoE	Sources
11.7	The patient must be offered the opportunity to bring along her partner or a relative/trusted confidant to any talks, starting with when she is given the diagnosis and including all following discussions and meetings during therapy and follow-up.	EC		
11.8	During the consultation with her physician, the patient's individual preferences, needs, worries and fears must be elicited and taken into account. If the patient needs several consultations for this, then she must be offered further consultations.	EC		

### 6.2.3 Conveying information and educating the patient

No.	Recommendation	GoR	LoE	Sources
11.9	Informing and educating the patient must start early, and the information must be conveyed in accordance with the basic principles of patient-centered communication, which encourages participatory decision-making.	EC		

### 6.2.4 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		

In Germany, the contact data of nearby self-help groups can be obtained from the Contact and Information Center to Encourage and Support Self-help Groups (NAKOS):

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

Contact data on counseling options and other points of call in Germany for patients with endometrial cancer will also be made available in an accompanying patient guideline. After its publication online, this patient guideline (in German) will be freely accessible on the homepage of the Oncology Guideline Program and the homepage of the AWMF:

- <http://www.leitlinienprogramm-onkologie.de/patientenleitlinien/>
- <http://www.awmf.org/leitlinien/patienteninformation.html>

### 6.2.5 Information about therapy options

No.	Recommendation	GoR	LoE	Sources
11.11	Patients with endometrial cancer must be informed about the therapy options described in this guideline which are relevant for them and must be educated about the chances of success associated with the respective options and the potential effects of the respective treatments. It is particularly important to inform the patient of the potential impact on her physical appearance, her sex life, her bladder and bowel control (incontinence), and the impact on areas which affect her self-concept as a woman (self-perception, fertility, menopausal symptoms).	EC		



### 6.3 Palliative care and the treatment of endometrial cancer

No.	Recommendation	GoR	LoE	Sources
11.12.1	All patients must be offered palliative care after receiving a diagnosis of incurable disease, irrespective of whether tumor-specific therapy is carried out or not.	A	2	[58–67]
11.12.2	Specialist palliative care must be incorporated into the oncological decision-making processes, e.g., through the involvement of interdisciplinary tumor conferences.	EC		
11.12.3	Patients with incurable disease who are in a highly complex situation must be offered specialist palliative care.	A	2	[58–67]

### 6.4 Rehabilitation

This chapter was compiled and adapted from the existing German-language S3-guideline on patients with cervical cancer: “Diagnostik, Therapie und Nachsorge der Patientin mit Zervixkarzinom,” version 1. 0, September 2014, AWMF registry number 032/033OL, <http://www.leitlinienprogramm-onkologie.de/leitlinien/zervixkarzinom/>) [68].

No.	Recommendation	GoR	LoE	Sources
11.13	Medical oncological rehabilitation aims to specifically treat the sequelae of disease and therapy. All patients with endometrial cancer must be informed and counseled about their legal options to apply for and use available rehabilitation services.	EC		
11.14	Patients must not only be carefully questioned to determine whether they are experiencing therapy-related disorders (for example, abdominal wall disorders and adhesion symptoms, sexual dysfunction, pain during sexual intercourse, vaginal dryness, bladder and bowel disorders) and treated for any such disorders during primary therapy but must also be questioned and treated during rehabilitation and follow-up.	EC		

### 6.5 Physiotherapy during rehabilitation after endometrial cancer

#### 6.5.1 Treatment of incontinence

No.	Recommendation	GoR	LoE	Sources
11.15	Patients treated for endometrial cancer who develop urinary incontinence must be offered appropriate therapy as outlined in the German-language S2e-guideline on incontinence: “Interdisziplinäre S2e-Leitlinie für die Diagnostik und Therapie der Belastungsinkontinenz der Frau” [69].	EC		
11.16	Patients treated for endometrial cancer who develop fecal incontinence should be offered pelvic floor training.	EC		

#### 6.5.2 Treatment of lymphedema

No.	Recommendation	GoR	LoE	Sources
11.17	A combined therapy consisting of compression, skin care, manual lymph drainage and therapeutic exercise should be offered to patients with manifest lymphedema.	EC		

#### 6.5.3 Alleviating fatigue symptoms

No.	Recommendation	GoR	LoE	Sources
11.18	Patients experiencing fatigue symptoms should be offered active physical exercise (weight training and/or endurance training).	B	2	[70–87]

## 7 Healthcare facilities and quality indicators

### 7.1 Healthcare facilities

#### 7.1.1 Treatment in oncology centers

No.	Recommendation	GoR	LoE	Sources
12.1	Patients with endometrial cancer should be treated by an interdisciplinary team. The team should consist of a network of specialists from all the necessary medical specialties and cover all aspects of patient care. The most feasible place to achieve this is in a certified center.	EC		

#### 7.1.2 Interdisciplinary tumor conference

No.	Recommendation	GoR	LoE	Sources
12.2	Patients with endometrial cancer must be presented to an interdisciplinary tumor conference.	EC		

## Conflict of Interest

For conflict of interests see guideline report: [https://www.leitlinienprogramm-onkologie.de/fileadmin/user\\_upload/Downloads/Leitlinien/Endometriumkarzinom/LL\\_Endometriumkarzinom\\_Leitlinienreport\\_1.0.pdf](https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Endometriumkarzinom/LL_Endometriumkarzinom_Leitlinienreport_1.0.pdf), last accessed on 13.08.2018.

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