Leitlinienprogramm Onkologie

Endometrial Cancer

Long version 2.0 – September 2022
AWMF register number: 032/034-OL

Guideline (Long version)

DKG KREBSGESELLSCHAFT
Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.
AWMF

Important Updates

This is new!
This has changed!

All guideline statements and recommendations, as well as all background text, were reviewed based on the systematically researched and assessed literature from 2016 to 2020. They were either confirmed or modified. Where necessary, new statements and recommendations were added. A detailed overview is provided in Chapter 17.3.

New items include:

Chapter 4.5

- Introduction of molecular classification of endometrial carcinoma (EC) as a prognostic and predictive factor
- Introduction of two-stage grading of endometrioid EC
- Her2 analysis in serous EC
- Significance of isolated tumor cells and micrometastases in the sentinel lymph node

Chapter 4

- Clarification of the recommendation and algorithm for the workup of abnormal premenopausal bleeding

Chapter 5

- Reassessment of complex endometrial hyperplasia without atypia
- Consideration of p53 and L1CAM expression in the indication for fertility-preserving therapy

Chapter 6

- Consideration of molecular classification and lymphatic vessel invasion (LVSI) in the indication for surgical procedures, such as sentinel node biopsy (SNB) and systematic lymphonodectomy
- technical performance of SNB and evaluation of the findings
- Option of neoadjuvant chemotherapy for primarily unresectable situations
- Algorithms for stage- and risk-dependent indication to perform certain surgical procedures

Chapter 7

- Consideration of molecular classification and lymphatic vessel invasion when determining indications
- Greater importance of the combination of radiotherapy and chemotherapy
- Integration of the S3 cross-sectional guideline “Supportive therapy in oncological patients” Long version 1.3 - February 2020, AWMF register number: 032/054OL(https://www.leitlinienprogramm-onkologie.de/leitlinien/supportive-therapie/)
- Algorithms for stage- and risk-dependent indications for adjuvant therapies

Chapter 8

- Consideration of molecular classification in the indication process
- Greater importance of the combination of radiotherapy and chemotherapy

- Precise definition of recommended chemotherapy regimens
- Integration of the S3 cross-sectional guideline “Supportive therapy in oncological patients” Long version 1.3 - February 2020, AWMF register number: 032/054OL(https://www.leitlinienprogramm-onkologie.de/leitlinien/supportive-therapie/)
- Algorithms for stage- and risk-dependent indications for adjuvant therapies

Chapter 9

- Definition of optimal palliative chemotherapy
- Option of administration of trastuzumab in Her2-positive advanced or relapsed serous EC
- Option of administration of immune checkpoint inhibitors as second line therapy in mismatch-repair-deficient/microsatellite-unstable recurrences
- Option to administer pembrolizumab/lenvatinib as second line therapy for mismatch-repair-competent/microsatellite-stable recurrences
- Integration of the S3- cross-sectional guideline “Supportive therapy in oncological patients” long version 1.3 - February 2020, AWMF register number: 032/054OL(https://www.leitlinienprogramm-onkologie.de/leitlinien/supportive-therapie/)

Chapter 10

- Determination of MMR proteins in all EC as part of histological diagnosis and risk stratification
- Update of the algorithm for the clarification of the presence of Lynch syndrome

Chapter 11

- Integration of the S3 cross-sectional guideline “S3-Leitlinie Psychoonkologische Diagnostik, Beratung und Behandlung von erwachsenen Krebspatienten” Version 1.1 - January 2014, AWMF register number: 032/051OL(https://www.leitlinienprogramm-onkologie.de/leitlinien/psychoonkologie/)
- Integration of the S3 cross-sectional guideline “Extended S3 Guideline palliative care for patients with a non-curable cancer” Long version 2.2 - September 2020, AWMF register number: 128/001OL(https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/)
- Specific palliative measures in EC
- Diagnosis and therapy of tumor-related fatigue

Chapter 12

- Recommendation of the introduction of a geriatric assessment before surgery or chemotherapy

Chapter 13

- Development of care algorithms for patients with EC

Table of Contents

1 Information about this Guideline

1.1 Editors

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

1.2 Leading Scientific Societies

Arbeitsgemeinschaft Gynäkologische Onkologie der DGGG und DKG (AGO)

Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V. (DGGG)

1.3 Funding of the Guideline

This Guideline was supported by the German Cancer Aid within the framework of the German Guideline Program in Oncology.

1.4 Contact

Office Leitlinienprogramm Onkologie
c/o Deutsche Krebsgesellschaft e. V.
Kuno-Fischer-Straße 8
14057 Berlin

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

1.5 How to cite

German German Guideline Program in Oncology (German Cancer Society, German Cancer Aid, AWMF): Endometrial Cancer, Long version 2.0, 2022, AWMF Registration Number: 032/034-OL https://www.leitlinienprogramm-onkologie.de/leitlinien/endometriumkarzinom/; Accessed [dd.mm.yyy]

1.6 Special comment

Medicine is subject to a continuous development process, so that all information, in particular on diagnostic and therapeutic procedures, can correspond only to the state of knowledge at the time of printing of the guideline. The greatest possible care has been taken with regard to the recommendations given for therapy and the selection and dosage of medications. Nevertheless, users are urged to consult the manufacturers' package inserts and expert information for verification and, in case of doubt, to consult a specialist. In the general interest, any discrepancies should be reported to the OL editorial office.

The user remains responsible for any diagnostic and therapeutic application, medication and dosage.

In this Guideline, registered trademarks (protected trade names) are not specially marked. It can therefore not be concluded from the absence of a corresponding reference that it is a free trade name.

1.7 Objectives of the German Guideline Program in Oncology (GGPO)

The Association of the Scientific Medical Societies in Germany (AWMF), the German Cancer Society (DKG) and the German Cancer Aid Foundation (Stiftung Deutsche Krebshilfe) have set themselves the goal of jointly promoting and supporting the development, updating and use of scientifically based and practicable guidelines in oncology with the Guideline Program in Oncology (OL). The basis of this program is based on the medical-scientific findings of the professional societies and the DKG, the consensus of medical experts, users and patients, as well as on the set of rules for guideline development of the AWMF and the professional support and funding by the German Cancer Aid. In order to reflect the current state of medical knowledge and to take medical progress into account, guidelines must be regularly reviewed and updated. The application of the AWMF regulations should be the basis for the development of high quality oncological guidelines. Since guidelines are an important instrument of quality assurance and quality management in oncology, they should be introduced into everyday care in a targeted and sustainable manner. Thus, active implementation measures and also evaluation programs are an important part of the promotion of the German Guideline Program in Oncology. The aim of the program is to create professional and medium-term financially secure conditions for the development and provision of high-quality guidelines in Germany. This is because these high-quality guidelines not only serve the structured transfer of knowledge but can also find their place in shaping the structures of the healthcare system. Mention should be made here of evidence-based guidelines as a basis for creating and updating disease management programs or the use of quality indicators extracted from guidelines as part of the certification of organ tumor centers.

1.8 Additional documents relating to this Guideline

This document is the long version of the S3 Guideline on endometrial cancer. In addition to the long version, there will be the following supplementary documents to this Guideline:

- Guideline Report on the update of the Guideline
- Document with evidence tables for the Guideline
- Short version of the Guideline
- Patient Guideline
- English translation

All guideline documents can be accessed via the following pages:

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

Documents on previous versions of the Guideline are available in the guideline archive at: https://www.leitlinienprogramm-onkologie.de/leitlinien/endometriumkarzinom/.

The Guideline is also included in the German Guideline Program in Oncology app.

For more information, visit: https://www.leitlinienprogramm-onkologie.de/app/

1.9 Composition of the Guideline Group

1.9.1 Guideline coordination

The Guideline is published by the German Guideline Program in Oncology (GGPO) of the German Cancer Society (DKG). The lead professional society is the German Society of Gynecology and Obstetrics (DGGG). The Guideline is part of the German Guideline Program in Oncology (GGPO) supported by the German Cancer Society (DKG) together with the German Cancer Aid (DKH) and the AWMF. The coordinator was appointed by the lead society (DGGG). He determined the composition and distribution of tasks of the Guideline steering group as follows:

Coordinator: Prof. Dr. Günter Emons; Göttingen
Co-coordinator: Prof. Dr. Eric Steiner; Rüsselsheim
Editors: Saskia Erdogan, M.A.; Göttingen, Sylvia Weber; Göttingen

The tasks of the steering group included contact and feedback with the participating professional societies and organizations, implementing the methodological guidelines, preparation of a project plan, management of the financial resources, support of the content-related work of the experts, compilation and editing of the texts prepared by the experts and working groups, and documentation of a Guideline report.

Steering group

Prof. Dr. Günter Emons; Göttingen
Prof. Dr. Eric Steiner; Rüsselsheim
Kerstin Paradies; Hamburg
Dr. Christoph Uleer; Hildesheim
Prof. Dr. Dirk Vordermark; Halle/Saale

1.9.2 Involved Professional Societies and Organizations

Table 1: Participating professional associations and organizations (alphabetical)

Participating professional associations and organizations (alphabetical)	Representative(s)
AG Endoskopische Gynäkologie der DGGG	Prof. Dr. Ingo Runnebaum Prof. Dr. Uwe Ulrich
AGO-Studiengruppe	Prof. Dr. Stefan Kommoss
Arbeitsgemeinschaft Deutscher Tumorzentren e.V. (ADT)	Prof. Dr. Olaf Ortmann
Arbeitsgemeinschaft Gynäkologische Onkologie der DGGG und DKG (AGO)	Prof. Dr. Peter Mallmann Prof. Dr. Ingolf Juhasz-Böss
Arbeitsgemeinschaft Konferenz Onkologische Kranken- und Kinderkrankenpflege in der DKG (KOK)	Kerstin Paradies
Arbeitsgemeinschaft Palliativmedizin der Deutschen Krebsgesellschaft e. V. (APM)	Prof. Dr. Birgit van Oorschot Dr. Joan E. Panke
Arbeitsgemeinschaft Prävention und integrative Medizin in der Onkologie der Deutschen Krebsgesellschaft (PRiO)	Prof. Dr. Volker Hanf Prof. Dr. Oliver Micke
Arbeitsgemeinschaft Radiologische Onkologie (ARO)	Prof. Dr. Stefan Höcht Prof. Dr. Vratislav Strnad
Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie (AGSMO)	Prof. Dr. Petra Feyer

Participating professional associations and organizations (alphabetical)	Representative(s)
Arbeitsgemeinschaft erbliche Tumorerkrankungen in der DKG (AET)	Prof. Dr. Stefan Aretz Prof. Dr. Rita Schmutzler
Arbeitsgemeinschaft für Psychoonkologie in der DKG (PSO)	Prof.Dr. Joachim Weis PD Dr. Ute Goerling
Arbeitsgemeinschaft für onkologische Rehabilitation und Sozialmedizin (AGORS)	Dr. Timm Dauelsberg
Arbeitsgemeinschaft internistische Onkologie der DKG e.V. (AIO)	Dr. Volker Hagen Prof. Dr. Anne Letsch
Berufsverband Niedergelassener und ambulant tätiger Gynäkologischer Onkologen in Deutschland e.V.	Dr. Christoph Uleer
Berufsverband der Deutschen Strahlentherapeuten e. V. (BVDST)	Prof. Dr. Peter Niehoff Prof. Dr. Franz-Josef Prott
Berufsverband der Frauenärzte (BVF)	Dr. Wolfgang Cremer
Beteiligte Fachexperten (ohne Stimmrecht)	PD Dr. Marco J. Battista PD Dr. Dr. Gerd J. Bauerschmitz Prof. Dr. Markus Fleisch Prof. Dr. Sigurd Lax
Beteiligte Fachexperten (ohne Stimmrecht)	Prof. Dr. Clemens Tempfer Dr. Barbara Zimmer
Bundesarbeitsgemeinschaft Leitender Ärztinnen und Ärzte in der Frauenheilkunde und Geburtshilfe (BLFG)	Prof. Dr. Michael Friedrich
Bundesverband Deutscher Pathologen e.V. (BDP)	Prof. Dr. Lars-Christian Horn Prof. Dr. Doris Mayr
Deutsche Gesellschaft für Allgemein- u. Viszeralchirurgie (DGAV)	Prof. Dr. Jan Langrehr
Deutsche Gesellschaft für Endokrinologie (DGE) e.V.	Prof. Dr. Matthias W. Beckmann PD Dr. Sebastian Jud
Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V. (DGGG)	Prof. Dr. Sara Y. Brucker

Participating professional associations and organizations (alphabetical)	Representative(s)
Deutsche Gesellschaft für Gynäkologische Endokrinologie und Fortpflanzungsmedizin e.V.	Prof. Dr. Ludwig Kiesel Dr. Ralf Witteler
Deutsche Gesellschaft für Humangenetik (GfH)	Dr. Verena Steinke-Lange Dr. Nils Rahner
Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie e.V. (DGHO)	Prof. Dr. Anne Letsch Dr. Volker Hagen
Deutsche Gesellschaft für Nuklearmedizin e.V. (DGN)	Prof. Dr. Michael J. Reinhardt Prof. Dr. Michael Kreißl
Deutsche Gesellschaft für Palliativmedizin e.V. (DGP)	Prof. Dr. Anne Letsch
Deutsche Gesellschaft für Pathologie e.V. (DGP)	Prof. Dr. Lars-Christian Horn Prof. Dr. Doris Mayr
Deutsche Gesellschaft für Radioonkologie e.V. (DEGRO)	Prof. Dr. Dirk Vordermark Prof. Dr. Katja Lindel
Deutsche Gesellschaft für Ultraschall in der Medizin e.V. (DEGUM)	Prof. Dr. Dieter Grab Prof. Dr. Werner Bader Prof. Dr. Heinrich Prömpeler
Deutsche Menopause Gesellschaft (DMG)	Prof. Dr. Thomas Römer Prof. Dr. Joseph Neulen
Deutsche Röntgengesellschaft e.V.	Dr. Theresa Mokry
Frauenselbsthilfe Krebs e.V. (FSH)	Heidemarie Haase Miriam Schallenberg
Kompetenz-Centrum Onkologie (KCO)	Dr. Barbara Zimmer Ilka Luckas
Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO)	Prof. Dr. Werner Lichtenegger Prof. Dr. Alexander Mustea
Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe (SGGG)	Prof. Dr. Michael D. Mueller PD Dr. Edward Wight
Semi-Colon, Familienhilfe Darmkrebs e.V.	Simone Widhalm Nicola Reents

Participating professional associations and organizations (alphabetical)	Representative(s)
Zentralverband der Physiotherapeuten/ Krankengymnasten (ZVK)	Ulla Henscher Reina Tholen
Österreichische Gesellschaft für Gynäkologie und Geburtshilfe (OEGGG)	Prof. Dr. Alain-Gustave Zeimet Prof. Dr. Edgar Petru

Consulting

Physicians from the Competence Center for Oncology of the Medical Services (Medizinischer Dienst der Krankenkassen) were involved in an advisory capacity in the development of this S3 Guideline on individual aspects with sociomedical relevance.

In addition, the following professional societies were consulted for the guideline process:

- Working Group of Oncological Pathology of the DKG; this is represented by the DGP (German Society of Pathology).
- German Society for Surgery (DGCH); however, they have not nominated a representative.
- German Society for General Medicine and Family Medicine (DEGAM); however, they have not appointed a representative.
- German Society of Urology (DGU); however, they have not nominated a representative.

1.9.3 Patient Involvement

The representatives of the patient organizations Frauenselbsthilfe Krebs e. V., Heidemarie Haase and Miriam Schallenberg, and Semi Colon, Simone Widhalm and Nicola Reents were involved in the consensuses during the preparation of the Guideline.

1.9.4 Methodological Support

By the German Guideline Program in Oncology and the Association of the Scientific Medical Societies e.V.:

- Dr. Monika Nothacker, MPH (AWMF Institute for Medical Knowledge Management (AWMF-IMWi).
- Dr. Susanne Blödt, MScPH (AWMF Institute for Medical Knowledge Management (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
- Dipl. Biologe Gregor Wenzel, Office of the German Guideline Program in Oncology c/o DKG

By external contractors:

- Dr. Paul Freudenberger (Berlin) and Dr. Nadine Steubesand (Kiel) User Group of Clinical Guideline Services GmbH; in the systematic literature search and subsequent evidence assessment including preparation of the evidence tables for the methods report.
- PD Dr. Simone Wesselmann, MBA; German Cancer Society - Certification Division (coordination in the preparation of the quality indicators).

1.10 Abbreviations Used

Table 2: Abbreviations Used

Abbreviation	Explanation
AB	General population
ACR	American College of Radiology
AEH	Atypical endometrial hyperplasia
AET	Working Group on Hereditary Tumor Diseases of the DKG
AG	Working group
AHB	Follow-up treatment
AK	Antibody
ASCO	American Society of Clinical Oncology
ASTEC	A Study in the Treatment of Endometrial Cancer
AUC	Area Under the Curve
BWS	Thoracic spine
CAP	College of American Pathologists
CEB	Basel Institute for Clinical Epidemiology & Biostatistics of the University of Basel
CEBM	Centre for Evidence-Based Medicine (Oxford, UK)
CEE	conjugated equine estrogens (engl.: conjugated equine estrogens)
CGS User Group	Clinical Guidelines Services User Group, Kiel + Berlin
CI (eng)	Confidence Interval
COEIN	Coagulopathy (AUB-C = Coagulopathy), ovulatory dysfunction (AUB-O), endometrial pathology (AUB-E), iatrogenic (AUB-I), unclassified (AUB-N).
CoI	Conflict of Interest
COS	(Engl. controlled ovarian stimulation) controlled ovarian stimulation
CS	Cowden Syndrome
CT	Computed tomography

Abbreviation	Explanation
DELBI	German guideline assessment tool
DELPHI	Multi-stage survey process
DFS	disease-free survival (DFS)
DKG	German Cancer Society
DKH	German Cancer Aid Foundation
EB	Endometrial biopsy
EBRT	External Beam Radiotherapy = percutaneous radiotherapy
EC	Endometrial Cancer
EK	Expert consensus
EORTC	European Organisation for Research and Treatment of Cancer
EPIC	The European Prospective Investigation into Cancer and Nutrition
ETS	hereditary tumor syndrome
FDG	Fluorodeoxyglucose
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
FKS	Case-control study(s)
FSH	Follicle stimulating hormone
G-CSF (eng)	granulocyte colony-stimulating factor
GGPO	German Guideline Program in Oncology
G-I-N	Guidelines International Network
GenDG	Gene Diagnostics Act
GnRH	Gonadotropin releasing hormones
GOG	Gynecologic Oncology Group
Gy	Gray
HADS	Hospital Anxiety and Depression Scale

Abbreviation	Explanation
HE4	human epididymis protein 4
HNPCC (eng)	Hereditary Non-polyposis Colorectal Carcinoma Syndrome (hereditary colorectal carcinoma without polyposis)
HR	Hazard ratio
HRT	Hormone Replacement Therapy
HSK	Hysteroscopy
HWS	Cervical spine
ICD (eng)	International Classification of Diseases, international classification of diseases
ICF	International Classification of Functioning, Disability and Health
IHC	Immunohistochemical examination
IKNL	Integraal Kankercentrum Nederland
IQWiG	Institute for Quality and Efficiency in Health Care
IR	incidence ratio (German: Inzidenz-Ratio, Incidenceverhältnis)
KRK	Colorectal carcinoma
KS	Cohort study(s)
LA	Guideline Adaptation
LDR	Low Dose Rate
LFS	Li-Fraumeni Syndrome
LK	Lymph nodes
LNE	Lymphonodectomy/ lymphadenectomy
LR	likelihood ratio (Engl.: probability ratio)
LS	Lynch syndrome
LVSI	lymphovascular space invasion (Engl.: lymphatic vessel invasion)
LZR	Lifetime risk

Abbreviation	Explanation
MA	Meta-analysis
MAP	MUTYH-associated polyposis
MDR	medium dosed rate (Engl.: average dosing rate)
MGA	Megestrol acetate
MMMT	malignant mullerian mixed tumor/ malignant mesodermal mixed tumor: carcinosarcoma
MPA	Medroxyprogesterone acetate
MRT / MR	Magnetic resonance imaging
MSA	Microsatellite analysis
MSI	Microsatellite instability
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Database (USA)
PALM	Polyp (AUB-P), Adenomyosis (AUB-A), Leiomyoma (AUB-L), Malignancy and Hyperplasia (AUB-M).
PCOS	Polycystic Ovary Syndrome = Stein-Leventhal Syndrome
pCR	pathological complete remission (Engl.: pathological complete remission)
PHTS	PTEN hamartoma tumor syndrome
PMB	postmenopausal bleeding
PPV	Positive Predictive Value
QoL	Quality of Life
RCT (eng)	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
RR	Relative risk
SEER	Surveillance, Epidemiology, and End Results (USA).
SLNB	Sentinel lymph node biopsy (sentinel lymph node biopsy)

Abbreviation	Explanation
TVS	Transvaginal sonography
WHR	waist to hip ratio (tt.: ratio waist to hip)

2 Introduction

2.1 Scope and Purpose

2.1.1 Objective and Key Questions

The goal orientation of the interdisciplinary S3 Guideline on Endometrial Carcinoma includes informing and advising women about diagnostics (clinical, imaging or surgical), the various therapeutic options (surgery, radiation, drug treatment) and, in particular, their temporal and modular combinations in the different stages of the disease, i.e. precancerous, early stages, advanced stages and palliative situation. In addition, the treatment of rare histological subtypes as well as hereditary variants is addressed.

The possibilities of preserving reproductive capacity while maintaining oncological safety, rehabilitation measures, aftercare, palliative therapy and psycho-oncological support will be discussed. This is necessary in the case of endometrial carcinoma, which changes the sexual life of women to a relevant extent, especially after the application of radiation. The recommendations are addressed to treating physicians, nursing professionals and medical partners involved in the treatment of patients with endometrial carcinoma.

By reviewing the evidence, the optimal early detection and diagnosis of endometrial carcinoma and its precursors are elicited. There is potential here to improve early detection through consistent attention to appropriate symptoms. At the same time, there is very likely great potential to reduce unnecessary alarm and costs by avoiding diagnostic measures that do not make sense.

Evidence-based risk-adapted therapy can avoid unnecessary radical surgery and non-meaningful adjuvant radiotherapy and/or chemotherapy in women with low-risk endometrial cancer. On the one hand, this significantly reduces therapy-induced morbidity and increases the patients' quality of life. On the other hand, unnecessary costs are avoided. For women with endometrial carcinoma at high risk of recurrence the Guideline defines the optimal surgical radicality as well as the adjuvant chemotherapy and/or adjuvant radiotherapy that may be required. The evidence-based optimal use of the different therapeutic modalities should improve survival and quality of life of these patients. The S3 Guideline on Endometrial Cancer is intended to provide a basis for the work of certified gynecologic cancer centers. The quality indicators based on this Guideline are incorporated into the certification process of these centers.

2.1.2 Target Audience

The interdisciplinary Guideline on Endometrial Carcinoma (ICD-10 C54.1 [1]) covers patients with precancerous lesions (ICD-10 N85.1 [1]) and invasive carcinomas of the endometrium. The recommendations of the Guideline are aimed at physicians and healthcare professionals involved in the care of patients with endometrial carcinoma. These are primarily gynecologists, gynecologic oncologists, radiologists, pathologists, radiation oncologists, medical oncologists, psycho-oncologists, palliative care physicians, physical therapists, nurses, general practitioners, and urologists.

The Guideline, in particular the patient version, is also aimed at all women suffering from endometrial carcinoma and their relatives. The scope of application of the Guideline includes the outpatient and inpatient care sector: detection of early symptoms and follow-up care is largely the work of colleagues in private practice, while surgical treatment takes place in the inpatient sector. Radiation therapy and systemic drug therapy take place both in the area of the practicing colleagues and in the corresponding outpatient departments of larger hospitals.

The Guideline also targets:

- Medical-scientific professional societies and professional associations;
- Women's advocacy groups (women's health organizations, patient and self-help organizations);
- Quality assurance institutions and projects at the federal and state level (e.g. Working Group of German Tumor Centers, etc.);
- Health policy institutions and decision-makers at the federal and state levels;
- Payers.

2.1.3 Validity and Update Process

Version 2.0 of the S3 Guideline is valid until the next update; the validity period is set to 5 years. Regular updates are planned; in case of urgent need for changes, these will be published separately. Comments and suggestions for the update process are explicitly welcome and can be addressed to the guideline secretariat: endometrium@leitlinienprogramm-onkologie.de.

2.2 Methodology

The methodological approach used in the preparation of this Guideline is described in the Guideline report. This is freely available on the Internet on the pages of the German Guideline Program in Oncology and the pages of the AWMF.

2.2.1 Levels of Evidence (LoE)

In this Guideline, the Oxford Centre for Evidence-Based Medicine's 2011 version of the scheme was used to classify the evidence.

Table 1: Levels of Evidence according to Oxford Centre for Evidence-Based Medicine 2011

Question	Level 1*	Level 2*	Level 3*	Level 4*	Level 5
How widespread is the problem?	Local and current random sample or census (complete survey).	Systematic review of surveys that can be applied to local circumstances**	Local survey that is not based on a random sample**	Case series**	Not applicable
Is this diagnostic or controlling test accurate? (Diagnostic)	Systematic review of cross-sectional studies with reference standard applied throughout and blinding	Single cross-sectional study with reference standard applied throughout and blinding	Non-consecutive*** study or study without applied reference standard**	Case-control study or study with inappropriate or non-independent reference standard**	Expert opinion based on pathophysiological considerations
What would happen if we did not apply therapy? (prognosis)	Expert opinion based on pathophysiological considerations.	Single cohort study of patients in the early stages of the disease (inception cohort study)	Cohort study or control arm of a randomized trial*.	Case series or case-control study or a prognostic cohort study with low methodological quality1**	Not applicable
Does this approach help? (use of the intervention)	Systematic review of randomized trials or N-of-1 studies2	Randomized trial or observational study with dramatic effects	Controlled cohort study/follow-up study3**	Case series or case-control studies or studies with historical controls**	Expert opinion based on pathophysiological considerations.

Question	Level 1*	Level 2*	Level 3*	Level 4*	Level 5
What are common side effects? (harm of intervention)	Systematic review of either randomized trials or embedded case-control studies4. Or N-of-1 study with patients matching the research question or observational study with dramatic effects	Randomized trial or (exceptionally) observational study with dramatic effects	Controlled cohort study/follow-up (post-marketing surveillance) study, with sufficient number of cases to identify a common side effect. If long-term side effects are to be recorded, the follow-up must be sufficient**.	Case series or case-control studies or studies with historical controls**.	Expert opinion based on pathophysiological considerations.
What are rare side effects? (harm of the intervention)	Systematic review of randomized trials or N-of-1 studies.	Randomized trial or (exceptionally) observational study with dramatic effects	Controlled cohort study/follow-up (post-marketing surveillance) study, with sufficient number of cases to identify a common side effect. If long-term side effects are to be recorded, the follow-up must be sufficient**.	Case series or case-control studies or studies with historical controls**.	Expert opinion based on pathophysiological considerations
Is this screening test useful? (screening)	Systematic review of randomized studies	Randomized trial		Case series or case-control studies or studies with historical controls**	Expert opinion based on pathophysiological considerations

*Level may be downgraded because of study quality, extended confidence intervals (imprecise effect estimates), inconsistencies between studies, or because the absolute effect value is very small, as well as lack of transferability (study question does not correspond to the clinically relevant question). An upgrade of the evidence level is possible in case of large or very large effects.** As a general rule, a systematic review is always better than a single study.

Question	Level 1*	Level 2*	Level 3*	Level 4*	Level 5

*** Consecutive inclusion = patients are continuously recruited.
1 The STROBE statement, among others, can be used for quality assessment: http://www.strobe-statement.org/index.php?id=strobe-aims.
2 Single-patient studies in which patients receive alternating intervention and control intervention.
3 Follow-up study of a population from a completed RCT.
4 Study in which cases and controls are drawn from an ongoing cohort study.
Translation of the original English text by Dr. M. Nothacker, MPH (AMFW); Dr. M. Follmann, MPH, MSc (OL) and Dipl.-Soz.Wiss T. Langer (OL).

Source: Howick, J., et al. The 2011 Oxford CEBM Levels of Evidence (Introductory Document). 2011; Available from: http://www.cebm.net/index.aspx?o=5653.

2.2.2 Grades of Recommendation (GoR)

The methodology of the German Guideline Program in Oncology provides for the assignment of grades of recommendation by the Guideline authors within the framework of a formal consensus process. Accordingly, moderated nominal group processes or structured consensus conferences were conducted by the AWMF [2]. Within these processes, the recommendations were formally voted on by the voting mandate holders (see Chapter 1.9.2). The results of the respective votes (consensus strength) are assigned to the recommendations according to the categories in Table 6.

In the Guideline, the level of evidence of the underlying studies and, in the case of recommendations, the strength of the recommendation (= degree of recommendation) are shown for all evidence-based statements and recommendations. With regard to the strength of the recommendation, three grades of recommendation are distinguished in this Guideline (see table below), which are also reflected in the wording of the recommendations in each case.

The degrees of recommendation express the degree of certainty that the expected benefit of the intervention outweighs the possible harm (net benefit) and that the expected positive effects reach a level that is relevant for patients. In the case of negative recommendations (should not), safety is correspondingly expressed in terms of a lack of benefit or potential harm. In the graduation of recommendations, in addition to the results of the underlying studies –, the clinical relevance of the effectiveness measures investigated in the studies, the observed effect sizes, the consistency of the study results –, the applicability of the study results to the patient target group, the feasibility of implementation in everyday medical practice or ethical obligations, and patient preferences are taken into account [3], [2].

Recommendations are thematically-related, action-guiding core sentences of the Guideline, which are developed by the Guideline Group and agreed upon in formal consensus procedures.

Table 2: Scheme of recommendation grading

Recommendation Grade	Description	Expression
A	Strong recommendation	shall
B	Recommendation	should
0	Recommendation open	can

Table 3: **Determinations regarding consensus strength**

Consensus strength	Percentage consensus
Strong consensus	> 95% of those voting
Consensus	> 75-95% of the voters
Majority consensus	> 50-75% of the voters
Dissent	< 50% of the voters

2.2.3 Statements

Statements are presentations or explanations of specific facts or issues without an immediate call to action. They are adopted in accordance with the procedure for recommendations as part of a formal consensus process and can be based either on study results or on expert opinions.

2.2.4 Expert Consensus (EC)

Recommendations for which no systematic literature search was performed are referred to as expert consensus (EC). As a rule, these recommendations address procedures of good clinical practice. No systematic literature search was performed for these recommendations. The studies cited in the background texts were selected by the experts involved. No symbols or letters were used for the graduation of the expert consensus; the strength of the consensus point results from the wording used (shall/should/can) according to the gradation in the table for the gradation of recommendations.

2.2.5 Independence and Disclosure of Possible Conflicts of Interest

German Cancer Aid provided the financial resources through the German Guideline Program in Oncology (OL). These funds were used for personnel costs, office supplies, literature procurement, and the consensus conferences. Working group meetings and conferences were held entirely online in 2020 and 2021. The Guideline was developed with editorial independence from the funding organization. All members provided a written declaration of any conflicts of interest during the guideline process. The Guideline group was asked to review the declarations of conflicts of interest again before the first online consensus conference (March 8, 2021) and to provide any corrections or additions to the Guideline secretariat. The disclosed conflicts of interest can be found in the Guideline Report for this Guideline.

Obtaining declarations of conflicts ofinterest

Declarations of conflicts ofinterest were obtained from all Guideline group members at the beginning of the Guideline project. The AWMF template “Declaration of Conflicts of Interest” (see Guideline Report) was used for this purpose. All funding projects such as DFG and BMBF were declared. The Guideline coordinator's declaration of interest was forwarded to the OL Office for review, and the others were

reviewed for thematic relevance and relevance by the Guideline coordinator. The AWMF classification of low, moderate, and high was used to assess the relevance of the conflicts of interest. Conflicts of interest of moderate relevance were seen as connections to industry-sponsored studies, third-party funded projects, and advisory boards that demonstrate a thematic relation to endometrial cancer. High relevance was seen for ownership interests (patents, shareholdings, etc.). The assessment revealed only conflicts of interest rated as “low” or “moderate”.

Dealing with conflicts of interest

Conflicts of interest of moderate relevance resulted in abstention from voting on the corresponding recommendations. In some cases, this was implemented electronically in such a way that all persons could vote, but subgroup analyses were subsequently performed with regard to persons with and without a moderate conflict of interest (outcome with participation of all vs. outcome with exclusion of persons with conflict of interest). Alternatively, however, abstention due to conflict of interest could be documented separately.

At the first consensus meeting on March 8, 2021 (videoconference), it was unanimously agreed that mandate holders who had led studies on “endometrial carcinoma” should not vote on the corresponding statements and recommendations. However, they could provide documents and further information and participate in the discussion. Third-party funding from industry and advisory boards should be indicated. The company name (third-party funding) should be mentioned. If third-party funding is disclosed, it should be made transparent from which company it came and on what it was spent. Individuals who have received industry-sponsored third-party funding related to endometrial cancer or who are members of an advisory board related to this indication should not vote on the statements and recommendations affected by this or subgroup analyses were performed here.

At this point, we would like to thank all collaborators for their exclusively voluntary work on the project!

3 Epidemiology and risk factors, prevention of endometrial cancer

3.1 Epidemiology and risk factors

3.1.1 Age

3.1	Evidence-based statement	checked 2022
LoE 1	The risk of endometrial cancer increases with age.	
	[4]	
	Strong Consensus	

Background

Endometrial carcinoma (EC) (ICD-10 C54.1 [1]) ranks 7th among malignancies in women worldwide, with an annual incidence of 142,000 new cases. Regional variations in incidence are found, with North America and Western European countries leading the way with an age-standardized annual incidence of EC between 9.9 and 15.0 per 100,000 women. The cumulative risk of developing EC by age 75 is reported to be 1.7% in the United States, the country with the highest rate of disease.

Annually, 42,000 women worldwide die from EC. These cases account for 1.9% of all cancer-related deaths of women. The median 5-year survival rate in the highest incidence countries is reported to range from 72% in Europe to 84% in the United States.

Approximately 11,000 new cases are diagnosed annually in Germany. EC is the fifth most common malignancy in women, accounting for 4.8%, and the most common pelvic malignancy. The incidence of EC increases steadily with age until 70 years of age. Endometrial carcinomas are most commonly diagnosed between the ages of 70 and 84. Thereafter, there is a decline in incidence. The lifetime risk of developing EC in Germany is 1.9%. The median age at diagnosis of EC is 68 years [4].

Table 3: Overview of the most important epidemiological measures for Germany, ICD-10 C54-C55

	Women (2011)	Women (2012)	Women (forecast for 2022)
New cases	10,990	11,090	10,600
Crude morbidity rate *	26.5	26.6	25.7
Standardized disease rate *,**	16.2	16.5	15.1
Mean age of onset	69	68	-
Deaths	2,602	2,600	2,659
Crudemortality rate *	6.3	6.2	6.3
Standardized mortality rate *,**	3.0	3.0	3.0
Prevalence	45,700 after 5 years	83,300 after 10 years	
	after 5 years	after 10 years	
Absolute survival rate (2015-2016)****	70 (66-73)	57 (52-61)	
Relative survival rate (2015-2016)****	78 (75-82)	74 (69-79)	

* per 100,000 persons

** age-standardized according to old European population

*** median

**** in percent (lowest and highest value of the included federal states)

Source: Robert Koch Institute (ed.) and the Society of Epidemiological Cancer Registries in Germany (ed.), Cancer in Germany 2017/2018. 13th edition, Berlin, 2021.

3.1.2 Hormone replacement therapy (HRT) without progestin protection

3.2	Evidence-based statement	checked 2022
LoE **2**	Hormone replacement therapy with estrogens alone without progestin protection is a risk factor for the occurrence of endometrial cancer in non-hysterectomized women. The effect depends on the duration of use.	
	[5], [6], [7], [8], [9], [10], [11], [12]	
	Strong Consensus	

Background

In the development of hormone-dependent type I EC, long-term use of estrogens without progestin protection is considered an important risk factor. In the prospective Million Women cohort study, the relative risk (RR) versus no hormone replacement therapy was 1.45 (95% confidence interval [CI] 1.02–2.06) [13]. In a prospective cohort study of > 30,000 users, the relative risk was higher for estrogen monotherapy and was 2.7 (95%-CI 2.2–3.4) [14]. Nelson et al. [15] also report a similarly high relative risk of 2.3 (95%-CI 2.1–2.5) for estrogen monotherapy in a meta-analysis of 29 observational studies. This is also consistent with older data from Grady et al. [16]. In this meta-analysis, long-term estrogen therapy ≥ 10 years even resulted in a 9.5-fold increased risk of EC [16] (meta-analysis of 30 case-control and cohort studies; RR = 2.3 [95%-CI 2.1–2.5] for users versus nonusers; RR = 9.5 [95%-CI 7.4–12.3] for the subgroup of users ≥ 10 years).

Finally, the prospective cohort study by Allen et al. [17] of > 115,000 women also found a doubling of the risk of EC for users of estrogen monotherapy with intact uterine mucosa (HR = 2.52 [95%-CI 1.8–3.6]) [17].

Overall, the risk of EC appears to be significantly increased with estrogen therapy without progestin protection, and such therapy should therefore not be undertaken in non-hysterectomized women.

In a recent review of 31 studies and 21,306 women, 9 of 12 studies of estrogen monotherapy with a uterus found a significantly increased risk of EC with ORs/HRs ranging from 1.46 to 4.46 [5]. The EC risk was most pronounced for obese women.

For further assessment, also refer to the current S3 Guideline ‘Peri- and Post-menopause – Diagnostics and Interventions’ (as of January 2020) (https://www.awmf.org/uploads/tx_szleitlinien/015-062l_S3_HT_Peri-Postmenopause-Diagnostik-Interventionen_2020-01_1.pdf).

3.1.3 Combined estrogen-progestin therapy

3.1.3.1 Continuous combined estrogen-progestin therapy

3.3	Evidence-based statement	checked 2022
LoE 2	Continuous combined hormone replacement therapy with estrogens and synthetic progestins has no or a protective effect on endometrial cancer risk.	
	[18]	
	Strong Consensus	

3.4	Evidence-based statement	modified 2022
LoE 4	Using progesterone or dydrogesterone as part of combined hormone replacement therapy, an increase in the risk of developing endometrial cancer has been observed when used for more than 5 years.	
	[19], [20]	
	Strong Consensus	

3.5	Evidence-based statement	checked 2022
LoE 3	Sequential combined hormone replacement therapy may increase the risk of developing endometrial cancer. The effect depends on the duration, type and dose of progestin use.	
	[6], [7], [21], [22], [9], [10], [12]	
	Strong Consensus	

3.6	Evidence-based statement	modified 2022
LoE 3	No increase in endometrial cancer risk has been observed with the use of sequential combined hormone replacement therapy with a duration of use < 5 years and use of a synthetic progestin for at least 10 days per month.	
	[7], [22], [9], [10]	
	Strong Consensus	

Background

In women with uterus and intact uterine mucosa, the proliferative effect of estradiol and the resulting increased risk of EC can be antagonized by combination with a progestin. Whether this can fully compensate for the increased risk of EC depends on the duration of progestogen therapy (based on the number of days per month with progestogen use), the type of progestogen, the dose of estrogen, and the total duration of use of hormone replacement therapy.

In the prospective randomized Women's Health Initiative (WHI) trial, a significantly reduced risk of EC (HR 0.59 [95%-CI 0.40–0.88]) was observed with continuous-combination hormone replacement therapy with conjugated equine estrogens (0.625 mg CEE) and medroxyprogesterone acetate (2.5 mg MPA) as a progestin in the postintervention phase of the trial with 13 years of follow-up [23]. However, EC risk was not a primary study endpoint in the WHI trial.

In contrast, data from observational studies regarding the risk of EC with continuous combined hormone replacement therapy are inconsistent. For example, in the prospective Million Women Cohort Study [13], use of continuous-combined hormone replacement therapy was associated with a significantly reduced risk of EC (RR = 0.71 [95%-CI 0.6–0.9]), as was a case-control study of > 1800 long-term users [24], (OR = 0.37 [95%-CI 0.2–0.6]) and the European prospective cohort study EPIC [17], (HR = 0.24 [95%-CI 0.08–0.8]). In contrast, other studies found neither an increase nor a decrease in risk, such as a meta-analysis of 7 observational studies by Nelson et al. [15]. In contrast, studies of long-term use of continuous-combination hormone replacement therapy with >10 years of use documented a significant increase in risk of developing EC (OR = 2.1 [95%-CI 1.3–3.3]) [25].

However, further observational studies did not confirm an increase in risk even with longer durations of use of ≥ 5 years, ≥ 6 years, and > 10 years [5].

In a recent review of 31 studies and 21,306 women, 10 of 19 studies of continuous combined hormone replacement therapy with synthetic progestins found a significantly reduced risk of EC, with ORs/HRs ranging from 0.24 to 0.71 [5].

It is possible that the type of progestin used may influence EC risk. For example, the use of micronized progesterone or dydrogesterone as part of continuous combined HRT may result in inadequate endometrial protection. This is suggested by the results of the prospective E3N cohort study of > 65,000 French women assigned to continuous combined hormone replacement therapy ith natural progestogens such as micronized progesterone and dydrogesterone, a synthetic progestin that is structurally very similar to progesterone and is similarly termed retroprogesterone, show an increased risk of EC at > 5-year duration of use (for progesterone HR = 2.7 [95%-CI 1.9–3.8], for dydrogesterone HR = 1.7 [95%-CI: 1.06- 2.70]) [26].

The mean number of days of use per month was 22.5 for micronized progesterone and 23.5 for dydrogesterone. The authors conclude that the combination of estradiol with natural progestins such as progesterone and dydrogesterone is not sufficiently effective for endometrial protection even when used continuously. It should be noted that the number of days of progestin use was not recorded in this study. Furthermore, a duration of therapy < 5 years was not associated with an increased risk of EC.

In the prospective randomized five-arm PEPI study, the impact of 1) CEE 0.625 mg/day, 2) CEE 0.625 mg/day + MPA 10 mg/day for 12 days/month, 3) CEE 0.625 mg/day + MPA 2,5 mg/day, and 4) CEE 0.625 mg/day + oral micronized progesterone 200 mg/day for 12 days/month versus placebo in 596 postmenopausal women studied over a 3-year period [27]. In this study, rates of endometrial hyperplasia with or without atypia were not increased in all 3 combination arms compared with placebo. However, because of the low statistical power, with approximately 120 women per study arm, it cannot be concluded with certainty from the results of this study that a dose of oral micronized progesterone of 200 mg/day for at least 12 days per month is adequate for endometrial protection as part of combined hormone replacement therapy. Data from randomized trials of endometrial protection of vaginally administered micronized progesterone or lower doses than 200 mg/day of orally administered micronized progesterone are not available.

BMI represents another important influencing factor. In a meta-analysis of 9 observational studies, combined hormone replacement therapy reduced the increased risk of EC in obese women in all BMI categories studied (see table below) [28].

Table 4: Risk of endometrial cancer in relation to BMI and combined HRT use

BMI	RR	EC risk in non-users	EC risk in users
27	1.22 (1.19-1.24)	1.31 (95% CI 1.2-2.4)	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)

Source: [28]

Background

Sequential use of a progestogen is also used as part of combined hormone replacement therapy to reduce endometrial stimulation. In general, the number of days of progestin use per month correlates with the level of EC risk in terms of an inverse relation. However, for sequential combined hormone replacement therapy, the data are also inconsistent with respect to EC risk. For example, the aforementioned Million Women Cohort Study [13] and the meta-analysis by Nelson et al. [15] describe a neutral effect of sequential-combined hormone replacement therapy, i.e., no increase in EC risk. However, the study by Nelson et al. [15] was a systematic literature review and meta-analysis of 7 observational studies of the incidence of endometrial cancer in users of combined hormone replacement therapy, and no distinction was made between sequential and continuous hormone replacement therapy.

In contrast, Lacey et al. [14] (RR = 3.0 [95%-CI 2.0–4.6] for < 15 progestin use days/month) and Allen et al. [17] (HR = 1.52 [95%-CI 1.0–2.3] (progestin use days/month not reported) described a significant increase in risk, as did Razavi et al.

[25], for a shorter duration of use with < 10 progestogens per month (OR = 4.4 [95%-CI 1.7–11.2]).

In a recent review of 31 studies and 21,306 women, 6 of 12 studies of sequential combined hormone replacement therapy with synthetic progestins found a significantly increased risk of EC, with ORs/HRs ranging from 1.38 to 4.35 [5]. No increased risk of EC was found in the remaining 6 studies. The number of days of progestin use per month was a significant modulator of EC risk. A reduced risk of EC was observed only in a subgroup analysis of one study (< 5 years of use).

Also, in a Danish registry study of > 900,000 women, Morch et al. found an increased risk of EC for sequential combined estrogen-progestin therapy (RR 2.06; 95%-CI 1.88-2.27) [19], as did Sjögren et al. in a systematic review of 28 studies [22].

One reason for the heterogeneity of the study results is probably the different number of days the progestin was taken and the different types of progestins used. For example, in the aforementioned European prospective cohort study EPIC, an analysis of the risk of EC depending on the type of progestin used in the context of sequential hormone replacement therapy showed a significantly increased risk for micronized progesterone (HR = 2.42 [95%-CI 1.5–3.8]) but not for progesterone derivatives (HR = 1.23 [95%-CI 0.8–1.8]) and testosterone derivatives (HR = 1.09 [95%-CI 0.7–1.6]) [17]. As a caveat, the number of days of progestin use and the progesterone dose were not recorded in this study. For further assessment, reference is also made to the current S3 Guideline 'Peri- and Post-Menopause – Diagnostics and Interventions' (as of January 2020) (https://www.awmf.org/uploads/tx_szleitlinien/015-062l_S3_HT_Peri-Postmenopause-Diagnostik-Interventionen_2020-01_1.pdf).

Based on the published studies, the Guideline authors are of the opinion that sequential combined hormone replacement therapy with a duration of use < 5 years and using a synthetic progestogen can be considered safe with regard to the risk of EC.

3.1.4 Tamoxifen

3.7	Evidence-based statement	checked 2022
LoE **1**	Tamoxifen therapy is a risk factor for the occurrence of endometrial carcinoma. The effect depends on the duration of use.	
	[29], [30], [31], [32], [33]	
	Strong Consensus	

Background

Tamoxifen use is considered an established risk factor for the occurrence of EC. In a meta-analysis of 23 randomized trials, Braithwaite et al. [34] calculated a 2.7-fold increase in the relative risk of developing EC (RR = 2.7 [95%-CI 1.9–3.7]). Also, in a meta-analysis of three tamoxifen prevention trials, Nelson et al. [35] reached a similar

conclusion and quantified the relative risk increase over placebo as 2.13 (95%-CI 1.4–3.3).

A Cochrane Collaboration analysis of the effects and side effects of tamoxifen in women with hormone receptor-positive breast cancer indicates a doubling of EC risk in the case of 1 to 2 years of tamoxifen therapy and a quadrupling in the case of at least 5 years of tamoxifen therapy [36]. Al-Mubarak et al. [37] examined the impact of tamoxifen therapy >5 years versus 5 years of therapy and calculated a further doubling of EC risk in the case of prolonging tamoxifen therapy to 10 years (RR = 2.06 [95%-CI 1.6–2.6]). The number needed to harm, that is, the number of women who can be treated before a woman is harmed by therapy in terms of additional EC, was 89 in this analysis.

A recent review indicates that there is a 2- to 7-fold increased risk of EC with tamoxifen use of > 2 years, especially in women with pre-existing endometrial pathologies [38].

Tamoxifen-induced endometrial carcinomas have a higher proportion of type II carcinomas (8/34 [24%] versus 28/495 [6%]) [39]. With regard to weighing the therapeutic benefit of tamoxifen in adjuvant therapy of estrogen receptor-positive breast carcinoma and the increased risk of developing EC, reference is made to the interdisciplinary S3 Guideline 'Early detection, diagnosis, therapy and follow-up of breast carcinoma' (as of February 2020; AWMF registry number 032-045OL; https://www.awmf.org/uploads/tx_szleitlinien/032-045OLk_S3_Mammakarzinom_2020-02.pdf).

3.1.5 Oral contraceptives

3.8	Evidence-based statement	checked 2022
LoE 3	Oral contraceptives reduce the risk of developing endometrial cancer. The strength of the effect depends on the duration of use.	
	[40], [41], [42]	
	Strong Consensus	

Background

Use of oral contraceptives is uniformly associated in the literature with a reduced risk of developing EC. Numerous prospective and retrospective observational studies consistently describe a risk-reducing effect. Schlesselman et al. [43] analyzed 10 case-control studies in 1997 and calculated a risk-reducing effect dependent on duration of use (RR = 0.44 [95%-CI not reported in this paper]; RR = 0.33 and RR = 0.28 for 4, 8, and 12 years of use, respectively). Numerous recent studies reached a similar conclusion, such as Gorenoi et al. 2007 [44] (RR = 0.7 [95%-CI not reported in this paper]) and Gierisch et al. 2013 [45] (OR = 0.57 [95%-CI 0.4–0.8]). From data from the prospective EPIC study of > 300,000 pill users and control subjects, Dossus et al. 2010 [46] calculated a risk reduction of more than one-third (HR = 0.65 [95%-CI 0.6–

0.7]), with long-term pill use resulting in an even greater risk reduction (HR = 0.58 [95%-CI 0.4–0.8] for pill use ≥ 10 years versus ≤1 year).

A recent review of 4 case-control studies and 5 cohort studies involving 308,198 women and 3.9 million years of follow-up showed a risk reduction of about half (OR 0.57; 95%-CI 0.43-0.77) for women who had used or were using a pill [40].

The protective effect of the pill affects endometrial cancers and ovarian cancers, with the protective effect persisting until 30 years after discontinuation of the pill [47]. Other uterine malignancies such as uterine sarcomas occur as frequently in pill users as in non-users [47].

3.1.6 Ovarian stimulation therapy

3.9	Evidence-based statement	checked 2022
LoE **3**	Ovarian stimulation therapy increases endometrial cancer risk compared with population-based controls but not compared with infertile women.	
	[48], [49], [50]	
	Strong Consensus	

Background

Controlled ovarian stimulation using gonadotropins, clomiphene and selective estrogen receptor modulators (SERMs) is used to obtain oocytes in the context of assisted reproduction. Endometrial proliferation also occurs as part of these therapies. Case-control studies and cohort studies have reported an increased risk of EC in women after such therapies. Parazzini et al.[51] found a threefold increase in EC risk (OR = 3.26 [95%-CI 1.1–9.9]) in a case-control study of 1,362 women. However, Siristatidis et al. [52] demonstrated in a meta-analysis of 9 case-control studies that the increase in EC risk was detectable only when compared with population-based controls (RR = 2.04 [95%-CI 1.2–3.4]), but not when compared with infertile controls (RR = 0.45 [95%-CI 0.2–1.1]). Therefore, the reason for the EC risk associated with ovarian stimulation is likely due to the infertility itself rather than the infertility treatment. In a Cochrane meta-analysis, there was also no effect of stimulation treatment in 6 studies with subfertile women as controls while 15 studies with population-based controls showed an increased risk of EC after stimulation treatment [50]. Possibly the number of cycles and the dose of drugs used also play a role. In 5/15 studies in the Cochrane meta-analysis, only subfertile women were studied, and an association was seen between an increased risk of EC and a high number of stimulation cycles (> 7) or a high cumulative dose of clomiphene (> 2000 mg).

3.1.7 Tibolone

3.10	Evidence-based statement	checked 2022
LoE 3	An increased risk of developing endometrial cancer has been observed with tibolone.	
	[7], [53], [22], [9]	
	Strong Consensus	

Background

The synthetic steroid tibolone, a 19-testosterone derivative, has estrogenic, gestagenic and weak androgenic effects, especially via its active metabolites. Tibolone has been approved in Germany since 1999 for the treatment of menopausal symptoms resulting from the natural and iatrogenic onset of menopause. In the prospective Million Women cohort study, tibolone use versus no hormone replacement therapy was associated with a significantly increased risk of developing endometrial cancer (RR = 1.79 [95%-CI 1.4–2.2]) [13].

This increase in risk was confirmed in another prospective cohort study by Allen et al. [17], involving > 115,000 women (HR = 2.96 [95%-CI 1.7–5.3]). In a prospective randomized placebo-controlled study of 3,519 postmenopausal women with osteoporosis, use of 1.25 mg tibolone once daily for 3 years also resulted in a fourfold increase in the rate of vaginal bleeding (2.8% versus 10.8%), a doubling of the rate of endometrial hyperplasia, and a borderline significant increase in the risk of EC [54], (4 versus 0 cases; p = 0.06).

The review by Sjögren et al. (28 studies; systematic review) also showed an increased risk of EC for tibolone [22].

In the Cochrane meta-analysis by Formoso et al., an analysis of 8 RCTs showed no increase in EC risk compared with placebo (OR 2.04; 95%-CI 0.79-5.24), with only 21 EC cases occurring in the 8 included studies [55].

3.1.8 Other biological risk factors

3.11	Evidence-based statement	checked 2022
LoE **3**	Late menarche age and late age at birth of last child are associated with reduced risk, and late menopausal age is associated with increased risk of endometrial cancer.	
	[56], [57], [58]	
	Strong Consensus	

3.12	Evidence-based statement	checked 2022
LoE **3**	Diabetes mellitus, impaired glucose tolerance, metabolic syndrome, and polycystic ovary syndrome (PCOS) increase the risk of endometrial cancer.	
	[59], [60], [61], [62], [63], [64], [65], [66], [67], [68], [69], [70], [71], [72], [73]	
	Strong Consensus	

3.13	Evidence-based statement	checked 2022
LoE **3**	An elevated body mass index (BMI) increases the risk of developing endometrial cancer.	
	[74], [75], [76], [77], [78], [79]	
	Strong Consensus	

3.14	Evidence-based statement	modified 2022
LoE **3**	Hereditary predisposition in the context of Lynch syndrome or Cowden syndrome increases the risk of endometrial cancer.	
	[80], [81]	
	Strong Consensus	

Background

The association between EC risk and age at menarche and menopause and age at birth of last child is well established by epidemiologic studies. Specifically, late menarche age and late age at birth of last child reduce the risk of EC occurrence, whereas late menopausal age increases the risk. Setiawan et al. [82] calculated a relative risk reduction of 13% per 5-year increase in age at birth of last child in a meta-analysis of 17 case-control and cohort studies. In a prospective cohort study of > 121,000 women, the risk of EC was halved if the last child was born at age 40 or later. If menarche age was ≥15 years, the relative risk reduction was 34% (RR = 0.76 [95%-CI 0.5–0.9]). If age at menopause ≥ was 55 years, EC risk increased 1.53-fold (95%-CI 1.1–2.1) [83]. The large prospective cohort study EPIC with > 300,000 women came to similar conclusions [46]. In this study, the relative risk reduction at menarche age ≥ 15 years was 36% [RR = 0.64; 95%-CI 0.5–0.8]. A late menopausal age (≥ 55 years) doubled the risk (HR = 2.36 [95%-CI 1.7–3.2]).

Metabolic factors play an important role in the development of estrogen-dependent type I EC. The association between EC risk and metabolic diseases associated with impaired glucose tolerance is well established by epidemiological studies and has been known for decades. A number of systematic reviews and meta-analyses put the risk increase for diabetic women at a factor of 1.7 to 2.1 [84],[85], [86], [87], [88], [89]. However, whether cancer-specific mortality is also increased in diabetic women is controversial. Liao et al. [88] found significantly increased EC-specific mortality (RR = 1.32 [95%-CI 1.1–1.6]) in a meta-analysis of 23 cohort studies, although there was significant heterogeneity among the studies examined. Huang et al. [86] and Zhang et al. [87] failed to demonstrate this effect in a meta-analysis of 15 and 21 cohort studies, respectively.

Other parameters for impaired glucose tolerance, such as increased glycemic index and increased glycemic load, are also associated with increased risk of EC [90], [91], [92], [93]. The metabolic syndrome, characterized by the factors of abdominal obesity, hypertension, hypertriglyceridemia, and lowered HDL cholesterol, as well as increased glucose concentration in the blood or insulin resistance, also leads to an increase in the incidence of EC. In a large prospective cohort study of 290,000 women, the relative risk increase was 1.37 (95%-CI 1.3–1.5) [94]. Esposito et al. [95] give a relative risk of 1.61 (95%-CI 1.2–2.2) in a meta-analysis of 3 cohort studies.

Polycystic ovary syndrome (PCOS) also leads to impaired glucose tolerance in 50 to 80% of cases probably due to endocrine and metabolic disorders and/or genetic predisposition [96], [97]. In addition, anovulation results in reduced progestin exposure of the uterine mucosa. In women with PCOS, the risk of EC is significantly increased according to epidemiological studies. Retrospective cohort studies report an approximately 4-fold increased risk [98], [99]. Meta-analyses of a total of 14 case-control studies indicate a similar, although somewhat smaller, increase in risk (OR = 2.70 [95%-CI 1.0–7.3] to 4.05 [95%-CI 2.4–6.8]) [100], [101], [102].

Body mass index (BMI) level correlates linearly with EC risk. Ward et al. [103] calculated an 11% relative risk increase (95%-CI 1.09–1.13) in 6,905 women with hysterectomy per BMI step (+1). In a meta-analysis of 24 case-control and cohort studies, Crosbie et al. [28] report a 1.6-fold increase in risk (95%-CI 1.5–1.7) per 5 BMI steps. A similar result was found by Renehan et al. [104] (RR = 1.59 [95%-CI 1.5–1.7] per 5 BMI increments), based on a meta-analysis of 141 case-control and cohort studies). A BMI ≥ 30 doubles the risk of developing EC compared with normal weight individuals (BMI 18.5 to 24.9 as defined by the World Health Organization (WHO) [105], [106], [107].

The influence of ethnic factors on EC risk is not well established. Whether the increased proportion of Caucasians in collectives of women with EC is due to sociocultural or genetic factors is not known [107], [108].

Genetic factors may promote the development of EC. A very high lifetime risk of developing EC, as well as a broad spectrum of other malignancies, exists in several monogenic-hereditary tumor syndromes based on specific germline mutations, notably Lynch syndrome (HNPCC) (ICD-10 C18.9) [1], and Cowden syndrome (ICD-10 Q89.8) [1], or PTEN hamartoma tumor syndrome (see Chapter 10 "Hereditary endometrial carcinomas") [80]. Regardless of the proven carrier of specific germline mutations, a conspicuous family history increases the risk of developing EC. In a family constellation with at least one first-degree relative with EC, the risk increases almost twofold. In a meta-analysis of 16 case-control studies, Win et al. [109] calculated a relative risk of 1.82 (95%-CI 1.7–1.9) in the presence of a first-degree relative with EC and of 1.17 (95%-CI 1.0–1.3) in the presence of a first-degree relative with colon cancer. In contrast, a prominent family history of breast carcinoma, ovarian carcinoma, or cervical carcinoma was not associated with an increased risk of EC.

In an analysis of the US SEER database, a significantly increased risk of metachronous development of EC was found among 289,933 breast cancer survivors. This increased risk was independent of hormone receptor type and therefore cannot be explained by tamoxifen use alone [110]. Therefore, a positive history regarding breast carcinoma may also be a risk factor for the development of EC.

Dietary influences play an important role in carcinogenesis. Numerous dietary influencing factors have also been identified for EC in epidemiological studies. Although no clearly defined diet for EC prevention can be recommended based on the available data and the lack of dietary intervention studies, indications of which dietary components are more likely to be beneficial and which are more likely to be detrimental emerge from the study results. Bandera et al. [111] examined the proportion of dietary fiber in 7 case-control studies and calculated a risk reduction for developing EC of 18% (RR = 0.82; 95%-CI 0.8–0.9) per 5 grams dietary fiber/1000 kcal diet. A high proportion of soy in the diet is also associated with a reduced risk of EC (meta-analysis of 3 case-control and cohort studies; RR = 0.7 [95%-CI 0.6–0.9]) [112]. A multiethnic, prospective cohort study with > 46,000 participants examined the proportion of phytoestrogens in the diets of postmenopausal women and identified high isoflavone, daidzein and genistein levels as protective factors [113]. Other factors associated with reduced EC risk identified in meta-analyses of case-control studies include high beta-carotene from dietary sources [114], high vitamin C and vitamin E from dietary sources [114], and low total fat [111], and red meat [111]. Avoidance of sugary beverages ("soft drinks") was also associated with reduced risk of type I EC in the prospective cohort study "Iowa Women's Health Study" [115]. As a caveat, quantification of specific dietary details in these studies was collected using questionnaires for retrospective assessment of dietary components. Thus, there is a considerable risk of bias.

Coffee and tea consumption were identified as further influencing factors with a partially unexplained biological background that are associated with a reduced risk of EC. For reasons of space and not entirely clarified relevance, statements and recommendations were not made.

<u>On the reduced risk of EC by coffee consumption:</u>

[116], [117], (RR = 0.74 [95%-CI 0.6–0.8]; meta-analysis of 4 cohort studies;

[117]; RR = 0.71 [95%-CI 0.6–0.8]; meta-analysis of 16 case-control and cohort studies;

[118]; RR = 0.80 [95%-CI 0.7–0.9]; meta-analysis of 9 case-control and cohort studies;

[119]; RR = 0.65 [95%-CI 0.5–0.9]; prospective cohort study).

On the reduced risk of EC by tea consumption:

[120]; RR 0.85 [95%-CI 0.8–0.9]; meta-analysis of 7 case-control and cohort studies.

The following also lead to reduced EC risk:

Breastfeeding: [121]; RR 0.76 [95%-CI 0.59–0.98]; meta-analysis of 11 case-control studies and 3 cohort studies.

Calcium supplements: [122]; RR = 0.62 [95%-CI 0.4–0.9]; meta-analysis of 2 case-control studies.

Acetylsalicylic acid (ASA): [123]; RR = 0.78 [95%-CI 0.6–0.9]; meta-analysis of 9 case-control and cohort studies identified.

Cigarette smoking: Cigarette smoking is also associated with reduced endometrial cancer risk, particularly in postmenopausal smokers [124]: RR = 0.81 (95%-CI 0.7–0.9) for smokers versus non-smokers; RR = 0.71 (95%-CI 0.7–0.8) for postmenopausal smokers versus non-smokers; meta-analysis of 34 case-control and cohort studies.

Risk increase due to night work: In contrast to the above risk-reducing factors, night work is a risk factor for the development of EC. Night work was associated with a significantly increased risk of EC in a prospective cohort study [125]; RR = 1.47 [95%-CI 1.0–1.1]).

In a recent review of 171 published meta-analyses on a total of 53 risk factors for developing EC, BMI, waist-to-hip ratio and parity were found to be the strongest risk factors for developing EC [126].

3.2 Risk-reducing factors

3.15	Evidence-based statement	checked 2022
LoE 3	Physical activity is associated with a reduced risk of endometrial cancer.	
	[127], [128], [129], [130], [131], [132], [133]	
	Strong Consensus	

3.16	Evidence-based statement	checked 2022
LoE 3	The use of intrauterine devices (copper IUD or levonorgestrel IUD used therapeutically) is associated with a reduced risk of endometrial cancer.	
	[134], [135]	
	Strong Consensus	

Background

Epidemiological data, physiological considerations and data from observational studies suggest that EC risk can be reduced by approximately one-third by endurance-based physical activity. Randomized intervention trials on this question do not exist, so no specific physical activity can be named as optimal for protection against EC. However, the approximate amount of activity needed can be stated as at least 1 hour per week. In a meta-analysis of 6 case-control and cohort studies, Keum et al. [136] calculated a 5% risk reduction (RR = 0.95; 95%-CI 0.93–0.98) per 1 hour of physical activity per week, demonstrating a dose-dependent effect between 0 and 15 hours per week. In a prospective cohort study of > 109,000 individuals, Gierach et al. [137] found that marked physical activity of at least 5 hours per week reduced relative risk by 23% (RR = 0.77; 95%-CI 0.6–0.9). A comparable magnitude of protective effect was also found in other reviews, such as Moore et al. [138] (RR = 0.73 [95%-CI 0.6–0.9] for recreational exercise; meta-analysis of 9 cohort studies) and Voskuil et al. [139] (RR = 0.77 [95%-CI 0.7–0.9]; meta-analysis of 7 cohort studies).

Consistent with the association between physical activity and reduced EC risk, a meta-analysis of 8 case-control and cohort studies demonstrated an association between intensive TV consumption and an increase in EC risk (RR = 1.66 [95%-CI 1.2–2.3]) [140].

In a meta-analysis of 13 studies, Zhang et al. confirmed the risk-reducing influence of weight loss and bariatric surgery, but also indicated that alternating between weight loss and weight gain (‘weight cycling’) likely increased EC risk [128].

Intrauterine devices with and without local delivery of levonorgestrel reduce EC risk. In particular, a levonorgestrel intrauterine device results in effective and long-term suppression of uterine mucosal proliferation. This results in a halving of the risk of developing EC. Soini et al. [141], observed a significant 50% reduction in the incidence of endometrial cancer (IR 0.50; [95%-CI 0.3–0.7]) under and after use of the levonorgestrel IUD in a Finnish population-based cohort study of > 93,000 women receiving a levonorgestrel intrauterine device for hypermenorrhea with 855,000 years of observation [141]. A copper IUD without local hormone release also reduces EC risk, but with a lower degree of efficacy. In a meta-analysis of 17 case-control and cohort studies, the relative risk reduction was 19% (OR = 0.81; 95%-CI 0.7–0.9) [142].

Bariatric surgery is now an established form of surgical therapy for patients with marked obesity. The resulting caloric reduction and weight loss may also lead to a reduction in the risk of EC. Ward et al. report a significant risk reduction with a relative risk of 0.29 (95%-CI 0.3–0.3) in women after bariatric surgery using a retrospective cohort study with > 7 million records [143]. Bariatric surgery in highly obese women (BMI > 40) with EC has been described in a theoretical Markov model by Neff et al. as an effective intervention in terms of overall survival, increase in quality of life and overall cost-effectiveness [144].

A recent meta-analysis of 7 studies of 150,537 women after bariatric surgery and 1,461,938 controls demonstrates an EC risk reduction of 67% (RR 0.33; 95%-CI 0.21-0.51) [145].

3.3 Summary overview of risk-increasing and risk-reducing factors

Table 5: Risk of occurrence of endometrial carcinoma

… is increased…	… is decreased…
• with increasing age • by therapy with tamoxifen depending on the duration of therapy. • by hormone therapy with estrogens alone without progestin protection in non-hysterectomized women depending on the duration of use. • by long-term use (> 6 or > 10 years) of continuous-combined hormone therapy. • by sequential combined hormone therapy depending on the duration, type and dose of progestogen use. • when progesterone or dydrogesterone is used as part of continuous combined and sequential hormone therapy. • with use of tibolone. • with late menopause. • in diabetes mellitus, impaired glucose tolerance, metabolic syndrome and polycystic ovarian syndrome. • with increased body mass index. • with increased waist-hip ratio. • in the presence of a hereditary disposition (especially Lynch – or Cowden syndrome). • in the case of a positive family history of endometrial and/or colon carcinoma.	• by continuous combined hormone therapy with conjugated equine estrogens and medroxyprogesterone acetate as progestogen • when taking oral contraceptives depending on the duration of intake, • with late menarche age, • with late age at birth of the last child, • with physical activity. • with IUD use, especially levonorgestrel-IUD, • in smokers, • with increasing parity.

4 Early detection and diagnosis of endometrial carcinoma

4.1 Early detection/diagnosis in asymptomatic women

4.1.1 Asymptomatic women without increased risk

4.1	Consensus-based statement	checked 2022
EC	The available data do **not** show that screening of asymptomatic women at no increased risk for endometrial cancer with transvaginal ultrasound reduces endometrial cancer-specific mortality.	
	Strong Consensus	

4.2	Consensus-based recommendation	checked 2022
EC	Transvaginal ultrasonography in asymptomatic women without increased risk of endometrial cancer for the purpose of early detection of endometrial cancer shall not be performed.	
	Consensus	

Background

When considering diagnostic procedures for clinical suspicion of the presence of endometrial carcinoma, these should be distinguished from procedures for possible early detection – also in the context of a screening procedure. The question of the value of a sonographic examination was analyzed via an external literature search [146], which is also freely available on the Internet, e.g., on the pages of the German Guideline Program in Oncology (http://www.leitlinienprogramm-onkologie.de/home/) and the pages of the AWMF ([German Society of Gynecology and Obstetrics, AWMF et al. 2009]). Only one relevant study was identified. This study, published as a congressional abstract by Woolas et al. [147], examined a sub-collective of 3,646 asymptomatic women with an intact uterus, who were screened annually with transvaginal ultrasound as part of the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) [148] .

The screening program ran for eight years and women had an average of 5.5 screening examinations (total number: 19,866). In 250 women, the thickness of the endometrium on at least one examination was ≥10 mm. Endometrial carcinoma was found in 7.2% (18/250) of these women and severe atypical hyperplasia in 0.4% (1/250). Among women with an endometrial thickness <10 mm, endometrial carcinoma was found in 0.1% (5/3,396) and simple atypical hyperplasia in 0.4% (2/3,396) at further follow-up. Two of these seven pathologies were found in the interval, although the authors do not describe whether these were hyperplasias

and/or carcinomas. The disease-specific mortality due to endometrial carcinoma was 0% (0/3,646).

From the same study group, the diagnostic value of transvaginal measurements of endometrial thickness were also determined in a sub-collective from the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) [148].

In the intervention arm of the study (n= 48230), measurement of endometrial thickness at the thickest point in the sagittal plane from anterior to posterior was performed by specially qualified colleagues as part of the transvaginal examinations of the adnexa. Follow-up data were collected through national health registries and mail surveys.

After exclusion of women after hysterectomy or lack of documentation of endometrial thickness, 36,867 cases were available for analysis. Of these, 136 women were diagnosed with endometrial carcinoma or atypical endometrial hyperplasia within one year of transvaginal sonography. The authors calculated a value of 5.15 mm as the ideal cut-off for endometrial thickness to detect carcinoma or hyperplasia. This gave a sensitivity of 80.5% and a specificity of 86.2%; that is, 20% of endometrial carcinomas present were not detected with ultrasound.

A cut-off value of 5 mm showed a sensitivity of 80.5% as well as a specificity of 85.7%. For a cut-off of 10 mm, corresponding values were 54.1% and 97.2%. The combination of endometrial thickness of ≥5 mm and abnormal structure on ultrasound was associated with a sensitivity of 85.3% and a specificity of 80.4%.

When restricted to the 96 cases of carcinoma and hyperplasia diagnosed without history of postmenopausal bleeding, the authors calculated a sensitivity of 77.1% and a specificity of 85.5% [149].

In a meta-analysis performed by Breijer et al. [150] of 32 studies published until 2011 on the diagnostic value of transvaginal sonography for the early detection of endometrial carcinoma or atypical endometrial hyperplasia, in a total cohort of 11,100 asymptomatic postmenopausal women, an incidence of 0.62% (95%CI, 0.42–0.82%) for endometrial carcinoma and of 0.59% (95%-CI, 0.22–0.96%) for atypical hyperplasia was found. For a threshold of ≥5mm, endometrial carcinomas with a threshold of ≥5mm endometrial thickness were detected in the analyzed data pool with a sensitivity of 0.83 and a specificity of 0.72.

Alcázar et al. [151] performed a meta-analysis to test the hypothesis put forward by Smith-Bindman et al. [152] that asymptomatic postmenopausal women with an endometrial thickness ≥11mm are at comparable risk for endometrial carcinoma to women with postmenopausal bleeding and an endometrial thickness ≥ 5mm. Based on 4751 screened asymptomatic postmenopausal women from 9 studies, a relative risk of 2.59 (95%-CI:1.66-4.05, P <.001) for endometrial carcinoma was calculated for an endometrial thickness ≥11mm [151].

Sonographic screening by measuring endometrial thickness is not recommended given the low incidence of endometrial carcinoma in asymptomatic women, inadequate discriminatory power between benign and malignant findings and lack of evidence of a reduction in mortality in screened collectives.

However, there is evidence of a significantly increased risk of endometrial cancer in asymptomatic postmenopausal women with endometrial thickness ≥11mm.

Histologic evaluation should be considered in women who have such findings on vaginal ultrasonography and cannot be explained by hormone replacement therapy or tamoxifen administration, especially if other morphological evidence of endometrial carcinoma [153] is present in an ultrasound

4.1.2 Asymptomatic women at increased risk

4.3	Consensus-based statement	checked 2022
EC	Available data do not show that screening of asymptomatic women at increased risk for endometrial cancer (such as Lynch syndrome, obesity, diabetes mellitus, hormone replacement therapy, metabolic syndrome, PCO syndrome) with transvaginal ultrasound reduces endometrial cancer-specific mortality.	
	Strong Consensus	

4.4	Evidence-based statement	checked 2022
LoE **4**	Available data do not show that screening with endometrial biopsy, Pipelle, Tao Brush, tumor marker, fractional curretage or hysteroscopy of asymptomatic women at increased risk for endometrial cancer (such as Lynch syndrome, obesity, diabetes mellitus, hormone replacement therapy, metabolic syndrome, PCO syndrome) reduces endometrial cancer-specific mortality.	
	[154], [155], [156]	
	Strong Consensus	

4.5	Consensus-based recommendation	checked 2022
EC	Transvaginal ultrasonography in asymptomatic women at increased risk for endometrial cancer (such as Lynch syndrome, obesity, diabetes mellitus, hormone replacement therapy, metabolic syndrome, PCO syndrome) for the purpose of early detection of endometrial cancer shall not be performed.	
	Strong Consensus	

Background

Performing screening measures in sub-populations at increased risk for endometrial cancer such as obesity, diabetes mellitus, ongoing hormone replacement therapy, tamoxifen therapy, and known hyperplasia in previously performedcurrettages does not result in a clinically relevant improvement in accuracy in asymptomatic women. In the above-mentioned case-control study by Jacobs et al. [148], 25% of the collective had specific risk factors for endometrial cancer. Multivariate data analysis revealed

irrelevant improved sensitivities and specificities in the sub-collective with specific risk factors.

An external literature review was performed to evaluate the utility of transvaginal ultrasound screening in patients with Lynch syndrome [156]. Of seven included screening studies, no study performed relevant comparisons for evaluating the benefit of screening with transvaginal ultrasound. According to the external literature analysis [156], the studies on Lynch syndrome are already conceptually poorly suited for the evaluation of a benefit of transvaginal ultrasound as screening, since a whole series of tests was used for screening.

A robust assessment of the benefit of screening is not possible based on the available evidence. There is currently no survival benefit of regular screening of patients with Lynch syndrome.

In the study by Manchanda et al. [154] with a prospective cohort study, 41 Lynch patients were followed up with transvaginal sonography, ambulatory hysteroscopy, and Pipelle biopsies according to a strict protocol. Four carcinomas and ten non-critical pathologies were detected. Thereby, in this relatively small group of affected patients, ambulatory hysteroscopy showed a NPV of 100%. Pipelle allowed differentiation between benign changes and carcinomas.

In the comparative review by Helder-Woolderink et al. [155], two screening methods were tested against each other. Annual transvaginal ultrasonography with CA-125 over a five-year period and in a second study, also five years long, with additional endometrial biopsy. Here, adding endometrial biopsy showed no benefit in screening this high-risk population.

In the case of a familial burden in Lynch syndrome (HNPCC), a structured algorithm for early detection of endometrial cancer can be offered to mutation carriers according to the recommendations of the German and the international HNPCC consortium. An improvement in overall survival by this screening has not been shown (see Chapter “Hereditary Endometrial Carcinoma”; [157]).

4.1.3 Asymptomatic women on tamoxifen therapy

4.6	Evidence-based recommendation	modified 2022
GoR **A**	In asymptomatic patients on tamoxifen therapy, transvaginal ultrasound examination for early detection of endometrial carcinoma shall not be performed. This also applies to prolonged therapy over 10 years.	
LoE **3**	[29], [158], [159], [160], [161], [162], [163]	
	Consensus	

Background

Tamoxifen is a selective estrogen receptor modulator and is widely used in breast cancer therapy. However, in the study by Gao et al. [164], transvaginal sonography in 97 patients showed a specificity of only 63.6% with a sensitivity of only 81.1%. The positive predictive value was only 72.9% and the negative predictive value was 73.7%. This underlines the fact that transvaginal ultrasonography is very poorly able to reliably detect pathological changes of the endometrium during the follow-up of tamoxifen therapy.

In the work of Bertelli et al. [165], a study of 164 asymptomatic patients underwent transvaginal sonography. In this study, although 54% of postmenopausal patients had sonographic thickness greater than 5 mm, this imaging did not correlate with pathologic changes in the mucosa.

This unfavorable predictive value of transvaginal sonography during tamoxifen therapy was also confirmed in the study by Gerber et al. [166]. In 247 tamoxifen-treated patients (20 to 30 mg/day for >2 years) and 98 patients in the control group, transvaginal sonography was performed every six months for five years. In patients with more than 10 mm of endometrial thickness, the examination was then performed every three months. Endometrial thickness was 3.5 ±1.1 mm before treatment and increased to 9.2 ± 5.1 mm after three years ($p < 0.0001$), and this increase was significant compared to the control group. Fifty-two patients with thickened and/or suspicious endometrium underwent histologic evaluation with hysteroscopy and curettage. Twenty-eight patients showed atrophy, polyps were found in nine patients, hyperplasia in four patients, and endometrial carcinoma in one patient. Four perforation lesions occurred [166].

In another review by Fung-Kee-Fung et al. [167], all patients with endometrial carcinoma also showed vaginal bleeding as a clinical sign of severe endometrial pathology. Over six years, 304 women were enrolled in the study. At baseline, all patients received an endometrial biopsy. Over this period, 1,061 ultrasounds were performed. Thirty-two percent of the ultrasounds described abnormal findings. Eighty percent of these abnormal findings resulted in histologic evidence of a polyp, and six endometrial carcinomas were detected; all of these patients also had irregular vaginal bleeding. For a cut-off of 9 mm, sensitivity was 63.3%, specificity was 60.4%, PPV was 43.3%, and NPV was 77.5%. The PPV for endometrial carcinoma was 1.4% [167].

In a longitudinal cohort study from 2007 to 2012 of 151 patients on tamoxifen therapy, Saccardi et al. [168] showed that there was no case of endometrial carcinoma in the absence of atypical bleeding, regardless of endometrial thickness or duration of tamoxifen therapy.

4.1.4 Postmenopausal hormone replacement therapy (HRT)

Postmenopause, endometrial thickness is influenced by the use of hormone replacement therapy (HRT), as is the risk for the occurrence of endometrial cancer. The type of HRT is also important for sonographic assessment of endometrial thickness. In the study by Van den Bosch et al. [169] with a total of 238 women, the average endometrial thickness under continuous combined estrogen-progestin HRT was 3.5 ± 1.6 mm, whereas the endometrial thickness under tibolone use was 4.1 ± 1.9 mm and under sequential HRT use was 5.5 ± 2.5 mm [169]. Thus, endometrial thickness under sequential HRT is significantly thicker by 1.4 mm than under tibolone or continuous HRT (p = 0.0001). Thus, if the cut-off values of patients without HRT are used for patients taking HRT, there is a lower diagnostic specificity for the detection of endometrial carcinoma, especially in patients taking sequential HRT.

4.2 Work up for abnormal premenopausal uterine bleeding

4.7	Evidence-based statement	checked 2022
LoE 2	The risk of endometrial cancer or atypical endometrial hyperplasia in premenopausal women with abnormal uterine bleeding is less than 1.5%.	
	[170]	
	Strong Consensus	

4.8	Consensus-based recommendation	modified 2022
EC	In women with premenopausal abnormal uterine bleeding, pathologic findings that do not pertain to this Guideline (e.g., disturbed early pregnancy, cervical pathology, fibroids) should first be excluded clinically and sonographically. In women with endometrial findings without sonographic malignancy criteria and without risk factors (suspicious cytology, obesity, Lynch syndrome, diabetes, polyps), conservative therapy should be attempted initially unless the bleeding is hemodynamically relevant. If conservative therapy fails, hysteroscopy/curettage should be performed.	
	Consensus	

4.9	Evidence-based statement	checked 2022
LoE 3	For the reliable diagnosis of endometrial carcinoma, hysteroscopy in combination with fractionated curettage is the gold standard.	
	[171], [172], [173]	
	Strong Consensus	

4.10	Evidence-based statement	checked 2022
LoE 3	Diagnostic procedures such as Pipelle and Tao Brush in the symptomatic patient have shown comparable positive and negative predictive values in the diagnosis of endometrial cancer as curettage plus hysteroscopy in smaller series. However, larger comparative studies are lacking.	
	[174]	
	Strong Consensus	

4.11	Consensus-based statement	checked 2022
EC	There is currently no nationwide, quality-assured availability of procedures such as Pipelle and Tao Brush in Germany.	
	Strong Consensus	

Background

Pennant et al. [175] analyzed data from 65 studies of 29,095 premenopausal women with abnormal uterine bleeding who had undergone histologic evaluation in a systematic review. The risk of endometrial cancer was 0.33% (95%-CI 0.23–0.58%). The risk of endometrial carcinoma or atypical endometrial hyperplasia was 1.31% (95%-CI 0.96–1.8). If increased/prolonged menstrual bleeding (menorrhagia) was present, the risk of endometrial cancer was 0.11% (95%-CI 0.04–0.32), and if intermenstrual bleeding (metrorrhagia)was present, it was 0.52% (95 CI 0.23–1.16%). The authors concluded that premenopausal women with abnormal uterine bleeding should first receive medical treatment. Only if this does not work should further workup be done [175].

Van den Bosch et al. [176] found endometrial cancer in only 1.2% of cases and atypical hyperplasia in 0.7% in 1373 premenopausal patients with atypical uterine bleeding. The most frequent diagnoses in this collective were functional bleeding, intracavitary fibroids or benign endometrial polyps. Endometrial thickness measured sonographically was not useful for differential diagnosis between benign and

malignant findings in premenopause because of lack of discriminatory power. The authors recommend careful sonographic evaluation of the morphology of the uterine wall and endometrium using the IETA (International Endometrial Tumor Analysis) criteria [177]. Smoothly circumscribed findings, presentation of a noninterrupted midline echo, typical triple layering of the endometrium and color Doppler sonographic exclusion of atypical vascular patterns are considered benign criteria.

A FIGO classification is available [178] for the cause of abnormal premenopausal hemorrhage (AUB) (ICD-10 N92.4) [1].

Pathophysiologically, atypical premenopausal bleeding according to the PALM-COIEN classification of FIGO is in most cases based on benign changes or functional causes.

Depending on the cause of bleeding, a number of drug treatments are available for both acute hemodynamically ineffective bleeding and chronic bleeding disorders, in addition to surgical treatment of benign conditions (e.g., uterus myomatosus or adenomyosis uteri). Only AUB-M (malignancy and hyperplasia) and AUB-E (endometrial pathology) fall within the scope of this Guideline. In particular, the patient's body mass index is important for the exclusion of AUB-M and AUB-E, respectively.

In the work of Wise et al. [179], 916 patients were retrospectively evaluated. 5% of the patients had complex hyperplasia or endometrial carcinoma. This showed that women with a BMI ≥30 kg/m2 had a fourfold higher risk of atypical hyperplasia or carcinoma (95%-CI 1.36–11.74). Also nulliparity (OR = 3.08; 95%-CI 1.43–6.64) and severe anemia (OR = 2.23; 95%-CI 1.14–4.35) were associated with increased incidence of endometrial pathology. Age, diabetes mellitus or menstrual history had no influence [179].

A retrospective cohort study shows a possible clinical benefit of determinations of tumor markers such as HE4, CA 125 or CA 19-9 in risk stratification of women with atypical uterine bleeding [180].

In Li's meta-analysis, the pooled sensitivity for HE4 was 0.65 (0.56-0.73) with a specificity of 0.91 (0.84-0.95) [181]

Data are insufficient to recommend the use of tumor markers for the early diagnosis of endometrial cancer.

The leading symptom of endometrial carcinoma is atypical vaginal bleeding. Since in premenopause in almost 99% of cases the bleeding is due to benign causes, the histological workup can be limited to risk groups with increased risk (obesity, suspicious cytology, Lynch syndrome, etc.) or to cases with suspicious sonography (very high endometrium > 2cm, inhomogeneous internal pattern, suspected invasion).

In general, the first surgical work-up is a uterine endoscopy, usually performed on an outpatient basis, with histology obtained. Several days to weeks elapse before final surgical treatment. There are few data on the influence of this waiting time on the prognosis of the carcinoma. Matsuo et al. [182] studied 435 patients with endometrioid adenocarcinoma with a waiting time between 1–177 days for definitive surgical treatment. No difference in overall survival was found between the groups.

No studies were identified for non-endometrioid carcinoma [182]. In the systematic quantitative review by Clark et al. [183], over 56 studies with a total of 26,346 women, LR of 60.9 (CI 51.2–72.5), the importance of hysteroscopy as a diagnostic

tool is outlined, but due to the relatively poor LR of 0.15 (CI 0.13–0.18) for a negative (unremarkable) result, significantly limits the diagnostic power in terms of distinguishing between certainly malignant and benign. In a retrospective cohort study by Svirsky et al. [184], among 639 patients with abnormal uterine bleeding, curettage alone could reliably detect a cause in only 8.4% of cases.

"Blind" endometrial biopsy is not considered effective for the definite exclusion of endometrial carcinoma because focal lesions, if any, are not detected. The agreement between grading on the abradate with grading on the hysterectomy specimen was investigated by Leitao et al. [185]. Out of 1,423 patients, 490 were ultimately included in the analysis. There was 85% agreement in grading between the abradate and hysterectomy specimen. Huang et al. [186], found an agreement of 93.8% to 97% for well-differentiated carcinomas and 99.2% to 100% for poorly differentiated carcinomas for 360 patients.

With regard to clear identification of malignant disease, the question arises as to whether hysteroscopy alone provides reliable identification of malignant changes. In the review by Deckardt et al. [187], 1,286 patients with vaginal bleeding were studied. In this study, two of 29 patients with endometrial carcinoma were found to have a sonographic thickness of less than 5 mm, and endometrial carcinoma was missed during hysteroscopy in ten patients. However, in this case the surgeon could only answer yes or no to the question about carcinoma [187]. In the work of Dueholm et al. [188], using a scoring system with surface changes, necrosis and papillary changes, a sensitivity of 89% and a specificity of 92% were achieved with a score above 3, but the agreement of the evaluation was not convincing (kappa = 0.56 (0.42–0.71) [188]. In cases of clinical suspicion of endometrial carcinoma, hysteroscopy, even with the use of scoring systems, has not been able to reliably differentiate between premalignant and malignant changes.

Two procedures for endometrial sampling without a need for anesthesia are offered. The first is the Pipelle, in which tissue sampling is performed within the uterine cavity by means of a vacuum. This is created by manually pulling back the inner piston of the Pipelle. The other is the Tao Brush. Here, a wide brush, similar to a Pap smear, is inserted into the cavum uteri and evaluable tissue is obtained with multiple rotations. In the study by Guido et al. [189], 65 patients with confirmed endometrial cancer were examined, and a sensitivity of 83% ±5% (54/65) was found. 127 patients were examined in the study by Tanriverdi et al. [190], first by Pipelle and then by classical method. The agreement was 79% (100/129).

In the study by Del Priore et al. [191], 101 patients (mean age 58 years, range 35–86) received either Tao brush biopsy or Pipelle sampling. 21 carcinomas were detected, sensitivity was 86%, PPV 100% NPV 98%. In the study by Fakhar et al. [192], 100 patients were examined with Pipelle followed by normal scraping. Two endometrial carcinomas were found and for these, Pipelle examination showed sensitivity, specificity, PPV and NPV of 100% in diagnosing endometrial carcinoma.

In the study by Abdelazim et al. [193], 220 patients underwent a Tao Brush procedure prior to actual classical dilation and curettage. Tao Brush demonstrated a sensitivity, specificity, PPV, and NPV of 100% for the detection or exclusion of endometrial cancer. In the work of Sanam and Majid [194], 130 patients who came for examination with vaginal bleeding were analyzed. Initially, Pipelle application was performed, followed by classical dilatation and curettage. The agreement in diagnosis was 100%. In the work of Wu et al., first 200 [195], then in the further study another

633 Tao breast examinations were evaluated [196]. The sensitivity was 100% and the specificity 96% for carcinomas.

In the comparative study by Williams et al. [197] with 200 patients, the Tao Brush showed better material yield than the Pipelle ($p < 0.001$). In women without delivery, both procedures were equally likely to be unfeasible ($p < 0.001$). Postmenopausal women were more likely to obtain inadequate samples with the Pipelle ($p < 0.001$). Patients preferred Tao Brush ($p < 0.001$). Also in the review paper by Critchley et al. [198], it is clear that among minimally invasive diagnostic procedures, Tao Brush achieves a comparable status to hysteroscopy.

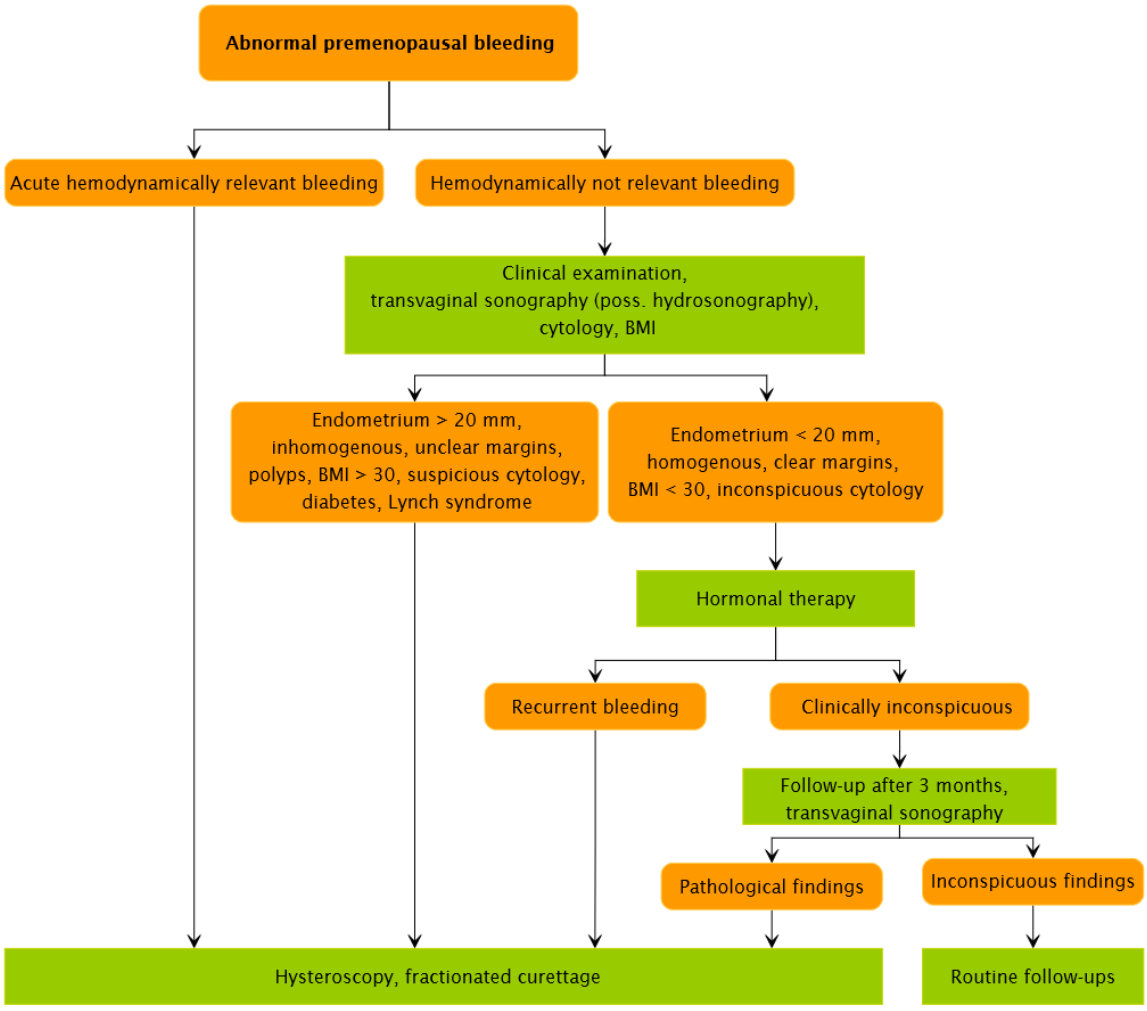
In the work of Al-Azemi et al. [199], the changes of the endometrial mucosa under Tamoxifen were controlled by Pipelle. Among 50 patients controlled over a maximum of 69 months using the Pipelle method, no carcinoma was detected, but endometrial hyperplasia with and without atypia was detected. Surgical workup could thus be more targeted.

In the meta-analysis by Narice, a comparable quality between the use of Pipelle and a simple D/C is described from the data of more than 7300 documented records. Thus, this simple procedure is assigned a place in the outpatient workup for abnormal uterine bleeding in the premenopausal patient. In this analysis, Pipelle is superior to all other outpatient procedures [200].

Of all the outpatient endometrial biopsy procedures, Tao Brush shows the best results, followed by Pipelle. There is too little conclusive data for the SAP-1 and Li Brush procedures and other methods. However, the two main methods have some significant limitations. The Pipelle captures only a small portion of the endometrial surface and can detect focal changes only “randomly”. For both the Pipelle and the Tao Brush, there is also a high rate of unsuccessful attempts of up to 22% in nulliparae. Furthermore, there is currently insufficient experience in clinical routine with these outpatient diagnostic procedures in Germany.

In any case, cytological workup is part of the workup of premenopausal or postmenopausal atypical uterine bleeding. In the meta-analysis by Verdoodt [201], special attention is paid to the detection of atypical glandular cells in HPV-negative patients. Here, patients over 50 years of age showed a risk of 18% for non-HPV-related carcinoma. Therefore, histological clarification should be performed in any case in these cases.

4.2.1 Algorithm for work-up in abnormal premenopausal uterine bleeding



Abbreviation: BMI = Body mass index

Figure 1: Clarification in case of abnormal premenopausal bleeding

4.3 Work-up for postmenopausal bleeding (PMB)

4.12	Evidence-based recommendation	checked 2022
GoR **B**	A woman with first-time postmenopausal bleeding and endometrial thickness ≤ 3 mm (double) should initially have a sonographic and clinical follow-up in three months.	
LoE **1**	[202]	
	Consensus	

4.13	Consensus-based recommendation	checked 2022
EC	Persistence or recurrence of clinical symptoms or increase in endometrial thickness shall lead to histologic evaluation.	
	Strong Consensus	

Background

Endometrial cancer presents with postmenopausal vaginal bleeding (ICD-10 N95.0) as an early symptom [1]. This is also the case in patients at risk. Thus, again, approximately 75% of endometrial carcinomas can be diagnosed at FIGO I stage. The importance of bleeding is also confirmed in Clarke's meta-analysis. Here, the pooled prevalence for bleeding as a symptom of existing endometrial cancer (all stages and histologies) was 91% (CI 87%-93%). However, that not all bleeding meant endometrial carcinoma was reflected in the likewise pooled prevalence for endometrial carcinoma in the presence of existing bleeding. This was only 9% (CI 8%-11%) [203].

Data from 2,896 patients are analyzed in the systematic review by Timmermans et al. [204]. It is shown that an endometrial thickness of less than 3 mm almost excludes endometrial pathology with a sensitivity of 98%.

With a prevalence of endometrial carcinoma in postmenopausal bleeding of approximately 10% (pretest probability), EC can thus be largely excluded.

In contrast, Clarke's meta-analysis clearly shows that in the evaluation of any endometrial mucosal elevation, the pooled risk for endometrial carcinoma increases to 19% [203]. However, it should be noted that in patients with a polyp, the risk of endometrial carcinoma is only 3%. In the experimental analysis of the data, for an endometrial mucosal thickness of 5 mm, a PPV of 7.4% is shown, and for a thickness of 10 mm, PPV is 14.3%. However, the data apply only to endometrioid carcinomas.

Transvaginal sonography can detect intracavitary lesions. In the meta-analysis by Bittencourt, the sensitivity for 2D contrast sonography to detect a polyp was 93% (95%-CI 89-96%) with a specificity of 81% (95%-CI 76%-86%) [205]. According to the

meta-analysis by Nieuwenhuis, 3D saline contrast sonography has no significant advantages for the detection of a polyp compared to the 2D technique, sensitivity was higher with the 3D technique at 96.3% (95%-CI 79.4%-99.4%), but specificity was comparable and statistically the differences were not significant [206]. Vroom's meta-analysis showed a sensitivity of 85.1% (95%-CI 66.9-100%) and a specificity of 84.5% (95%-CI 68.1-100%) for saline contrast sonography [207].

4.3.1 Algorithm for work-up of bleeding in peri- or postmenopausal women

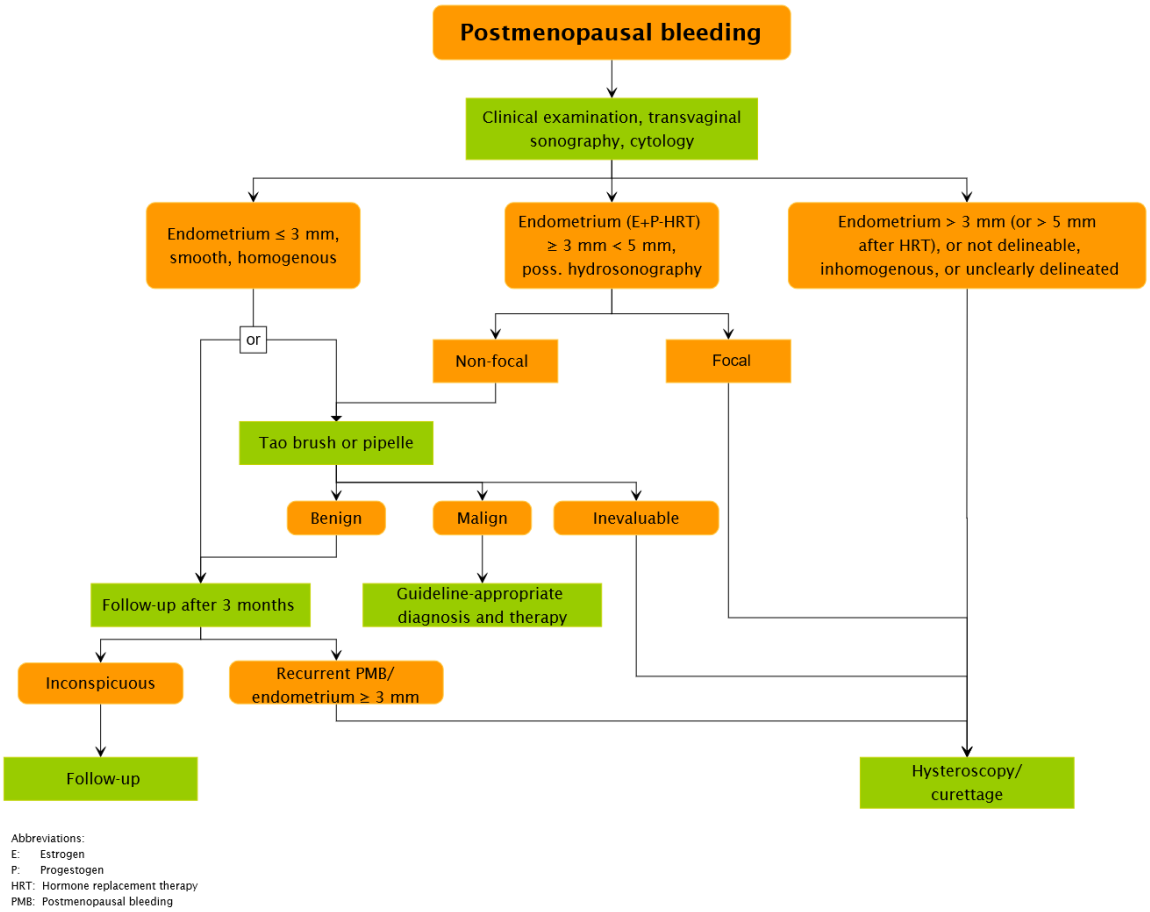


Figure 2: Algorithm "Diagnostic procedure for bleeding in peri- or postmenopausal women"

4.4 Imaging diagnostics

4.4.1 General imaging

4.14	Consensus-based statement	checked 2022
EC	In endometrial cancer, surgical staging with histopathological examination is the reference method for local spread diagnosis. For distant metastases outside the usual surgical area, imaging is the primary diagnostic method.	
	Strong Consensus	

Background

In endometrial carcinoma, surgical staging with histopathological examination is the reference method for local spread diagnosis. Imaging is complementary to this. Depending on the individual clinical indication, imaging may be useful to obtain an overview of the surgical site preoperatively, to plan the further procedure and to additionally clarify tumor-specific focal findings if necessary.

In some patients, complete surgical staging including lymphadenectomy is not possible or not planned.

In this case, imaging provides non-invasive diagnostic information about the local extent of endometrial carcinoma, infiltration of adjacent organs and metastases. For distant metastases outside the usual surgical area, cross-sectional imaging is the primary diagnostic method.

4.4.2 Basic imaging diagnostics

4.4.2.1 Chest X-ray

In the primary diagnosis of endometrial carcinoma, chest X-ray in 2 planes is recommended by the ICNL and ACR Guidelines [208], [209]. As a baseline examination, its primary purpose is to assess preoperative cardiopulmonary status while allowing for the evaluation of rare pulmonary metastasis. The preoperative chest x-ray further serves as a baseline finding for possible follow-up examinations.

In initial manifestation of endometrial carcinoma, pulmonary distant metastases, although rare overall, result in FIGO stage IV. In a retrospective multicenter study, Amkreutz et al. [210] reported that pulmonary metastases of endometrial carcinoma were found in 1.3% (7 of 541) patients on chest x-rays. All affected patients had high-risk subtypes (serous, clear cell, or high grade endometrioid), and the incidence of pulmonary metastases was 4.1% for these subtypes. No pulmonary metastases were found on chest x-rays in patients with low-risk endometrial carcinoma subtypes. 243 other patients had not received chest imaging at primary diagnosis. The authors concluded that patients with low-risk endometrial carcinoma subtypes may not require chest x-rays for metastasis detection. In patients with high-risk subtypes,

pulmonary metastases are present in approximately 4% of patients according to the study by Amkreutz et al. [210], and their detection may be therapeutically relevant.

4.4.2.2 Abdominal sonography

Abdominal ultrasonography is a basic examination, especially for the evaluation of the internal organs, including a possible pre-existing urinary transport disorder. However, due to bowel gas layering, assessment of the lesser pelvis and retroperitoneum is limited. In accordance with the ACR Guideline [209], transabdominal sonography is not considered appropriate for staging endometrial cancer.

4.4.2.3 Transvaginal sonography

4.15	Evidence-based recommendation	checked 2022
GoR **B**	In histologically-confirmed primary endometrial carcinoma, transvaginal sonography should be performed to assess myometrial infiltration and cervical infiltration.	
LoE **3**	[211]	
	Strong Consensus	

4.16	Consensus-based statement	checked 2022
EC	Preoperative imaging by transvaginal sonography is used for documentation and surgical planning, even though the final locoregional staging is surgical-histologic.	
	Strong Consensus	

Background

In primary endometrial carcinoma, transvaginal sonography (TVS) is a clinically established basic examination. It is used for preoperative assessment of myometrial infiltration and possible cervical and parametrial infiltration.

In the prospective study (74 patients) by Savelli et al. [212], TVS and MRI showed similar diagnostic accuracies in preoperative staging for endometrial cancer for the assessment of myometrial infiltration and cervical infiltration. The authors discuss that expert-performed TVS shows good accuracy in local staging of endometrial carcinoma, and therefore MRI should be offered only when TVS has poor image quality for cost reasons [212]. However, due to the limited field of examination, TVS does not allow a comprehensive assessment of locoregional lymph nodes. In addition to Savelli et al. [212], the Dutch Guideline [208] discusses other studies on TVS, and the overall conclusion is that MRI in particular is recommended for primary EC when

there is a clinical indication for imaging. In this regard, the meta-analysis by Alcázar [151], [213] no statistically significant difference is shown between the detection rate of deep myometrial infiltration via TVS or an MRI examination. For the detection of cervical stromal infiltration, the meta-analysis by [212], for TVS a pooled sensitivity of 63% (95%-CI 51%-74%) and a specificity of 91% (95%-CI 87-94%) is calculated. This means that approximately the same values are achieved as for MRI.

4.4.3 Cross-sectional imaging for local spread diagnostics

4.17	Evidence-based recommendation	checked 2022
GoR **B**	In primary endometrial carcinoma, MRI should be performed for preoperative evaluation of myometrial infiltration and cervical involvement if transvaginal sonography is not informative.	
LoE **3**	[211]	
	Strong Consensus	

4.18	Evidence-based recommendation	checked 2022
GoR **B**	If needed for non-invasive assessment of locoregional lymph nodes, e.g., imaging diagnostics to determine spread prior to primary radiotherapy or planning surgical approach for advanced carcinoma disease (cT3), this should be done by cross-sectional imaging (CT/MRI).	
LoE **3**	[214], [215], [216], [217], [218], [219]	
	Strong Consensus	

4.19	Consensus-based recommendation	checked 2022
EC	In the case of primary radiotherapy, locoregional diagnostics to determine spread should be performed by MRI if possible. If MRI is not possible, CT should be performed as an alternative.	
	Strong Consensus	

Background

Cross-sectional imaging for local spread diagnosis in primary endometrial carcinoma can simultaneously assess myometrial infiltration (< 50% versus ≥ 50%), cervical stromal infiltration and locoregional lymph node metastases. MRI, CT and PET-CT are available as methods. In comparison to sonography, air and bone are not obstacles. Furthermore, cross-sectional imaging is performed slice-by-slice and is also available, for example, intraoperatively as imaging material. In the following, scientific results on cross-sectional imaging in local spread diagnosis of primary endometrial carcinoma are presented.

4.4.3.1 Myometrial infiltration

To assess myometrial infiltration, current ACR and ICNL guidelines recommend MRI when imaging is clinically indicated [214], [215]. This MRI should meet certain minimum requirements as detailed by the European Society of Urogenital Radiology (ESUR). Thus, the use of antiperistaltic drugs (20 mg butylscopolamine i.m./i.v. or 1 mg glucagon i.v.) is recommended in the absence of contraindications. MRI should include a combination of native high-resolution T2-weighted sequences without fat saturation in at least sagittal and axial-oblique slices perpendicular to the uterine corpus (slice thickness ≤ 4 mm), further diffusion-weighted images with at least 2 b-values of 0 and 800-1000 s/mm2 in at least 1 plane (same plane perpendicular to the uterine corpus as T2w), and contrast-enhanced T1-weighted sequences 2 min 30 sec after contrast administration. Radiological findings should include the following: Thickness of endometrium and tumor size, depth of myometrial infiltration, cervical stromal infiltration, infiltration of uterine serosa, extension to adnexa, vaginal/parametrial infiltration, urinary bladder/rectum infiltration, lymph node status, infiltration of distant organs, presence of peritoneal carcinomatosis, and associated benign changes [220].

Image-based assessment of myometrial infiltration may also provide complementary information in the context of surgical planning. A prospective study by Haldorsen et al. [221] (55 patients) reported that MRI-based perfusion parameters of endometrial carcinoma correlated with histologic subtype ($p < 0.03$) and overall survival ($p < 0.05$), suggesting that preoperative MRI can be used for risk stratification.

In a meta-analysis of 50 studies (3,720 patients), Luomaranta et al. [222] evaluated the diagnostic accuracy of MRI for differentiating FIGO stage IA versus IB (< 50% versus ≥ 50% myometrial infiltration) and found a pooled sensitivity of 80.7% (95%-CI 76.8–84.1%) and specificity of 88.5% (95%-CI 85.3–91.1%). Similar diagnostic accuracies were reported in three other meta-analyses [223], [224], [225]. According to Luomaranta et al. [222], dynamic contrast-enhanced sequences are slightly more accurate than non-dynamic contrast-enhanced sequences. According to Andreano et al. [224], dynamic contrast-enhanced sequences and diffusion-weighted sequences have similar diagnostic accuracies without significant differences. If the administration of gadolinium-containing contrast agent is contraindicated in individual cases, the depth of myometrial infiltration can at least be assessed with diffusion-weighted sequences.

If pelvic MRI is not possible when there is a clinical question about myometrial infiltration (e.g. pacing), then imaging alternatives exist. In a meta-analysis, Kinkel et al. [223] found a high Q* value of 0.91 for contrast-enhanced MRI (9 studies, 332 patients). For comparison, the Q* value for transvaginal sonography was 0.85 (14 studies, 514 patients) [223]. For single-line detector CT, the Q* value was 0.79 (6 studies, 203 patients) [223]. A small prospective study (29 patients) with 16-line CT

reported a high diagnostic accuracy of 95%, but recommended further studies [226]. The current ACR Guideline also recommends that the role of computed tomography be further evaluated [209]. For the evaluation of myometrial infiltration, Antonsen et al. [219] found similar diagnostic accuracy for PET-CT as for MRI in a prospective multicenter study in a direct comparison of methods (111 patients), so PET-CT can also be used for this question. The role of PET-MRI [227] in the assessment of myometrial infiltration should be investigated in further studies.

It should be noted that the cost of PET-CT is covered by health insurance only upon request – and only if CT and MRI do not provide sufficient clarity.

4.4.3.2 Cervical stromal infiltration

When cervical stromal infiltration is suspected, current NCCN, ICNL, and ACR guidelines concur in recommending MRI, e.g. when chemotherapy and/or radiotherapy are primarily planned [228], [208], [209]. This MRI should include the same sequences as used to assess myometrial infiltration. If necessary, additional T2-weighted images axial and perpendicular to the cervical axis may be helpful [220].

Compared with FIGO stage I, the diagnosis of cervical stromal infiltration leads to upgrading to FIGO stage II and, if necessary, changes the surgical strategy. Similarly, FIGO stage II has a higher incidence of recurrence and lower disease-specific and overall survival than FIGO stage I. Preoperative imaging may support this stage differentiation.

In a meta-analysis (10 studies, 318 patients) by Kinkel et al. [223], the sensitivity of MRI for assessing cervical infiltration ranged from 66% to 100% and the specificity ranged from 92% to 100%. A meta-analysis by Luomaranta et al. [222] included 12 studies (1,153 patients) and found a pooled sensitivity of 57.0% (95%-CI 45.9–67.4%) and specificity of 94.8% (92.1–96.6%) for MRI. In this meta-analysis, a positive predictive value of 68.7% (60.5–75.8%) and a high negative predictive value of 90.5% (87.7–92.8%) were reported for MRI [222].

If pelvic MRI is not possible when there is a clinical question of cervical stromal infiltration (e.g. contraindication due to pacing), then transvaginal sonography is an imaging alternative [209]. Antonsen et al. [219] reported no significant differences between MRI, PET-CT and endovaginal sonography in a prospective multicenter study comparing methods directly (111 patients) (accuracy: PET-CT = 82.7%; MRI = 82.3%; sonography = 77.9%). The role of contrast-enhanced multidetector CT for this issue is under investigation [226], as is the role of PET-MRI [227].

4.4.4 Pelvic and para-aortic lymph node metastases

Diagnosis of pelvic or para-aortic lymph node metastases leads to FIGO stage III and requires appropriate lymphadenectomy if operable. When lymph node metastases are diagnosed, recurrences are more frequent and disease-specific and overall survival are lower than in early endometrial cancer.

A meta-analysis by Selman et al. [216] found a pooled sensitivity of 72% (95% CI 55–85%) and specificity of 97% (93–99%) for the evaluation of pelvic and para-aortic lymph node metastases for MRI with good study quality according to QUADAS-2 assessment. A meta-analysis by Luomaranta et al. [229] found a lower pooled sensitivity of 43.5% (95% CI 31.7–56.1%) with, however, high between-study heterogeneity (range for sensitivity: 0.17–0.71%; I-squared 91%) and unclear study

quality, whereas the specificity of 95.9% (92.9–97.6%) was also high. According to the ESUR recommendation, MRI for lymph node assessment should include an axial T2-weighted sequence and, for G3 endometrioid as well as non-endometrioid carcinomas, an additional axial DWI from the renal hili to the symphysis.

For CT (studies through 2000; most likely single-line CT), pooled sensitivity was 45% (95%-CI 28–64%) and specificity was 88% (78–94%) [227]. A meta-analysis by Chang et al. [230] on PET-CT included 7 studies (243 patients) and found a pooled sensitivity of 63.0% (95%-CI 48.7–75.7%) and specificity of 94.7% (90.4–97.4%). A meta-analysis by Kakhki et al. [218] included 8 studies of PET-CT (332 patients) and found a similar pooled sensitivity of 68.7% (95%-CI 57.7–78.2%) and specificity of 92.7% (90.0–94.9%). In a prospective multicenter study by Antonsen et al. [231], an accuracy of 90.5% for PET-CT and 90.2% for MRI was reported for the detection of locoregional lymph node metastases in a direct comparison of methods, so that PET-CT and MRI can be considered equivalent for this question. With transvaginal sonography, a comprehensive assessment of the locoregional lymph nodes is not possible due to the limited field of examination.

4.4.5 Imaging for distant metastases

4.20	Evidence-based recommendation	checked 2022
GoR **B**	If there is a reasonable suspicion of distant metastasis, possible distant metastases should be evaluated by cross-sectional imaging (and skeletal scintigraphy, if necessary) and histologic confirmation, if necessary, for treatment planning.	
LoE **3**	[214], [215], [218]	
	Strong Consensus	

Background

Imaging allows the diagnosis and accurate localization of distant metastases. At initial manifestation of endometrial carcinoma, the risk of distant metastases is low for low-grade subtypes, whereas it is increased for high-grade subtypes, as shown, for example, by Amkreutz et al. [210] for lung metastases. Distant metastases can occur in the lung, liver, skeleton and non-regional lymph nodes, among other regions. The diagnosis of distant metastases leads to FIGO stage IV.

If distant metastases are suspected, the ICNL, NCCN, and ACR guidelines recommend cross-sectional imaging before primary chemotherapy and/or radiotherapy or to plan surgical approach [208], [228], [209].

For the evaluation of distant metastases, recommendations are provided by the ACR Guideline. MRI with native and contrast-enhanced sequences is well suited in the abdomen and pelvis, whereas it is not established for the detection of pulmonary metastases. Contrast-enhanced CT is suitable for thorax, abdomen and pelvis [209]. A meta-analysis by Kakhki et al. [232] (16 studies, 807 patients) found a very high

pooled sensitivity of 95.7% (95%-CI 85.5–99.5%) and specificity of 95.4% (92.7–97.3%) for the assessment of distant metastases for PET-CT, making it very suitable for the question of distant metastases.

Table 6: Meta-analyses on the diagnostic accuracy of cross-sectional imaging in the initial diagnosis of primary endometrial carcinoma

Question	Studies	Patients	Sensitivity, pooled*	Specificity, pooled*	Source
Myometrial infiltration					
MRI	50	3720	80.7% (76.8–84.1%)	88.5% (85.3–91.1%)	[229]
MRI with CM	9	332	78.6–100%	71.4–100%	[223]
MRI with CM	9	442	86% (80–93%)	82% (74–90%)	[224]
MRI with DWI	9	442	86% (80–93%)	86% (78–94%)	[224]
MRI with DWI	7	320	90% (81–95%)	89% (79–94%)	[225]
CT	6	203	40–100%	75–100%	[223]
Cervical stromal infiltration					
MRI	12	1153	57.0% (45.9–67.4%)	94.8% (92.1–96.6%)	[229]
MRI with CM	10	318	66–100%	92–100%	[223]
Pelvic/para-aortic lymph node metastases					
MRI	4	211	72% (55–85%)	97% (93–99%)	[227]
MRI	10	862	43.5% (31.7–56.1%)	95.9% (92.9–97.6%)	[229]
CT	5	279	45% (28–64%)	88% (78–94%)	[227]
PET or PET-CT	7	243	63.0% (48.7–75.7%)	94.7% (90.4–97.4%)	[217]
PET-CT	8	332	63.0% (48.7–75.7%)	92.7% (90.0–94.9%)	[218]

Question	Studies	Patients	Sensitivity, pooled*	Specificity, pooled*	Source
Distant metastases					
PET or PET-CT	16	807	63.0% (48.7–75.7%)	95.4% (92.7–97.3%)	[218]
* = 95% confidence intervals in parentheses; CM= contrast medium; DWI = diffusion-weighted sequence					

4.5 Pathology

4.5.1 Pathogenesis of endometrial carcinoma

4.21	Consensus-based recommendation	new 2022
EC	Histopathological diagnosis of endometrial carcinoma results from the combination of histomorphological and immunohistochemical parameters and, if necessary, supplementary molecular pathological findings.	
	Strong Consensus	

A dualistic pathogenesis model based on clinicopathological criteria distinguishing 2 different types (type 1 and type 2) of endometrial carcinoma (EC) still has educational significance [233]. However, due to insufficient correlation between histomorphology and underlying pathogenetically significant alterations, the binary model is increasingly replaced by immunohistochemical or molecular classification [234], [235], [236], [237], [238].

The morphological prototype of type 1 EC is endometrioid carcinoma and that of type 2 EC is serous carcinoma [234], [239], [240]; see the following table). Due to a partial overlap of the two types and new molecular data, a molecular classification based on the TCGA project is preferred [234], [236].

Table 7: Binary/dualistic model of endometrial cancer

	Type 1 carcinomas	Type 2 carcinomas
Age	55 – 65 years	> 65 years
Clinical constellation	Obesity, hypertension, diabetes mellitus (metabolic syndrome)	No special features
Hyperestrogenism	Mostly	Absent in most cases
Stage	Mostly FIGO I	Mostly ≥ FIGO II
Prognosis	Favorable	Unfavorable
Hereditary background	Lynch syndrome, Cowden	poss. BRCA?
Endometrial hyperplasia	Mostly	None
Histologic subtype	Endometrioid	Serous, clear cell
Molecular alteration	PTEN, ARID-1A, MSI	TP53, HER2, PIK3CA
Molecular type	NSMP, MMR deficient, POLE mutated	TP53 mutated (serous-like)

Sources: [241], [242], [243], [244]

4.5.2 Precursor lesions of endometrial carcinoma

Non-atypical endometrial hyperplasia is classified as a high-risk lesion rather than a precancerous lesion [245], [246]. With a 14- to 45-fold increased risk, atypical endometrial hyperplasia is considered an obligate precancerous lesion for endometrioid EC [245], [247], [246], [248].

The term endometrioid intraepithelial neoplasia (EIN) is listed as a synonym in the WHO classification [234], and has identical biological characteristics to atypical hyperplasia [246], [249]. Hysterectomized patients with atypical endometrial hyperplasia/EIN show concordant endometrioid EC in 15-50% in the subsequent hysterectomy specimen [247], [249], [250], [251].

Table 8: WHO classification of endometrial hyperplasia (nomenclature)

Description	glandular-cystic hyperplasia	low/moderate grade adenomatous hyperplasia	high grade adenomatous hyperplasia
WHO 1994 / 2003	simple hyperplasia without atypia	complex hyperplasia without atypia	atypical hyperplasia
WHO 2014 and WHO 2020	non-atypical hyperplasia		atypical hyperplasia syn. endometrial intraepithelial neoplasia (EIN)

Serous intraepithelial carcinoma (SEIC) is not considered a precancerous lesion, but a superficial serous carcinoma [234], [240]. It may be associated with minimal invasion [252] and may occur in endometrial polyps [253]. Prognostically crucial is extrauterine spread. Clinicopathologic and immunohistochemical data suggest overlap with primary tubal carcinoma [253].

4.22	Consensus-based recommendation	checked 2022
EC	The terminology and morphologic diagnosis of endometrial hyperplasia shall be based on the current edition of the WHO classification.	
	Strong Consensus	

4.5.3 Tumor typing of endometrial carcinoma

The exact tumor typing is therapeutically and prognostically relevant [254], [234]. In doubtful cases, additional immunohistochemical examinations are recommended [255], [256], [257], [258], [259], [260], [261], [262]. The vast majority of EC (~80%) are endometrioid carcinomas, followed by serous (3-10%), and clear cell (2-3%) EC, and carcinosarcoma (2%); [256] [262], [263], [234]. Undifferentiated or dedifferentiated EC is even rarer at < 1%; remaining intestinal-type mucinous EC, squamous cell carcinoma and mesonephric-like EC are rarities [234]; [264] [265] Endometrioid carcinomas may frequently have squamous as well as mucinous areas, but these differentiation patterns are without clinical relevance [234].

Mixed EC is defined by WHO as a carcinoma consisting of at least 2 distinct histologic types that can be differentiated from each other [234], one of which is either serous or clear cell differentiated. A quantitative threshold as in the 2014 WHO classification of 5% is not applicable [234], [262].

4.23	Consensus-based statement	modified 2022
EC	Mixed carcinomas of the endometrium have two or more histologic subtypes according to the WHO classification (2020), with one of these components being either serous or clear cell.	
	Strong Consensus	

Carcinosarcomas (synonym: malignant mixed Müllerian tumors/ MMMT) typically consist of a highly malignant epithelial and mesenchymal component each [266], [267], [257]. The mesenchymal component is designated as either homologous (structures found in the uterus, such as smooth muscle) or heterologous (structures not found in the uterus, such as cartilage and bone). Carcinosarcomas are classified as EC with epithelial-mesenchymal transformation based on clinicopathologic and molecular parameters [268], [267], [269] and classified as EC in the TNM system [234], [270]

4.24	Consensus-based recommendation	checked 2022
EC	Molecular pathologically, carcinosarcomas (malignant Müllerian mixed tumors, MMMT) are assigned to carcinomas. Histological evaluation of carcinosarcomas shall be performed according to the current WHO classification. FIGO and TNM classification shall be analogous to that for endometrial carcinoma.	
	Strong Consensus	

4.5.4 Histological grading in endometrial carcinoma

Histopathologic grading of endometrioid carcinomas is performed according to FIGO criteria based on the presence of solid non-squamous portions.

- G1: < 5% solid portions
- G2: 6–50% solid portions
- G3: > 50% solid portions

Based on prognostic studies (including [243]), according to the International Society of Gynecologic Pathologists (ISGyP; [238]), and the current WHO classification [234], based on prognostic studies [243], G1- and G2-EC are grouped as FIGO low grade and G3-EC as FIGO high-grade [254]. For adequate documentation in cancer centers, it is recommended to note both grading types in the report of findings.

Detection of high-grade cellular atypia results in upgrading by one grade each [263], [256], [237]. In case of high-grade atypia, serous EC should be excluded by immunohistochemistry [260], [257]. Due to their biological behavior, serous and clear cell carcinomas are not graded according to WHO, but are by definition classified as G3, as are carcinosarcomas and de- or undifferentiated EC. In the medium term, it can be assumed that histomorphologic grading will be supplemented, or possibly replaced, by molecular risk assessment [237] [271], [272], [244]. Grading of

neuroendocrine tumors is based on the classification of neuroendocrine tumors of the gastrointestinal tract [234].

4.25	Consensus-based recommendation	new 2022
EC	Endometrioid carcinomas are graded according to FIGO. According to WHO, a two-stage grading “low grade” (G1 or G2) and “high grade” (G3) should be preferred. Serous, clear cell, de- or undifferentiated endometrial carcinomas as well as carcinosarcomas are by definition high-grade carcinomas.	
	Strong Consensus	

4.5.5 Determination of the invasion depth

The depth of invasion is measured from the adjacent non-cancerous endometrium to the deepest point of tumor infiltration. For exophytic growing tumors, an imaginary line from the endometrium closest to the tumor through the tumor serves as the starting point for the measurement [273], [274]; see the following figure).

If the carcinoma originated in an endometriosis/adenomyosis, the depth of invasion is measured from the boundary of the adenomyosis to the deepest point of infiltration.

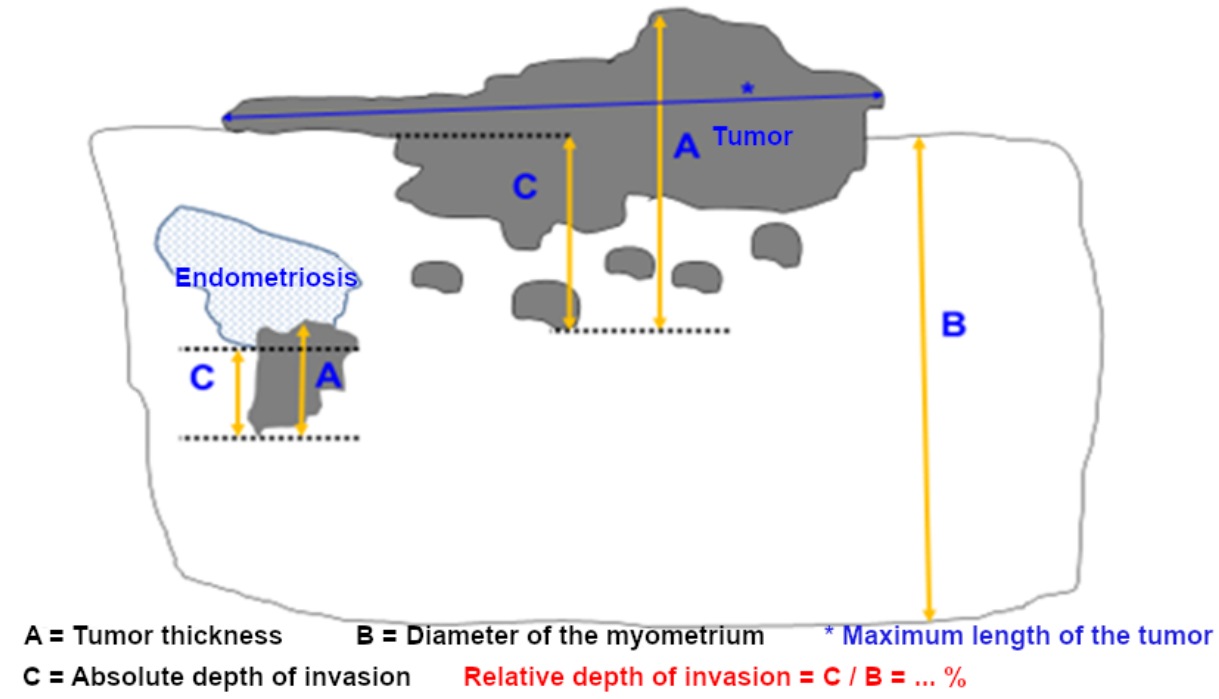


Figure 3: Measurement of depth of invasion in endometrial carcinoma

Determining the depth of invasion can be problematic because there is no sharp boundary between endometrium and myometrium [275], [276]. Infiltrative growth is present when tumor glands have direct contact with the surrounding myometrium, in some cases there is little peritumoral desmoplasia and surrounding endometrial

stroma is absent. Van Gieson staining to demonstrate desmoplasia and CD10 immunohistochemistry to demonstrate endometrial stroma may be helpful in cases of doubt [276].

Ingrowth of carcinoma into pre-existing endometriosis may mimic myometrial infiltration and has no prognostic significance. The following findings favor the diagnosis of co-involvement of endometriosis [275]; [277], [273]:

- Evidence of benign endometrial glands in the immediate vicinity of tumor associations,
- Evidence of benign glands between tumor glands,
- Absence of peritumoral desmoplasia,
- Absence of peritumoral inflammation,
- Round contour of the lesion with sharp border to the surrounding myometrium.

Usually, the anterior and posterior uterine walls have the same thickness [278], so that, if necessary, the opposite wall thickness in each case can be used as a reference value of myometrial thickness to determine the depth of invasion.

4.5.6 Definition of TNM-relevant parameters

The definition of the parameters below is identical to the guidelines in vulvar, vaginal and cervical carcinoma.

Perineural sheath infiltration (Pn category) is defined as the detection of tumor cells in perineural clefts, regardless of their extent and whether or not the nerve itself is infiltrated [279], [280]. Periganglionic infiltration can be classified as Pn1.

Lymphatic vessel infiltration (L category) is defined by the detection of tumor cells lying singly or in groups within cavities that are clearly lined by endothelium (L1; [281], [282]. According to the TNM, detection of tumor cells within cleft spaces without clear endothelial lining is classified as L0 (no lymphovascular infiltration) [283]; these are usually shrinkage-related fixation artifacts. Furthermore, lymphovascular pseudoinvasion should be differentiated as a morphologic pattern of the MELF invasion pattern [281], [274]) and when laparoscopic and robotic-assisted surgical procedures are used [282], [284]. Routine use of immunohistochemistry to detect endothelia (e.g. D2-40/podoplanin) is not indicated outside of studies [281], [283], [285]. Despite different definitions, quantification of lymphatic vessel infiltration is prognostically relevant in different stages and histologic types of EC [286], [287], [288], [289], [290], [291]. Lymphatic vessel infiltration should be indicated in the report of findings and classified as follows ([281]; [274]):

- No lymphatic vessel infiltration (L0),
- Focal lymphatic vessel infiltration (L1): involvement of < 3 lymphatic vessels in overview magnification,
- Extensive (syn. “substantial”) lymphatic vessel infiltration (L1): involvement of ≥ 3 lymphatic vessels in overview magnification.

4.26	Consensus-based recommendation	new 2022
EC	Quantification of lymphatic vessel infiltration should be included in the histopathologic report of findings. Focal lymphatic vessel infiltration is defined as involvement of < 3 lymphatic vessels and extensive ("substantial") lymphatic vessel infiltration as an involvement of ≥ 3 lymphatic vessels.	
	Strong Consensus	

Lymphatic vessel infiltration is best assessed at 25-40x magnification.

There is good interobserver correlation for both the detection of lymphatic vessel infiltration and its quantification [285].

Venous invasion (V category) distinguishes between macroscopically visible (V2) and histologically confirmed venous infiltration (V1; (Wittekind 2011) [283]. Microscopic V1 category is defined in the TNM as the detection of tumor cells within the vein lumen and/or the detection of tumor cells infiltrating the vein wall [283].

4.5.7 Additional immunohistochemical tests

4.5.7.1 HER2 analysis in serous EC

HER2 status is currently of practical relevance only in serous EC [234]. Regarding overall survival, patients with FIGO stage III/IV or recurrence of serous endometrial carcinoma benefit from a combination of chemotherapy and HER-2 inhibition with prolongation of overall survival by about 5 months [292], making HER2 a potential therapeutic target [292], [293], [294]. In accordance with ISGyP recommendations, HER-2 expression is determined by analogy to gastric carcinoma with analysis of a latero-basal staining pattern [294], [295], [296], with re-evaluation of immunohistochemically doubtful cases by an in situ method [295]:

- IHC score 3+: > 30 of tumor cells with strong complete or basolateral/lateral membrane staining,
- IHC score 2+: < 30 with strong complete or basolateral/lateral membrane staining OR weak to moderate complete staining in > 10% of tumor cells (in situ testing required),
- IHC score 1+: very weak incomplete membrane staining of any percentage OR weak complete membrane staining in < 10% of tumor cells,
- IHC score 0: no positive tumor cells.

25 to 30% of serous EC show immunohistochemical Her2 overexpression or gene amplification [293], [294], [297] with a concordance rate of both methods of 75% [293]. There is good interobserver correlation of HER-2 determination in immunohistochemistry [295]. The concordance rate between curettage and hysterectomy is reported to be 84% [296], [295] and the discordance rate between primary tumor and metastasis is 55% [295] . ISGyP recommends that HER2 status be determined at the initial diagnosis of serous EC. Due to the above-mentioned

discordance rate, HER-2 status should be re-evaluated at recurrence or (distant) metastasis.

4.27	Consensus-based recommendation	new 2022
EC	Because of a potential therapeutic consequence, HER2 status should be determined in serous endometrial carcinoma.	
	Strong Consensus	

Few primary serous EC exhibit disruption of other DNA repair mechanisms and thus HRD [298], [297], [237]. During tumor progression and metastasis, the gain of an HDR is reported in serous EC [299].

4.5.8 Frozen section examination in endometrial carcinoma, malignant mixed Müllerian tumor and atypical endometrial hyperplasia

4.28	Consensus-based recommendation	checked 2022
EC	If pT1b and/or pT2 are clinically suspected, intraoperative histologic examination (frozen section) may be performed for verification.	
	Strong Consensus	

4.29	Consensus-based recommendation	checked 2022
EC	Myometrial infiltration depth or endocervical stromal infiltration shall be assessed macroscopically and microscopically.	
	Strong Consensus	

4.30	Consensus-based recommendation	checked 2022
EC	Frozen section examination shall not be performed primarily to assess histopathologic grading and to determine histologic tumor type.	
	Strong Consensus	

4.31	Consensus-based recommendation	checked 2022
EC	The tubes and ovaries shall be assessed macroscopically during the intraoperative frozen section examination, and findings suspicious for tumor shall be examined histologically.	
	Strong Consensus	

Background
Intraoperative frozen section assessment may be requested by clinicians for evaluation of local tumor spread and any necessary modification of the immediate surgical approach. This applies, for example, to cases in which FIGO stage IB or II lymphonodectomy is planned in the same session rather than a two-stage approach after final workup of the hysterectomy specimen.

Of importance are determination of myometrial invasion depth [300]; [277], [301], [239] and cervical stromal infiltration. Both parameters are relevant for staging and prognosis [302]; Wittekind 2011; [303], [239].

Macroscopic assessment of the depth of invasion during frozen section examination alone shows a concordance with final histology of about 80%, which increases to more than 90% with microscopic assessment [304], [305], [306], [251].

The inadequate macroscopic assessment of depth of invasion is especially true for endometrioid EC with a MELF (microcystic, elongated, fragmented glands; [307] or a minimal-deviation growth pattern [308]; both parameters cannot be assessed on curettage material. The same applies to serous adenocarcinomas with a glandular growth pattern [309], in which the diagnosis was not made on the curettage material. Therefore, after opening the uterus, the myometrial depth of invasion should be assessed macroscopically and verified histologically, especially for tumors > 2-3cm [310], [311].

The concordance rate between intraoperative frozen section examination and final findings regarding depth of invasion, tumor size, grading and histologic subtype is greater than 95% [312], [300], [251].
During frozen section examination, the endocervical stroma should be assessed macroscopically and, if tumor infiltration is suspected, microscopically [311], [313], [314], [315], [316], [251].

Assessment of grading of endometrioid adenocarcinomas has an insufficient sensitivity of 40% [310], [311] and, like assessment of histologic tumor type, should not be the sole question of frozen section examination. If an endometrioid adenocarcinoma is unequivocally upgraded during frozen section examination as an incidental finding or if a type II carcinoma is detected in endometrioid adenocarcinoma previously diagnosed atdilatation and curettage this should be reported to the surgeon [300].

Serous (type II) carcinomas of the endometrium and MMMT are so-called high-grade carcinomas of the uterus, so frozen section examination has no intraoperative consequences [317], [310].
Diagnostic certainty for low-grade carcinomas is significantly worse than for high-

grade carcinomas [318], [319]. This is also true for intraoperative frozen section examination of uteri with atypical endometrial hyperplasia [320] [321].

There is a discrepancy between intraoperative assessment of lymph nodes and final workup in endometrial carcinoma between 7–13% [322]; [323].

During the frozen section examination, it seems reasonable to evaluate the adnexa macroscopically, incising the ovaries along their short axis [239] and histologically assessing any tumor-suspicious findings on the tube or ovary.

If there are any intraoperative consequences, a frozen section examination of the sentinel lymph node (SLN) should be performed. There is no standard protocol for workup [305], [239] [281], but this should be done according to the recommendations of the AWMF Guidelines on vulvar and cervical carcinoma (S3 Guideline for Cervical Carcinoma (awmf.org)):

- All removed SLN should be examined,
- Complete examination of the SLN,
- Macroscopic workup as for SLN without frozen section examination (see below),
- Preparation of step sections (approx. 3) from the freezing block during frozen sectioning,
- Work-up of the paraffin-embedded tissue as described below.

4.5.9 Work-up of the tissue

4.32	Consensus-based recommendation	checked 2022
EC	The tissue of a (fractionated) curettage or an endometrial biopsy shall be fully embedded.	
	Strong Consensus	

4.33	Consensus-based recommendation	modified 2022
EC	The report of findings from a (fractionated) curettage or an endometrial biopsy shall comment on the presence and type of endometrial hyperplasia. If carcinoma is present, the histological tumor type shall be indicated according to the current WHO classification. If tumor tissue is detected in the cervical fraction of a fractionated curettage, a specific statement shall be made on the presence or absence of endocervical stromal infiltration.	
	Strong Consensus	

4.34	Consensus-based recommendation	modified 2022
EC	The report of findings of a hysterectomy specimen in endometrial carcinoma shall include the following information: • Histological type according to WHO (in case of mixed tumors components in %) • Grading • Staging (pT) • Evidence/absence of lymphatic or blood vessel invasion (L and V status). • Detection/absence of perineural sheath infiltrates (Pn status) • Metric indication of depth of invasion in relation to myometrial thickness in cm/mm • Three-dimensional tumor size in cm/mm • Metric measurement of the minimum distance to the vaginal resection margin if vaginal infiltration is present • R classification (UICC)	
	Strong Consensus	

Table 9: The new (revised 2020) FIGO/TNM classification of endometrial cancer.

TNM category	FIGO stages	Definition
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I[1]	Tumor limited to corpus uteri
T1a	IA[1]	Tumor confined to endometrium or infiltrates less than half of myometrium
T1b	IB	Tumor infiltrates half or more of the myometrium
T2	II	Tumor infiltrates the cervical stroma but does not spread beyond the uterus
T3 and/or N1or N2	III	Local and/or regional spread as described below:
T3a	IIIA	Tumor invades serosa and/or adnexa (direct spread or metastases)
T3b	IIIB	Vaginal or parametrial involvement (direct spread or metastases)
N1	IIIC1	Metastases in pelvic lymph nodes[2]

TNM category	FIGO stages	Definition
N2	IIIIC2	Metastases in para-aortic lymph nodes with or without metastases in pelvic lymph nodes
T4	IVA	Tumor infiltrates bladder and/or rectal mucosa[3]
M1	IVB	Distant metastases, including intra-abdominal metastases (excluding metastases to vagina, pelvic serosa, or adnexa, including metastases to inguinal and intra-abdominal lymph nodes other than para-aortic and/or pelvic lymph nodes).

1 Assessment of endocervical glands alone should be classified as stage I.
2 Positive cytology should be diagnosed separately and documented without change in stage.
3 The presence of bullous edema is not sufficient to classify a tumor as T4. Infiltration of the mucosa of the bladder or rectum requires evidence by biopsy.
Source: [324]

4.5.9.1 Dilatation and Curettage/endometrial biopsies

The tissue removed by curettage or biopsy should be embedded completely (cervical or corpus fraction separately) [325].

The false-negative rate of fractionated curettage regarding the detection of atypical endometrial hyperplasia or endometrioid EC is about 10% [326], [327]. In the majority of cases, the cause is lack of representativeness of the material obtained during curettage[328], [325], [329].

There is no uniform histopathological definition of inadequate material of an endometrial biopsy or curettage [330], [328], [325].

Histopathological definition of an inadequate curettage or endometrial biopsy in the postmenopausal period

Approximately 3% of all endometrial biopsies/curettages are diagnostically inadequate [325]. The preparation of serial sections does not increase the diagnostic certainty in this case [325]. Regardless of the representativeness of the tissue sent after a curettage, the risk of atypical endometrial hyperplasia or endometrioid EC in a subsequent hysterectomy is 0.74% [325].

When tumor tissue is detected in the cervical fraction, a statement should be mades whether infiltration of the endocervical stroma is present or whether the tumor tissue is isolated due to dislocation from the cavum uteri [331]; [332], [276].

4.5.9.2 Preparations after simple and radical hysterectomy for endometrial carcinoma

The pathology report of findings must comment on the size, weight and nature of the specimen with particular reference to the serosal characteristics [333]; [273], [276], [239].

The macroscopic description of the endometrial carcinoma or MMMT should include the exact anatomic location (isthmus or corpus uteri, anterior or posterior wall or uterine roof), three-dimensional metric tumor extent, growth type (e.g. polypoid, sessile, diffusely infiltrating) and relationship to the endocervix [333]; [273], [239].

In addition, there should be an indication of the presence or absence or length of the resected vaginal cuff [333]; [273]. The distal vaginal resection margin should be completely assessed circular (preferably after separation into posterior and anterior vaginal cuff) [276].

According to the recommendations of the ICCR and ISGyP [273], [239], [301], the morphological workup of the hysterectomy specimen should be done in such a way that all the information required in the following list can be collected [333]; [273], [276], [239].

The recommendation is to embed one paraffin block per 2 cm of greatest tumor extension in pure endometrioid and serous carcinomas and at least one block per cm of greatest tumor extension in rare carcinoma types, mixed carcinomas and in carcinosarcoma [333], [273], [276]. In the diagnosis or differential diagnosis of a de- or undifferentiated endometrial carcinoma, a more extensive embedding may be necessary.

If no macroscopically visible tumor is found in the hysterectomy specimen, embedding of three blocks each of non-tumorous endometrium from the anterior and posterior wall is recommended [334]. If no carcinoma is detectable histologically either (so-called vanishing endometrial cancer; [335]), complete embedding of the endometrium is recommended [239], whereby several samples of the endo-myometrial junction can be embedded in one block [276].

In endometrial carcinoma, there are also different patterns of invasion into the myometrium [243], [239]. In addition to the classic invasion pattern with infiltration of grouped glands with varying degrees of peritumoral desmoplasia and inflammatory response, there are carcinomas with growth similar to adenoma malignum [336], and the so-called MELF pattern (microcystic, elongated, fragmented glands) [337], [338]. The latter two are considered to have a less favorable prognosis, and the MELF pattern is considered to have a higher rate of lymphatic vessel invasion as well as (occult) lymph node metastases [336]; [307]; [339]; [340], [239], [281]. Therefore, reporting a specific invasion pattern in the histology report is recommended.

Lymphatic vessel invasions are frequently seen in serous EC, as well as in about 10-15% of endometrioid carcinomas. Results from the PORTEC-2 study have supported their prognostic relevance [341]. For definition of lymphatic vessel invasion and its quantification, see Chapter “Definition of TNM-relevant parameters”.

Involvement of the adnexa may be macroscopically occult, especially in serous EC [332]; [331], but is relevant for staging and prognosis. Therefore, macroscopically inconspicuous ovaries should be fully embedded with the immediately adjacent hilar/meso tissue [276], [239]; lamination along the short axis of the ovary is recommended as this allows more tissue to be histologically assessed [275]; [260], [239]. When working up the tubes, it is recommended to follow the SEE-FIM protocol [342], the so-called SEE-FIM-like protocol (see following figure); [239], [301], [343].

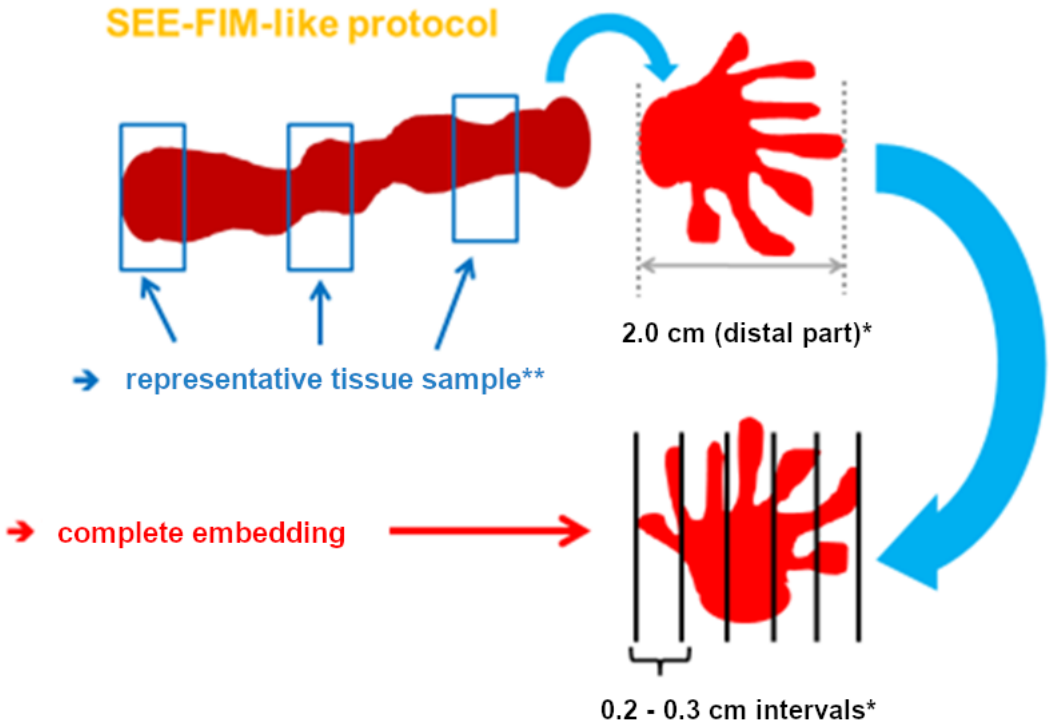


Figure 4: Tube reprocessing at the EC according to the SEE-FIM-like protocol

Legend to figure "Processing of the tubes in EC according to the SEE-FIM-like protocol"

*Amputation of the fimbria-bearing distal part with lamination in 0.2 to 0.3cm intervals, complete embedding

**Removal of approximately 3 transverse sections of the tube with inclusion of the portion near the uterus

[239], [301], [343]

4.35	Consensus-based recommendation	modified 2022
EC	Processing of the tubes should be based on the SEE-FIM-like protocol.	
	Strong Consensus	

Involvement of the tubes in EC can have different morphologic appearances [281], [344], [345], [346], [347]. In any case of tubal involvement, primary carcinoma originating from the tube should be excluded.

Tumor cells lying freely in the tubal lumen

Cells lying freely in the tubal lumen are seen especially after laparoscopic or robotic hysterectomies [344], [345] and in serous EC [346], but are rare at 2.5% [348]. This may be associated with a higher rate of positive peritoneal cytology and extrauterine spread (especially in serous EC) [346], [348], but has no prognostic significance [348]. Detection of tumor cells lying freely in the tubal lumen should be mentioned in the pathology report, but upstaging is not performed [281].

Metastasis to the tubal mucosa

If tumor cells are detected within the tubal epithelium, a coexistent serous in situ carcinoma of the tube (STIC) may need to be excluded by immunohistochemistry [260], [347], [347]. If there is involvement of the tubal mucosa by EC, upstaging is the result [281].

Involvement of the tubal wall with or without lymphatic vessel intrusions

If there is evidence of lymphatic vessel intrusions in the tubal wall without involvement of the tubal mucosa by a STIC and/or invasive carcinoma, but especially if there are lymphatic vessel intrusions in the mesosalpinx, this is involvement by the EC [281]. Whether this finding is to be evaluated only as L1 or leads to an upstaging is not clarified in the TNM classification (Wittekind 2011).

4.5.9.3 Sectioning in patients with risk-reducing hysterectomy with BSO for Lynch syndrome (RRHS)

Patients with risk-reducing hysterectomy with BSO (RRHS) show occult endometrial hyperplasia in 17-25% of cases [349], [350], occult EC in up to 12.5% [351], and ovarian carcinoma in approximately 4% [352].

Since occult endometrial hyperplasia and EC can occur circumscribed [349], [351], the following procedure is recommended in the absence of tumor at sectioning [352], [350], [349]:

- Representative embedding of the endo- and ectocervix
- Complete work-up of the isthmus endometrium (in the absence of TM detection, otherwise “more targeted sampling”, i.e. > 1 tumor block/ 2cm of greatest tumor extension)
- Complete work-up of the corpus endometrium (in the absence of TM detection, otherwise “more targeted sampling”)
- Complete workup of the distal portion of the tube/fimbrial funnel (so-called SEE-FIM-like protocol; [350], [239], [343])
- Representative embedding of ovarian tissue (complete embedding if necessary).

4.5.10 MMR/MSI analysis of endometrial hyperplasia/EIN

Compared to endometrial carcinomas, associated endometrial hyperplasias (CAH/EIN) show concordant loss of mismatch-repair proteins (MMR) in immunohistochemistry. Combined loss of MLH-1/PMS-2 predominates, followed by combined loss of MSH-2/MSH-6 as well as MSH-6 loss alone. Isolated loss of PMS-2 is rare. Loss of MLH-1 is caused by promoter methylation in more than 95% of cases [353], [354].
Using sequentially collected endometrial biopsies, it has been shown that mismatch-repair protein loss in non-neoplastic endometrium can precede invasive (MMR-deficient) EC by between 7 months and up to 12 years [355], [356]. In unselected endometrial hyperplasias, immunohistochemical loss of mismatch-repair proteins was observed in 4.5%, predominantly due to methylation of the MLH-1 promoter [357]. In analogy to the detection of Lynch syndrome in patients with EC, approximately 3% of all atypical endometrial hyperplasias with loss of MMR proteins originate from patients with Lynch syndrome. Routine immunohistochemistry of MMR proteins is not currently required in atypical endometrial hyperplasia. However, this should be

performed in patients with suspected Lynch syndrome or Lynch syndrome in the family history.

4.36	Consensus-based recommendation	new 2022
EC	Routine immunohistochemical analysis of MMR proteins shall not be performed in the setting of endometrial hyperplasia.	
	Strong Consensus	

4.5.11 Significance of the immunohistochemical determination of MMR proteins.

Immunohistochemical analysis of MMR proteins in EC has four main goals (see figure below):

- Classification of the individual tumor into the molecular classification [237], [272], [234],
- Resulting prognosis estimation (Wortmann et al.), [358],
- Identification of patients at risk for Lynch syndrome [359], [360], [272] and
- Potential therapeutic implications: Response to immune checkpoint inhibitor therapy [361], [362],
- Response to adjuvant radiotherapy [363]; in contrast, poor response to progestin therapy [364].

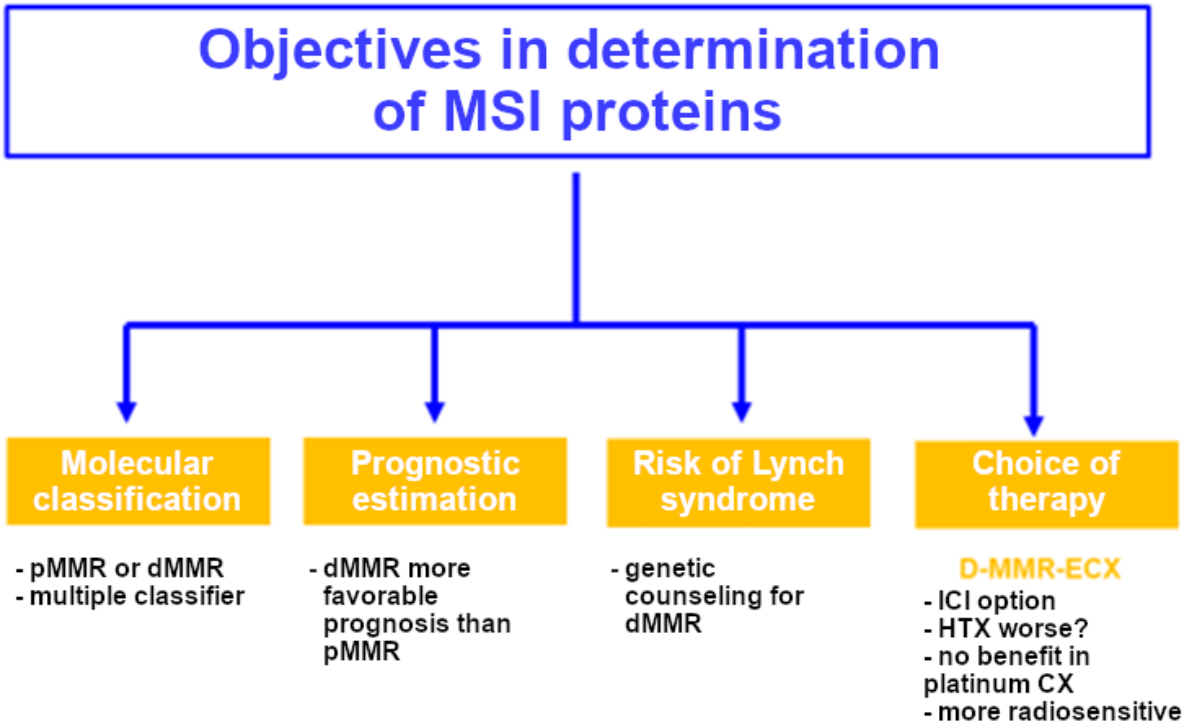


Figure 5: Objective of immunohistochemical analysis of mismatch repair proteins in endometrial carcinoma

4.5.12 Technical aspects of the immunohistochemical determination of MSI proteins

In analogy to the S3 Guideline for colorectal carcinomas [365], there is widespread consensus in the recommendations of ESMO and ISGyP regarding the preferential use of immunohistochemistry to determine MSI status or the MMR proteins [360], [235], [272], [366], [236]. This can be complemented by molecular analyses (methylation assay, MSI-PCR) if needed.

With respect to ESMO and ISGyP, the use of all four antibodies (MLH-1, PMS-2, MSH-2, MSH-6) is recommended [236], [272], [360]. In contrast to colorectal carcinoma, there are only a few studies in endometrial carcinoma regarding the comparison of two versus four immune markers of mismatch-repair proteins [367], [368], in which a total of 1,100 patients were analyzed. Both studies conclude that two MSI markers (PMS-2 and MSH-6) are equally effective as four markers (MLH-1, PMS-2, MSH-2, and MSH-6). However, only two MSI markers should be used only if reliable staining results and a safe interpretation in the respective institution are ensured when all four markers have been evaluated in advance [368]. Various studies as well as the German Society of Pathology (DGP) point out that the use of two MMR antibodies is possible as a more cost-effective alternative [369], [367], [368], [370], [371]. In any case, however, sequential addition of the remaining markers should always be possible if, among other things, in the respective case the staining is negative or only focally or patchily positive for one of the two initial markers (MSH-6 or PMS-2) or if the nuclear staining is weak [236], [360], [272].

Interpreting the immunohistochemical staining results with respect to MSI testing, there is a complete interobserver agreement of 90.4% corresponding to a kappa value of 0.92 [372]. These results were confirmed in a systematic review [373].

There is a concordance of more than 95% between immunohistochemical and molecular pathological analysis of MSI status [367], [374], so that, not least for economic reasons, a combination of both methods is generally not necessary [272], [369], but may be useful in individual cases with unclear test results [272].

In the case of MLH-1 failure, molecular pathology in the context of Lynch diagnostics should exclude MLH-1 promoter methylation [360].

Molecular testing of tumor tissue alone is not recommended, as a not insignificant proportion of MSH-6-deficient tumors may not be detected [360], [366], [369].

The procedure of MSI analysis is summarized algorithmically below (see figure).

Heterogeneous expression of MLH-1 and PMS-2 is rare and mostly due to methylation of the MLH-1 promoter in sporadic EC [375].

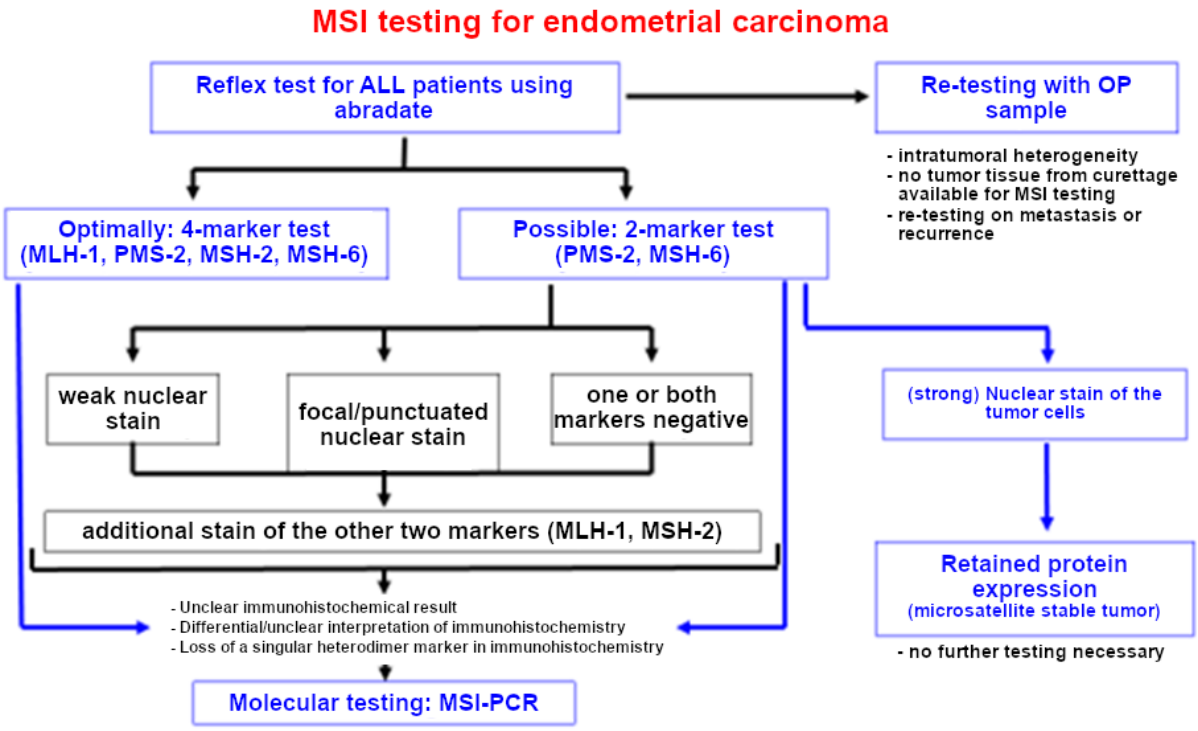


Figure 6: Algorithm of immunohistochemical analysis of MMR proteins in endometrial carcinoma

4.37	Consensus-based recommendation	new 2022
EC	MSI analysis in endometrial carcinoma shall be primarily immunohistochemical. The primary use of two antibodies (MSH-6 and PMS-2) is possible, with addition of the respective partner antibody (MSH2 or MLH1) in case of negative results. Immunohistochemical analysis of MMR proteins shall be supplemented by molecular pathological methods (MLH-1 promoter methylation, MSI-PCR) according to the indication. The exclusive use of molecular pathological methods shall not be performed. Combined analysis by immunohistochemistry and molecular pathology shall not be performed routinely.	
	Strong Consensus	

4.5.13 Time of MMR/MSI determination

Immunohistochemical determination of MMR proteins is critically influenced by pre-analytics, the most significant parameter of which is tissue fixation [376], [235], [377], https://www.thebagp.org/download/bagp-bgcs-nice-mmr-pathway/. In standard care, the tumor tissue of the hysterectomy specimen often shows autolysis-related changes and insufficient fixation [276]. Therefore, the ESMO as well as the British Association of Gynaecological Pathologists (BAGP) recommends the determination of the MMR or MSI status on the biopsy or curettage material [235],

https://www.thebagp.org/download/bagp-bgcs-nice-mmr-pathway/, because the fixation is better [369] and the result is already available for the pre-therapeutic tumor board. Repeating the examination on the surgical specimen may be useful if it shows tumor heterogeneity not visible on the biopsy or curettage material . If only a small amount of tumor tissue can be obtained by curettage the examination should be performed exclusively on the surgical specimen.

4.38	Evidence-based recommendation	new 2022
GoR **A**	Every newly diagnosed endometrial cancer shall be screened for MMR defect/MSI regardless of age and histological subtype. MMR/MSI analysis thus also serves to identify patients who shall be offered human genetic counseling.	
LoE **4**	[358], [378], [341], [363], [288], [379]	
	Strong Consensus	

4.5.14 Hereditary endometrial carcinoma

The most substantial hereditary EC occur in Lynch syndrome [366] [380] and Cowden syndrome [381], and less frequently in BRCA mutation carriers [382], [383].

About 3-5% of all EC are Lynch-associated [366], [384]. Previous data show that about one-third of all patients have no corresponding family history and EC is the “sentinel carcinoma” for Lynch syndrome, which is diagnosed after the age of 50 in about two-thirds of cases [385], [384], [386].

In particular, endometrioid EC mayshow morphological criteria suggestive of Lynch association [260], [387], [359]however, HE morphology is not a sufficient predictor [386] [359]. Therefore, immunohistochemical analysis of MMR proteins is indicated in every case of newly diagnosed EC regardless of patient age and histologic subtype [359], [272], [388], [389]. MMR immunohistochemical analysis in endometrial cancer is used to identify patients at risk who should subsequently be offered human genetic workup ([369], see Fig. 6).

EC in association with BRCA germline mutations (mostly BRCA-1; [383]) show mostly serous and more rarely G3 endometrioid histology, each with aberrant p53 expression and/or HRD [382]. Therefore, it seems reasonable to recommend appropriate human genetic counseling to patients with a conspicuous family history [389].

4.5.15 Molecular classification of endometrial carcinoma.

Based on the results of The Cancer Genome Atlas (TCGA) project [390], a morpho-molecular classification of EC has been developed in recent years [378], [391], [392], [393], [394]. This morpho-molecular classification is prognostically relevant [378], [395], [396], [397] and is increasingly implemented in therapeutic decisions [378], [398], [358], [237], [363], [399]. Therefore, depending on resources, its use is

recommended by WHO as well as ISGyP and other professional societies (ESGO, ESTRO, ESP) [234], [272], [236]. The most essential characteristics are included in Table 9“ and Table 10“ [237], [272], [390], [391], [395], [378], [358], [382]; [298], [400]. The diagnostic algorithm is summarized in Figure 7.

Molecular typing of EC is currently used only for endometrioid carcinoma, and data are very limited for the rarer histologic subtypes [234], [401], [393], [402], [403].

Molecular typing of EC should include at least immunohistochemical examination of MMR proteins and p53. POLE mutational analysis is required for complete classification, but there is currently no evidence for its practical relevance for low grade (G1-2), low stage (stage I/pT1) EC.

Risk stratification according to ESGO/ESTRO/ESP recommendation is presented in the table “Binary/dualistic model of endometrial cancer” in Chapter 4.5.

4.39	Evidence-based recommendation	new 2022
GoR **A**	In all histologically diagnosed primary EC, immunohistochemical determination of p53 as well as MMR proteins shall be performed.	
LoE **4**	[378], [363], [404], [405], [406], [407], [379]	
	Strong Consensus	

4.40	Evidence-based recommendation	new 2022
GoR **A**	In G3 or in intermediate, high intermediate, and high-risk EC, mutational analysis of the exonuclease domain of POLE shall be performed.	
LoE **4**	[378], [363], [404], [405], [406], [407], [379]	
	Consensus	

4.41	Consensus-based recommendation	new 2022
EC	Molecular classification (P53 and MMR deficiency) shall be performed preoperatively, i.e., on the curettage material or endometrial biopsy.	
	Strong Consensus	

4.42	Consensus-based recommendation	new 2022
EC	POLE mutation analysis can alternatively be performed postoperatively.	
	Strong Consensus	

Table 10: Clinicopathologic characteristics of each molecular type of endometrial carcinoma

	POLE mutant	MMR deficient	No special molecular profile	P53 abnormal
Frequency	9%	28%	50%	12%
Age	Younger women	All age groups	All ages	
Association with obesity	No	No	Yes	No
Relation to hyperestrogenism	No	No	Yes	No
Hereditary component	Rare	10% (Lynch)	Rare	BRCA possible
Precursor lesion	Atypical hyperplasia/EIN	Atypical hyperplasia/EIN	Atypical hyperplasia/EIN	None
Molecular alterations	POLE mutations	Microsatellite instability	Heterogeneous	P53 mutations
Number of mutations	Very high (ultramutated)	High (hypermutated)	Moderate	Low
Histology	Often endometrioid G3, TIL/PER	Endometrioid low/high grade, un-/dedifferentiated, TIL/PER	Endometrioid low grade	Serous, carcinosarcoma, endometrioid high grade
Diagnostics	POLE Mutation analysis	MMR Immunohistochemistry	Diagnosis of exclusion	P53 immunohistochemistry

	POLE mutant	MMR deficient	No special molecular profile	P53 abnormal
Immunohistochemistry	P53 wild type*, MMR normal*	P53 wild type*, MMR deficient	P53 wild type, MMR normal	P53 abnormal, MMR normal
Tumor stage	Often low	Wide range	Often low	Usually high, metastases frequent (lymph nodes, organ)
LVSI	Frequent	Frequent	Variable	Frequent
Prognosis	Very good	Good	Good	Poor

* In multiple classifiers, additional p53 may be abnormal or MMR deficient.

Abbreviations: TIL = tumor infiltrating lymphocytes, PER = peritumoral inflammation.

Sources: [382], [408], [358], [237], [378], [272], [395], [394], [391], [298]

Table 11: Risk stratification of endometrial carcinoma according to ESGO/ESTRO/ESP depending on molecular classification

Risk group	Molecular classification unknown	Molecular classification known [1,2]
Low	Stage IA endometrioid + low-grade[3] + LVSI negative or focal	Stage I-II **POLE-mut** endometrioid carcinoma, without residual tumor Stage IA **MMR-d/NSMP** endometrioid carcinoma, low-grade, LVI negative or focal
Intermediate	Stage IB endometrioid + low-grade* + LVI negative or focal Stage IA endometrioid + high-grade* + LVI negative or focal Stage IA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial infiltration	Stage IB **MMR-d/NSMP** endometrioid carcinoma, low-grade, LVI negative or focal Stage IA **MMR-d/NSMP** endometrioid carcinoma, high-grade, LVI negative or focal Stage IA **p53-abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed), without myometrial infiltration
High-intermediate	Stage I endometrioid + significant LVI regardless of grading and depth of invasion Stage IB endometrioid high-grade* regardless of LVI status Stage II	Stage I **MMR-d/NSMP** endometrioid carcinoma, substantial LVI, independent of grading and depth of invasion Stage IB **MMR-d/NSMP** endometrioid carcinoma, high-grade* independent of LVI Stage II **MMR-d/NSMP** endometrioid carcinoma
High	Stage III-IVA without residual tumor Stage I-IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial infiltration, without residual tumor	Stage III-IVA **MMR-d/NSMP** endometrioid carcinoma without residual tumor Stage I-IVA **p53-abn** endometrioid carcinoma with myometrial infiltration, without residual tumor Stage I-IVA **MMR-d/NSMP** serous or undifferentiated carcinoma or carcinosarcoma with myometrial infiltration, without residual tumor

Risk group	Molecular classification unknown	Molecular classification known [1,2]
Advanced metastatic	Stage III-IVA with residual tumor Stage IVB	Stage III-IVA with residual tumor, independent of molecular type Stage IVB, independent of molecular type

[1] For POLE-mutated stage III-IVA endometrial carcinomas and for MMR-deficient or NSMP clear cell endometrial carcinomas with myometrial infiltration, there are insufficient data to assign these patients to a prognostic risk group with respect to molecular classification. Prospective enrollment of these tumors is recommended.

[2] See text for "multiple classifier" (example: patients with POLE mutation and p53 aberration should be classified as POLE mutated).

[3] According to WHO, two-stage grading of endometrioid carcinomas is used; G1 and G2 carcinomas are considered low-grade, G3 carcinomas are considered high-grade (WHO 2020, Casey & Singh 2021).

LVI = lymphatic vessel infiltration, MMR-d= MMR deficient (corresponds to microsatellite instability), NSMP = no special molecular profile (molecular pathologically completely examined EC without POLE mutation and MMR deficiency and with p53 wild type), POLE-mut =polymerase E mutated.

Source: [236]

Currently, there is no immunohistochemical surrogate marker for the POLE mutation; therefore a molecular pathological analysis by Sanger sequencing or NGS including exomes 9 to 14 [391], [358] is necessary in any case. To what extent fluorescence-based SNaPshot analysis is possible as an alternative method [409] cannot be answered at present [272].

p53 immunohistochemistry is an accepted surrogate marker for a p53 mutation in gynecopathology [410], [237], including EC [411], which is also recommended by the WHO [234], and is an integral part of the molecular classification [378], [391]. At the same time, p53 immunohistochemistry is also used for correct morphological typing [392], [260], [257]. The interpretation of immunohistochemistry was developed in correlation with sequencing [412], [243]; recent data are oriented to high-grade serous ovarian cancer [413]. A comparison of immunohistochemistry between local and central pathology showed a concordance rate of more than 95% [411]. The same is true for the comparison of curettage material versus hysterectomy with a concordance rate of about 90% [414], [411] and the comparison of p53 immunohistochemistry and mutation analysis with 92.3% [415].

Diffuse/extended aberrant p53 expression is rare at 2–15% in G1 endometrioid (FIGO low grade) EC, but more common at 10-15% in G3 (FIGO high grade) endometrioid tumors [237]. Diffuse steroid hormone receptor expression and PTEN loss indicate endometrioid morphology. According to the ESMO/ESGO/ESTRO/ESP risk stratification (Table 3; [236]), these tumors are intermediate risk.

Endometrioid EC with aberrant p53 expression has a comparably unfavorable prognosis as serous EC [397].

A distinctive feature of EC is the so-called subclonal aberrant p53 expression, which is defined as an abrupt strong nuclear p53 expression (> 75% of tumor cell nuclei) in a circumscribed tumor area occupying > 10% of the total tumor [237], [358]. It is an expression of intratumoral heterogeneity with temporary mutation in the course of tumor progression and not a so-called founder mutation [413], [237], which has no

prognostic significance at the current state of knowledge [237]. Important is an exact calibration of the immunohistochemistry in the respective institute using a “low-expressor”-positive control (e.g. tonsil; [413]) and the use of optimally fixed tissue [410], [414]. The classification into the respective molecular subgroup should be done according to the predominant change.

Intratumor molecular heterogeneity is rare [416] and occurs in EC with multiple classifiers. It is not due to founder mutations but is an expression of tumor progression through epigenetic alterations [410]. Molecular subclassification is based on the predominant molecular alteration [410], [416].

If a molecular subclassification of EC is not possible, or if the results of this subclassification are inconclusive, the addition of NOS (not otherwise classified; e.g., well-differentiated endometrioid EC NOS) may be used in addition to the histological subtype [237]. EC with NSMP (no special molecular profile), in which a complete molecular examination has been performed but no classification into the category POLE-mutated, p53-aberrant or MSI-deficient, must be clearly distinguished from this. Because of the heterogeneity of this molecular group [403], [358], attempts were made to further stratify these tumors [396], [417], [418], [419], [420]. Nuclear beta-catenin reactivity correlates with a CTTNB exon 3 mutation [418], and also appears to be associated with a less favorable prognosis [417], [418], [420]. Similarly, immunohistochemical L1CAM positivity in NSMP-EC is prognostically unfavorable [421]. However, there is insufficient data to include CTTNB and L1CAM in the WHO or ESGO/ESTRO/ESP classification [236], [404]. In the present Guideline, the determination of L1CAM is listed with a recommendation grade of 0. It may be useful, for example, when considering fertility-preserving therapy of early EC.

Regarding a possible change in molecular subtype in the context of tumor progression or metastasis, few data are available. Preliminary results suggest that the molecular subtype remains stable and that only p53-aberrant (serous) EC may result in a therapeutically relevant HRD [299].

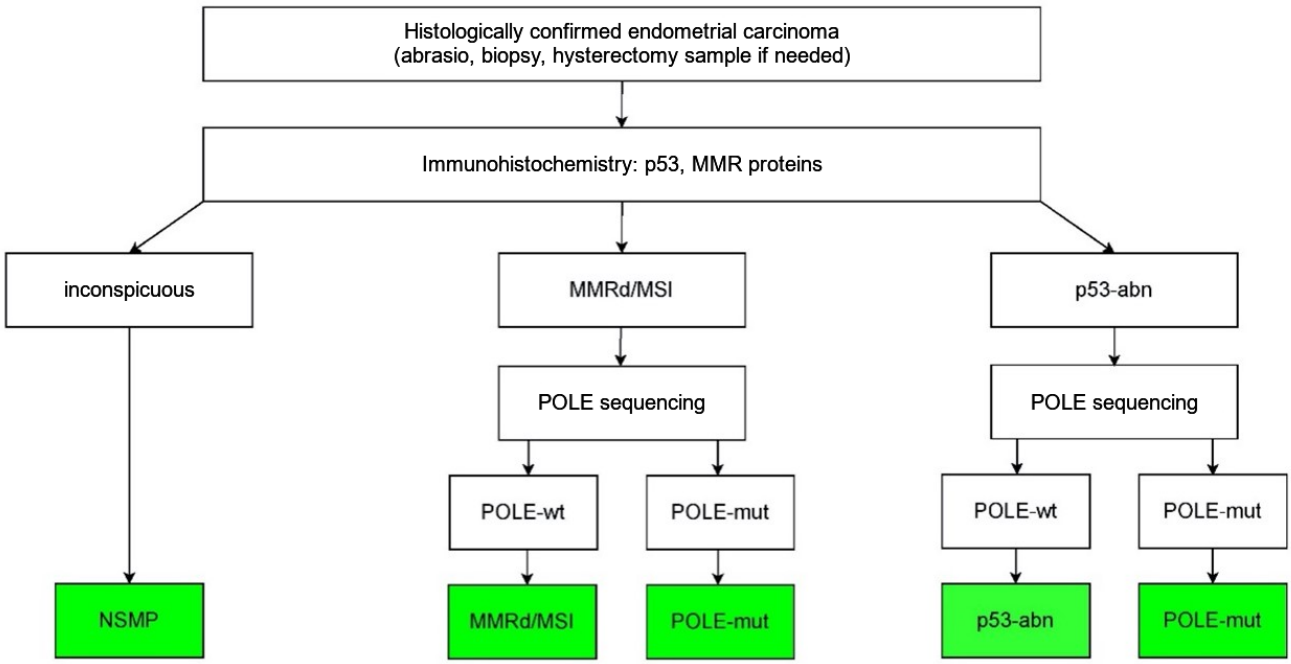
4.43	Evidence-based recommendation	new 2022
GoR **0**	In low risk EC, IHC determination of L1CAM can be performed.	
LoE **4**	[396], [358], [378], [422], [404], [407], [398]	
	Consensus	

4.5.16 Multiple molecular alterations ("multiple classifier")

3-5% of all EC are "multiple classifier", i.e. they have more than one molecular subtype (TCGA 2013, [358], [237]. In particular, this concerns EC with POLEmut or MSI, in the following constellations:

- POLEmut and MSI
- POLEmut and p53mut
- MSI and p53mut
- POLEmut, MSI and p53mut

However, these multiple molecular alterations appear to be without practical significance. POLE-mutated EC with immunohistochemically aberrant p53 expression (p53mut) behave like POLE-mutated EC with p53 wild type [358]. The same is true for MSI EC and aberrant p53 expression, MSI EC, EC with POLEmut, MSI and aberrant p53 expression and EC with POLEmut and MSI [358]. Multiple classifier EC are approximately 75% G3 carcinomas with endometrioid histology or FIGO stage I [358]. The impact of POLE mutation on tumor biologic behavior and the existence of "multiple classifier"-EC underscores the importance of POLE mutation analysis for molecular classification of EC [272], [237]. Although the data is limited, this is a rapidly developing new field of knowledge.



NSMP = no special molecular profile; p53 = TP53; p53-abn = p53 abnormal; MMR = mismatch repair protein; MMRd = mismatch repair protein deficient; MSI = microsatellite instability; POLE = polymerase epsilon; -wt = wild type; -mut = mutated

Cave: For all cases of EC with intermediate, high intermediate, or high risk (Table 11) according to histological criteria, POLE shall be sequenced.

Figure 7: Recommended algorithm for molecular classification of endometrial cancer

4.5.17 Curettage material versus hysterectomy specimen

There is a high concordance between studies on curettage material and hysterectomy specimen of 90-95% and molecular classification overall [414], [411], [423], [395], [393]. Therefore, risk stratification is in principle possible on the curettage material [238]. A repetition of the examination on the hysterectomy specimen is useful only if an additional tumor component is detected [416]. An indispensable prerequisite for adequate molecular classification is the use of optimally fixed tissue [413], [360]. This is usually more likely to be fulfilled on the curettage material than on the hysterectomy specimen.

4.44	Consensus-based recommendation	new 2022
EC	Molecular typing of endometrial carcinoma shall be performed on optimally fixed tissue, i. e. preferably on the curettage material. Due to a high concordance rate betweencurettage and hysterectomy specimens, a repeat determination on the surgical specimen shall not be performed if no additional tumor component is detectable on the hysterectomy specimen.	
	Strong Consensus	

4.5.18 PD-L1 expression

MMR-deficient and POLE-mutated EC are ultra- and hypermutated tumors, respectively [237], [400]; the same applies to the so-called multiple classifier [358]. In analogy to other tumor entities [424], MMR-deficient and POLE-mutated EC show an increased neoantigen expression with consecutive increased immunogenicity due to their genetic instability. Morphologically, some of these EC have numerous intra- and peritumoral lymphocytes (see table “ESGO/ESTRO/ESP – Risk stratification of endometrial carcinoma depending on the presence of molecular pathological test results”); [408], [237], [272]. Increased immunogenicity is also associated with increased PD-L1 expression [425], [426]. A possible relationship with methylation of the MLH1 promoter is unclear here [425], [426].

4.5.19 Workup and reporting of omentectomy specimens in endometrial carcinoma

4.45	Consensus-based recommendation	modified 2022
EC	At least oneparaffin block shall be examined from omentectomy specimens with macroscopic tumor infiltration in endometrial carcinoma. In the case of macroscopically absent tumor infiltration, four to six paraffin blocks (embedding of several specimens in one block is possible) shall be examined. Any additional abnormal findings (e.g., intraomental lymph nodes) shall be described macroscopically and examined histologically.	
	Strong Consensus	

Omentectomy is a standard surgical treatment for type II carcinoma and is performed in individual cases of endometrioid (type I) carcinoma and MMMT.

There are currently no uniform guidelines for the workup of omentectomy specimens in endometrial carcinoma, including recent recommendations from the College of American Pathologists Tumor Extent [333], and the International Collaboration on Cancer Reporting [273]. Therefore, the following points are based on results of studies in ovarian cancer [427], [428], [429].

Attention should be paid to the following points during macroscopic evaluation and tissue sampling [430]; CAP 2015, [276]:

- Three-dimensional size of the omental resectate in cm.
- Indication of the three-dimensional size of a tumor infiltration in cm,
- Lamellation in slices approximately 0.5 cm thick,
- Description of the number and size of intraomental lymph nodes (with workup as described in the lymphonodectomy section).
- Description and embedding of focal findings,
- In case of macroscopic tumor infiltration, embedding of 1 (to 2) paraffin blocks,
- In the absence of macroscopic tumor infiltration, embedding of 4 to 6 paraffin blocks (embedding of several specimens in one block is possible).

The histopathological report of findings should include the following information [430]; CAP 2015, [276]:

- Maximum extent of tumor infiltration in cm
- Indication of the histological type in case of tumor infiltration
- Number and status of intraomental lymph nodes
- Indication of any non-malignant findings (e.g., inflammatory changes, adipose tissue necrosis, mesothelial hyperplasia).

To document the diligence of the workup, it seems useful to indicate the number of examined samples or paraffin blocks in case of negative tumor detection (e.g., 7 samples in 5 blocks examined omental tissue without malignancy with 2 lymph nodes without metastases (0/2) as well as 1 cm older adipose tissue necrosis). The result of peritoneal cytology is not staging relevant [324], but correlates with (occult) involvement of the omentum [431]; [432].

4.5.20 Processing and reporting of lymphonodectomy specimens in endometrial cancer

4.46	Consensus-based recommendation	checked 2022
EC	For lymphonodectomy specimens as part of surgical therapy for endometrial cancer, all removed lymph nodes shall be completely embedded and examined histologically.	
	Strong Consensus	

4.47	Consensus-based recommendation	modified 2022
EC	Lymph nodes up to approximately 0.2 cm maximum extent should be embedded in toto, and larger lymph nodes should be bisected or lamellated along their short axis and also embedded completely.	
	Strong Consensus	

4.48	Consensus-based recommendation	checked 2022
EC	The report of findings of lymphonodectomy specimens in endometrial carcinoma shall include the following information: • Indication of the number of affected lymph nodes in relation to the number of removed lymph nodes in assignment to the sampling location (pelvic, para-aortic), • Indication of the extent of the largest lymph node metastasis in mm/cm, • Indication of absence/evidence of capsular rupture of lymph node metastasis(s), • Indication of evidence of isolated tumor cells in the lymph node and evidence of lymphatic vessel invasion in the perinodal adipose tissue and/or lymph node capsule.	
	Strong Consensus	

Background

The workup and reporting of lymphonodectomy specimens in endometrial carcinoma does not differ from the Guideline for cervical carcinoma ((awmf.org); [433], [343]. The same applies to the definition of isolated tumor cells and micro- versus macrometastases [343].

Ultrastaging with preparation of staged sections and/or additional immunohistochemical studies may increase the number of patients with isolated tumor cells or micrometastases in EC [434]. Ultrastaging with sequential sectioning and/or additional immunohistochemistry may increase the number of patients with

isolated tumor cells or micrometastases in EC [434]. However, ultrastaging of negative non-sentinel lymph nodes is not recommended [239], [281], [343].

The distinction between micro- and macrometastases is not staging relevant in endometrial cancer. Studies suggest that detection of isolated tumor cells (ITC) or micrometastases (pN1mic) may be prognostically significant [435], [436], [437]. However, not all studies separate ITC and micrometastases in their definition according to UICC [437] or both parameters are combined in the evaluation. According to the recommendations in the TNM, ITC and micrometastases and their differentiation should be noted in the histology report and included in the staging.

4.49	Consensus-based recommendation	new 2022
EC	Isolated tumor cells in the sentinel LC (< 0.2mm) (pN0 (i+) are per se not an indication for adjuvant radiotherapy and/or chemotherapy. This is recommended only in case of corresponding additional risks (e. g. p53 mutation, type II EC, LVSI).	
	Strong Consensus	

4.50	Consensus-based recommendation	new 2022
EC	For micrometastases (> 0.2 mm, < 2mm) (pN1(mi)), adjuvant radiotherapy and/or chemotherapy should be given.	
	Strong Consensus	

More positive sentinel nodes are detected by ultrastaging, especially in low and intermediate risk endometrial carcinomas [436], [438], [439]. In a good half of the cases of positive sentinel nodes, these are based on isolated tumor cells (ITC) or micrometastases [436], [438], [439], whose relevance for prognosis is at least unclear, possibly even irrelevant [436], [439]. Therefore, the generous performance of sentinel node biopsy with ultrastaging may also lead to unnecessary upstaging and initiation of adjuvant therapies that only increase morbidity without improving prognosis [436], [439]. Micrometastases (> 0.2 mm to ≤ 2 mm, pN1 (mi)) are considered by most experts to be metastatic disease indicating adjuvant therapy [435], [236].

In a retrospective study, when patients with micometastases were considered as nodal positive and received adjuvant therapywere shown to have the same PFS y as nodal-negative EC patients [435]. Whether this was due to a therapeutic effect or to the lack of relevance of the micrometastases cannot be clarified by this study.

Very few data are currently available on the possible prognostic significance of extracapsular spread in endometrial carcinoma [440]. Nevertheless, all AWMF guidelines as well as the ICCR recommend to mention extracapsular spread as standard in the report of findings [441].

Parametranous (mesometranous) lymph nodes belong to the regional lymph nodes in endometrial carcinoma [280] and should be subsumized under pelvic lymph nodes. Lymph node metastases of this location are classified as pN1 rather than pT3b. Intraomental lymph nodes also belong to the regional lymph nodes.

4.5.21 Workup of sentinel lymph nodes in EC

4.51	Consensus-based recommendation	modified 2022
EC	Sentinel lymph nodes in endometrial carcinoma shall be lamellated parallel to their short axis and fully embedded and examined in sequential sections. Sentinel lymph nodes that are negative in the hematoxylin-eosin stain shall additionally be examined by immunohistochemistry (so-called ultrastaging).	
	Strong Consensus	

Background

With regard to the histopathological examination of sentinel lymph nodes, there is currently no uniform protocol [239], [281], [442], yet ultrastaging of sentinel lymph nodes should always be performed [443], [444], [239], [281], [343], [434], [445], [236]. The workup of sentinel lymph nodes in endometrial carcinoma is based on the S3 Guideline for Cervical Carcinoma and the S2k Guideline for Vulvar Carcinoma, as well as the recommendations of the Society of Gynecologic Oncology (SGO) for EC [446].

In this approach, the sentinel lymph nodes should be lamellated along their short axis into approximately 0.2-cm-thick slices and completely embedded [239], [343], [447], [305]. At least three sequential sections should be made, each approximately 200 µm apart, and HE-stained (S3 Guideline for Cervical Carcinoma and S2k Guideline for Vulvar Carcinoma). If no tumor cells can be detected in the HE-stained section preparations, an immunohistochemical examination with a pan-cytokeratin antibody (e.g., AE1/AE3) should be performed [443], [444], [239], [281], [343], [445].

In case of intraoperative frozen section examination [305],[236], macroscopic workup is performed as described. The complete lymph node(s) are used for frozen sectioning. Three sequential sections should be made from the frozen blocks.

4.5.22 Morphological prognostic factors

The WHO classification, ISGyP and ESGO/ESTRO/ESP consensus recommend that prognostic assessment of EC be performed morpho-molecularly [234], [281], [236]. This consists of a combination of morphological, immunohistochemical and molecular pathological parameters [281], [237], [448], [236].

Established prognostic factors are tumor stage, evidence of lymph node metastases, histologic tumor type according to WHO, grading in endometrioid EC and molecular classification [281], [237], [448], [236], [238].

Grading in endometrioid EC follows the recommendations of FIGO, with G1 and G2-EC classified as low grade and G3-EC as high grade according to WHO (see above, [234], [281], [236].

Myometrial depth of invasion and endocervical stromal involvement are staging-relevant and prognosis-associated for FIGO and TNM. Involvement of endocervical glands is not staging-relevant in the FIGO or TNM classification and is subsumed in stage FIGO I/pT1. However, it is recommended to mention this finding in the pathology report.

Peritoneal cytology status is no longer staging relevant but should be mentioned in the histopathology report [281], [239].

The histological tumor type according to WHO is an integral part of the findings report [301], [281], [236], [237]. However, the exclusive importance of histological type is increasingly modified by molecular classification [237], [257], [260].

Mixed EC consist of ≥2 histologic types, one of which must be serous or clear cell, without regard to quantity.

Carcinosarcomas (MMMT) with heterologous mesenchymal component, higher tumor stage and large tumors appear to be prognostically unfavorable [266]; [449]. The majority of carcinosarcomas are molecular p53 mutated tumors [403].

In endometrioid EC, tumor size apparently has prognostic relevance [450].

Incompletely resected tumors (R1 or R2 situation) have a significantly higher local recurrence rate [451]; [452]. Therefore, incomplete tumor resection can be classified as a prognostically relevant factor.

The so-called MELF-pattern (microcystic, elongated and fragmented glands) as an invasion pattern in EC has prognostic significance due to a higher frequency of occult lymphatic vessel invasion, lymph node metastases as well as the association with epithelial-mesenchymal transition [453], [454]. To what extent tumor budding known from colorectal carcinoma is prognostically relevant [455], cannot be assessed at present.

In a study of more than 25,000 patients with stages FIGO IA/T1a and IB/T1b, lymh vascular space invasion (LVSI) showed a 4- to 10-fold increased risk of lymph node metastases [340]. Among LVSI-positive EC, the extent of LVSI is prognostically relevant [288], [285].

In many studies, venous infiltration is not explicitly evaluated or infiltration into small veins/venules is subsumed under vascular invasion or involvement of the lymphovascular space. Studies on the significance of venous infiltration are lacking [456]; [452].

Perineural sheath infiltration is a parameter that has been insufficiently studied in endometrial carcinoma [456]; [452].

Immunohistochemical detection of steroid hormone receptors correlates with endometrioid EC [238], [260]. Therefore, their prognostic significance should be considered unclear [457].

Regarding the significance of nomograms for prognostic assessment without or with inclusion of molecular data, there is currently insufficient evidence [458], [459], [460].

Other molecular markers outside of TCGA-based subclassification are currently not considered important in EC [238], [272].

Morphologic prognostic factors and the need to report them in the histopathologic report are summarized in the following table.

Table 12: Summary of standard*, risk, and prognostic factors and their treatment relevance in endometrial cancer and malignant mixed Müllerian tumor (MMMT; carcinosarcoma)

Name	Standard factor	Risk/Predictive factor	Therapeutic relevance
Tumor stage	yes	yes	yes
Myometrial invasion depth	yes	yes	yes
Lymph node status	yes	yes	yes
Histological tumor type according to WHO	yes	yes	yes
Size of lymph node metastases	yes	unclear	no
Number of metastatically affected lymph nodes	yes	unclear	no
Extracapsular spread of lymph node metastases	yes	unclear	no
Status of peritoneal cytology	yes	unclear	no
Perineural sheath infiltration (Pn status)	yes	unclear	no
Lymphatic vessel infiltration (L-status)	yes	yes	yes
Extent of lymphatic vessel infiltration	yes	yes	unclear
Vein invasion (V status)	yes	unclear	no
Resection margins	yes	yes	yes

Name	Standard factor	Risk/Predictive factor	Therapeutic relevance
(residual tumor status; R classification)			
Grading	yes	yes	yes
Tumor localization in the uterus	yes	unclear [1]	no
Three-dimensional tumor size in cm	yes	unclear [2]	no
Associated endometrial hyperplasia	no	no	no
Invasion pattern	yes	unclear[3]	no [4]
Hormone receptor status	no	unclear	no
L1CAM	no	yes / unclear	unclear
Molecular classification	complete molecular classification desirable	yes	yes
Molecular markers (except POLE, MMR, p53)	no	no	no
Nomograms	no	no	no

*The term standard factor describes parameters that are essential for the histopathological report or examination procedures that should be used routinely.

1 Tumor localization in the isthmus uteri may indicate a Lynch association. There may possibly be an increased risk of cervical infiltration based on topographic/anatomic proximity alone, to be assessed sonographically/radiologically.
2 Tumor size probably has prognostic significance in endometrioid EC. Molecular data are not included.
3,4 The MELF pattern is associated with a higher rate of (occult) lymphatic vessel invasion and consecutive higher number of lymph node metastases.

5 Therapy of precancerous lesions and early endometrial carcinoma

5.1 Endometrial hyperplasias

5.1.1 Endometrial hyperplasia without atypia

5.1	Evidence-based recommendation	modified 2022
GoR **B**	Simple endometrial hyperplasia without atypia should not be treated by hysterectomy.	
LoE **3**	[461], [338]	
	Strong Consensus	

5.2	Evidence-based recommendation	new 2022
GoR **0**	Hysterectomy may be considered for complex endometrial hyperplasia without atypia.	
LoE **3**	[461]	
	Strong Consensus	

Background

In its current nomenclature, WHO defines endometrial hyperplasia without atypia and atypical endometrial hyperplasia (AEH) synonymously: endometrial intraepithelial neoplasia = EIN [338].

Endometrial hyperplasia without atypia is a benign change that is usually observed or treated conservatively (e.g. systemic progestins, oral contraceptives, progestin IUD, weight reduction; caveat: estrogen/androgen-producing tumor) and is operated on only in exceptional cases. The risk of developing invasive carcinoma is 1% [338].

The group “complex endometrial hyperplasia without atypia” included in the previous WHO classification has been abandoned and is now included in the group “endometrial hyperplasia without atypia” [338], .

A recent systematic review and meta-analysis analyzed 12 studies of 804 patients with endometrial hyperplasia without atypia in curettage material or endometrial biopsy who subsequently underwent hysterectomy (HE). In 566 women with simple nonatypical endometrial hyperplasia, occult EC was found in 2% in the HE specimen In the 238 patients with complex nonatypical hyperplasia on curettage or biopsy, EC was present in the HEspecimen in 12.4% [461].

5.1.2 Atypical endometrial hyperplasia (AEH)

5.1.2.1 Approach to AEH in postmenopausal women or premenopausal women with completed family planning

5.3	Evidence-based recommendation	checked 2022
GoR **A**	In postmenopausal patients and in premenopausal patients with completed family planning and presence of atypical hyperplasia of the endometrium, total hysterectomy with bilateral salpingectomy and, if necessary, bilateral ovariectomy shall be performed.	
LoE **1**	[338], [231]	
	Strong Consensus	

Background

Endometrial hyperplasia with atypia has a risk of progression of up to 30% [338]. In up to 60%, invasive carcinoma is already present in the hysterectomy specimen when the diagnosis “endometrial hyperplasia with atypia” is made in the curettage or biopsy material 462].

The group “complex endometrial hyperplasia without atypia” included in the previous WHO classification has been abandoned and is now included in the group “endometrial hyperplasia without atypia” [338], .

For atypical endometrial hyperplasia (AEH) and EC pT1a, G1, total hysterectomy (+ adnexal extirpation) results in disease-specific 5-year survival of at least 99% [463]. With supracervical hysterectomy or endometrial ablation, endometrium remains in the uterus or cervical stump, respectively, so these operations are not recommended for AEH [464].

Considering the high risk of progression of atypical endometrial hyperplasia, possible limitations of quality of life due to hysterectomy (see S3 Guideline “Indication and methodology of hysterectomy for benign diseases”, version 1.2, April 2015, AWMF register number: 015/070, http://www.awmf.org/leitlinien/detail/ll/015-070.html) [465], recede into the background. Only an unfulfilled desire to have a child should open up a waiver of hysterectomy for atypical endometrial hyperplasia as an option.

5.1.2.2 Approach to AEH in premenopausal women

5.4	Consensus-based recommendation	modified 2022
EC	In the presence of atypical hyperplasia, the ovaries may be left in place when performing hysterectomy and bilateral salpingectomy in premenopausal women, provided there is no evidence of a hereditary predisposition to ovarian cancer (e.g., BRCA mutation or certain forms of Lynch syndrome).	
	Strong Consensus	

Background

There are no studies on the risks of leaving the adnexa in premenopausal women undergoing hysterectomy for AEH. Based on current knowledge, removal of both salpinges can be discussed with the patient for prophylaxis of tubal/ovarian/peritoneal carcinoma [466].

In endometrioid EC pT1, a meta-analysis of 5 case/control studies found no difference in overall survival when the ovaries were removed or left in place [467]. A later meta-analysis of 7 retrospective cohort studies of women with stage I EC (1,419 patients with ovarian preservation, 15,826 women with hysterectomy and bilateral adnexal extirpation found no significant differences in overall and disease-free survival between the two groups, even in premenopausal women (HR overall survival=0.99 ; 95%-CI= 0.56-3.93) [468], If one accepts these results (LoE 3) for early EC, it could also apply to AEH.

In women with AEH and with a familial predisposition to ovarian cancer, the ovaries should not be left in place. Since not all forms of Lynch syndrome are associated with an increased risk of ovarian cancer, if a germline mutation in the Lynch genes is detected, a consultation with a human geneticist competent in this field should be obtained before deciding on ovarian preservation (see Chapter 10).

5.1.2.3 Fertility preservation in women with AEH

5.5	Consensus-based recommendation	checked 2022
EC	If uterus preservation is desired, the uterus and adnexa may be left in place in the presence of atypical hyperplasia if the patient has been informed that the standard treatment almost always leading to cure is total hysterectomy, agrees to close monitoring and has been informed of the need for hysterectomy after the desire for a child has been fulfilled or abandoned.	
	Strong Consensus	

5.6	Consensus-based recommendation	checked 2022
EC	If uterus preservation is desired, the uterus and adnexa may be left in place in the presence of atypical hyperplasia if a hysteroscopy with targeted biopsy or with curettage was performed to confirm the diagnosis and the diagnosis “atypical hyperplasia” was made or confirmed by a pathologist experienced in gynecologic pathology.	
	Strong Consensus	

5.7	Consensus-based recommendation	checked 2022
EC	If uterus preservation is desired, the uterus and adnexa may be left in place in the presence of atypical hyperplasia if laparoscopy with vaginal ultrasound or MRI has been performed to best assess the risk of adnexal involvement and/or myometrial infiltration.	
	Strong Consensus	

5.8	Consensus-based recommendation	checked 2022
EC	If complete remission of AEH is seen after 6 months of conservative treatment, planned pregnancy should be pursued.	
	Strong Consensus	

5.9	Consensus-based recommendation	checked 2022
EC	If there is currently no desire to have a child, maintenance therapy shall be performed. An endometrial biopsy should be performed every 6 months.	
	Strong Consensus	

5.10	Evidence-based recommendation	checked 2022
GoR **A**	After fulfillment or abandonment of the desire to have children, a total hysterectomy (+/- bilateral salpingectomy +/-, bilateral ovariectomy) shall be performed.	
LoE **4**	[469], [470], [471], [472], [473]	
	Strong Consensus	

Background

Conservative therapy of AEH may be considered when there is still an unfulfilled desire to have children and fertility should be preserved.

To date, numerous papers have been published on conservative therapy for patients with atypical endometrial hyperplasia (AEH) and early EC [464], [474]. Few of these publications meet the quality criteria (minimum number of patients, minimum treatment duration, sufficient follow-up, and others) that would make them usable for a systematic review.

Since 2012, 5 meta-analyses and systematic reviews have appeared, which, although based on the same pool of publications, reached varying conclusions [475], [474]. The conservative therapies used varied considerably: hydroxyprogesterone 500 mg/d orally, medroxyprogesterone acetate 10–1800 mg/d orally, megestrol acetate 160 mg/d orally, natural progesterone 200 mg/d orally 14th–25th day of cycle, progestogen IUD among others [475], [474].

The group led by Bristow, a US gynecologic oncologist, found 45 eligible trials involving 391 patients. 66% of these women with AEH had complete remission with conservative therapy. AEH persisted in 14% of patients, and 23% relapsed after initial remission. 41% of women with conservatively treated AEH became pregnant [475].

A UK study group selected 34 publications with 154 patients; 86% of women had remission, 26% had recurrence, and 26% had a live birth [476].

An Australian working group found only 12 publications that met their criteria, with 117 patients. Here, 74% of women with AEH had a complete remission, 2.7% had persistent AEH, and 20% relapsed after an initial response [477].

A French study group found 24 trials that met their quality requirements, but published the pooled results for AEH and EC (see below) [478].

Therapy of AEH with a levonorgestrel IUD theoretically offers the advantage of high local progestin concentration with low systemic progestin exposure [474]. The available studies provide contradictory results and are methodologically inadequate (too small case numbers, retrospective case collections) [474]. The 2013 Cochrane Collaboration analysis concludes that there are no adequate studies demonstrating the safety and efficacy of a levonorgestrel IUD for the treatment of AEH [474].

Mandelbaum et al. retrospectively analyzed 245 patients with complex atypical endometrial hyperplasia who had been treated systemically (n=176) with progestogens or with a levonorgestrel -IUD (n=69). The progestin IUD resulted in complete remission in 79%, and systematic progestin treatment in 47%. (HR=3.32; 95% KI=2.39- 4.62). Progression to carcinoma occurred in 4.5% of women with progestin IUD and in 16% of patients with systemic progestin treatment (HR=0.28; 95%-CI=0.11-0.73). Especially morbidly obese patients benefited from progestin-IUD treatment [479].

5.1.2.4 Metformin and progestin therapy for endometrial hyperplasia

The oral antidiabetic drug metformin (MET) has been evaluated in a number of clinical trials as a therapeutic agent for the treatment of endometrial hyperplasia (EH). A Cochrane meta-analysis analyzing data through 2017 identified 3 randomized trials with a total of only 77 subjects and found no therapeutic effect for MET in terms of remission, progression or recurrence rates [480]. However, some recent studies found evidence of a therapeutic effect of MET. Tehrani et al. compared 40 mg megestrol acetate (MA) daily for 4 weeks combined with 1000 mg MET daily for 3 months or placebo [481] in 60 women with EH without atypia. After 3 months, remission rates (27/30 [93%] vs. 19/30 [70%]) differed significantly in favor of the MET group. In a retrospective analysis of 245 women with complex EH, concomitant MET use was associated with increased remission rates with levonorgestrel IUD (LNG-IUD) (87% vs. 59% at 6 months) but not with increased rates with oral progestin therapy (23% vs. 28% at 6 months) [482]. Yang et al. randomized 150 women with atypical EH or early EC G1/2 to megestrol acetate (160 mg 1x1 daily) with/without MET (500 mg 3x1 daily) [483]. After 4 months, combination therapy achieved higher complete remission rates (34% vs. 21%; p=0.09). However, after 8 months, this difference was no longer detectable.

Overall, based on the available data, MET cannot currently be recommended as an additional therapeutic agent for the treatment of EH due to the lack of clear evidence of efficacy.

Given the potential clinical consequences (including unnecessary hysterectomy in younger women versus inadequate appreciation of a potentially life-threatening cancer) and the great difficulties in pathologic differential diagnosis (EH without atypia, EH with atypia, well-differentiated endometrioid EC), it is reasonable to seek a second opinion from a pathologist particularly familiar with this problem [321].

Since there is no study-proven conservative treatment for AEH, only consensus-based recommendations can be made.

Since synchronous invasive EC is often not detected, it is advisable to also treat AEH conservatively with a dosage that is effective in manifest EC (medroxyprogesterone

acetate 200–250 mg/d orally; megestrol acetate 160–200 mg/d) (see Chapter 9, as well as Statement 5.18 in Chapter 5.2).

Histologic controls (Pipelle, hysteroscopy, dilatation and fractional curettage) at 6 months are recommended. If AEH persists or progression to EC occurs, hysterectomy is indicated [321]. Given the relevant recurrence rate after initially successful conservative treatment of AEH, hysterectomy should be performed after fulfillment or abandonment of the desire to have children [321], [478]. Studies on the quality of life under conservative therapy of AEH are not available.

5.2 Early endometrial cancer

5.2.1 Procedure for early endometrial carcinoma

5.11	Evidence-based statement	checked 2022
LoE **3**	In the presence of early endometrial carcinoma (endometrioid, pT1a G1), total hysterectomy with bilateral adnexal extirpation results in a disease-specific 5-year survival of 99%.	
	[484]	
	Strong Consensus	

Background

In the presence of early endometrial carcinoma (endometrioid pT1a, G1), total hysterectomy with bilateral adnexal extirpation results in a disease-specific 5-year survival of 99% [463].

5.2.2 Preservation of the adnexa in premenopausal women with early endometrial cancer

5.12	Consensus-based recommendation	modified 2022
EC	In the presence of endometrioid endometrial carcinoma G1, G2 pT1a, the ovaries may be left in place when performing hysterectomy and bilateral salpingectomy in premenopausal women, provided there is no evidence of hereditary predisposition to ovarian cancer (e.g., BRCA mutation, certain forms of Lynch syndrome) and the patient is informed of the risk.	
	Consensus	

Background

The data on preservation of the ovaries in early endometrial carcinoma are provided in the background text on AEH. However, it should be noted that even in young

women with early endometrial carcinoma G1 or pT1a, synchronous ovarian carcinomas or ovarian metastases may occur in up to 25% [485].

It should be noted that preoperative imaging and even intraoperative assessment of the ovaries did not reveal a proportion of these tumors [485].

In a retrospective cohort study of 282 young women (15–49 years) with endometrial cancer, 27 had Lynch syndrome (9.6%), 151 (53.4%) had estrogen dominance (obesity, PCOS, etc.), and 104 (36.8%) had neither Lynch syndrome nor estrogen dominance. Synchronous ovarian cancer was found in 23.1% of patients with Lynch syndrome, in 6.6% of women with estrogen dominance and in 21% of EC patients from the "neither nor" group [380].

5.2.3 Synchronous endometrial and ovarian cancer

Women with endometrial cancer (EC) rarely have synchronous ovarian cancer. In an analysis of the U.S. Surveillance, Epidemiology and End Results Program (SEER) file, among 56,986 patients with ovarian cancer, synchronous EC was found in 1709 (3%) cases [486]. In contrast, young women with EC have a significantly increased risk of synchronous endometrial and ovarian cancer (SEOC), reported in the literature to range from 11% to 36% [487], [488], [489], [485], [490]. This fact has important consequences for the counseling and therapy of young women with EC.

In >70% of cases, SEOC are synchronous endometrioid adenocarcinomas in both the endometrium and ovary. Based on this histological concordance and on clonality analyses, a common monoclonal origin has been proposed for SEOC [491]. In most cases of SEOC, both EC and ovarian cancer are diagnosed at an early stage of disease, and the prognosis of women with SEOC is therefore good. For example, Oranratanaphan et al. [487] report a 5-year survival rate of 64% in women with SEOC compared with only 48% in women with EC and ovarian metastasis.

The distinction between SEOC and EC with ovarian metastasis is sometimes difficult and is based on both clinicopathological criteria and immunohistochemical analyses such as PAX-8, which is expressed in primary ovarian cancer but not in EC metastases [492]. In the literature, the rate of ovarian metastases varies widely, ranging from 12% [485] to 87% [487], indicating difficult histopathological assignment.

However, accurate diagnosis and differentiation between SEOC and EC with ovarian metastasis is of great clinical importance, as patients with EC and ovarian metastasis are candidates for adjuvant chemotherapy or radiotherapy, but not patients with two early cancers, as would be the case with a diagnosis of SEOC. Therefore, in case of ambiguity, consultation with a reference pathologist is recommended.

Young women with SEOC are at increased risk for carrying a hereditary non-polyposis colon cancer (HNPCC) syndrome-associated mutation (Lynch syndrome). While the rate of Lynch syndrome in women with EC is approximately between 4% and 11% [493], young women with SEOC have Lynch syndrome in approximately 40% of cases [490]. Lynch syndrome screening should therefore be performed in young women with SEOC (see also Chapter 10 Recommendation 10.6).

5.2.4 Fertility preservation in women with early endometrial cancer

5.13	Consensus-based recommendation	modified 2022
EC	In women with incomplete family planning and endometrioid cT1a without myometrial infiltration, G1, p53-wt and L1CAM-negative endometrial carcinoma and a desire for fertility preservation, the uterus and adnexa can be left in place if the patient has been informed that the standard treatment almost always leading to cure is total hysterectomy and that the patient temporarily forgoes curative treatment of a malignancy on her own responsibility, knowing the potentially fatal consequences (progression of the disease, metastasis) even if a pregnancy is carried to term.	
	Strong Consensus	

5.14	Consensus-based recommendation	modified 2022
EC	If uterus preservation is desired, the uterus and adnexa can be preserved in the presence of endometrioid cT1a, without myometrial infiltration G1, p53-wt, and L1CAM-negative endometrial carcinoma if the patient has been recommended a consultation with a specialist in reproductive medicine to assess the chances of fulfilling a childbearing desire.	
	Strong Consensus	

5.15	Consensus-based recommendation	modified 2022
EC	If uterus preservation in endometrioid cT1a, without myometrial infiltration G1, p53-wt and L1CAM-negative endometrial carcinoma are desired, the uterus and adnexa can be left in place if the patient agrees to close monitoring and has been informed of the need for hysterectomy after fulfillment or abandonment of the desire to have children.	
	Strong Consensus	

5.16	Consensus-based recommendation	modified 2022
EC	In endometrioid cT1a without myometrial infiltration, G1, p53-wt and L1CAM-negative endometrial carcinoma and desire for fertility preservation, the uterus and adnexa can be left in place if a diagnosis of well-differentiated (G1) endometrioid EC expressing progesterone receptors has been made by hysteroscopy with targeted biopsy or with diatation and curettage and evaluation by a pathologist experienced in gynecologic pathology.	
	Strong Consensus	

5.17	Consensus-based recommendation	modified 2022
EC	In endometrioid cT1a without myometrial infiltration, G1, p53-wt, and L1CAM-negative endometrial cancer and desire for fertility preservation, the uterus and adnexa can be left in place if laparoscopy with vaginal ultrasound or if MRI has ruled out adnexal involvement or myometrial infiltration as much as possible.	
	Strong Consensus	

5.18	Consensus-based recommendation	modified 2022
EC	In endometrioid cT1a without myometrial infiltration, G1, p53-wt, and L1CAM-negative endometrial cancer and desire for fertility preservation, the uterus and adnexa can be left in place if sufficient drug treatment is given with medroxyprogesterone acetate 200-250 mg/d/p.o.) or megestrol acetate (160-200 mg/d/p.o.) or a levonorgestrel IUD (52 mg).	
	Strong Consensus	

5.19	Consensus-based recommendation	checked 2022
EC	If a complete remission of the endometrial carcinoma is diagnosed after six months of conservative treatment, the planned pregnancy should be pursued in cooperation with a specialist in reproductive medicine if necessary.	
	Consensus	

5.20	Consensus-based recommendation	modified 2022
EC	Patients with endometrioid cT1a without myometrial infiltration, G1, p53-wt, and L1CAM-negative endometrial cancer without a current desire to have children should receive maintenance therapy (levonorgestrel-IUD, oral contraceptives, cyclic progestins) and have an endometrial biopsy every 6 months.	
	Strong Consensus	

5.21	Consensus-based recommendation	checked 2022
EC	If there is no remission of the carcinoma after six months of conservative treatment, hysterectomy should be performed.	
	Strong Consensus	

5.22	Consensus-based recommendation	modified 2022
EC	If uterus preservation is desired, the uterus and adnexa can be left in the presence of endometrioid endometrial cancer (cT1a, G1, p53-wt, and L1CAM-negative) if the following conditions are met: • Information that the standard treatment almost always leading to cure is total hysterectomy, • Consent with close follow-up, • Information about the necessity of hysterectomy after fulfillment or abandonment of the desire to have a child, • Hysteroscopy with targeted biopsy or dilatation and curettage to confirm diagnosis, • Laparoscopy with vaginal ultrasound or MRI to rule out adnexal involvement/myometrial infiltration, • Diagnosis made or confirmed by a pathologist experienced in gynecologic pathology, • Treatment with MPA or MGA or LNG-IUD (52 mg), • After 6 months, repeat hysteroscopy withdilatation and curettage as well as imaging. If no remission, hysterectomy, • If complete remission, aim for pregnancy (expert in reproductive medicine), • If no current desire to have children: maintenance therapy and endometrial biopsy every 6 months, after fulfillment or abandonment of the desire to have children: total hysterectomy and bilateral adnexal extirpation recommended.	
	Consensus	

Background

EC are malignancies that usually lead to death if left untreated. The majority of early stage EC with good differentiation are cured in almost 100% of cases by hysterectomy. Forgoing this curative surgery requires a strict indication. There should be a concrete desire to have children and not just an abstract desire to preserve fertility. It should be explained to the patient that she is foregoing curative treatment of a malignancy, at least temporarily, with potentially fatal consequences (disease progression, metastasis), even if a pregnancy is carried to term [476].

Ruiz et al. analyzed data from 23,231 patients with EC stage I who were <50 years old. 873 of them had been treated conservatively. In multivariate analysis, stage IA

patients had a 5-year survival of 97.5% (hysterectomy) and 97.5% (conservative therapy with progestogens), respectively. For stage IB patients, survival rates were 97.5% (hysterectomy) and 75% (progestins) [494].

Gonthier et al. identified from the SEER database 1,106 women with EC G2 or G3 confined to the endometrium who were younger than 45 years of age. Uterus-preserving therapy was performed in 49 patients. The 5-year overall survival was 94.8% (hysterectomy) and 78.2% (uterus preservation) (HR=6.6; 95%-CI=3.3-13.4). Disease-specific survival was 99.3% (hysterectomy) and 86.2% (uterine preservation) (HR=15.8%; 95%-CI=5.5-45.2) [495].

Greenwald et al. determined the 15-year survival of 6,339 women with EC stage I G1/G2 from the SEER database (1993-2012). After propensity score matching, cancer-specific mortality was 9.2% (95%-CI=3.4%-24%) in women treated conservatively and 2.1% (95%-CI=1.5-2.8%) in patients after hysterectomy. However, by using other definitions, no significant difference in mortality was then found [496].

Gunderson et al. [475] reported 48% remissions of EC G1 with conservative therapy in a systematic review. The median time to response was 6 months. 35% of women whose EC initially responded, relapsed subsequently. 35% of patients with EC became pregnant.

Gallos et al. [476] reported a remission rate of 76%, a recurrence rate of 40% and a live birth rate of 28%. 3.6% of women developed ovarian cancer, 2% had progression to higher stages and 2 of 408 conservatively treated EC patients died from their disease.

An Australian analysis of the literature found complete remission with oral progestin therapy in 72% of EC patients and a recurrence rate of 20%. 3% of women had progression of EC while on progestin therapy [477].

A French analysis that pooled data for AEH and EC, found a remission rate of 81% and a recurrence rate (after initial response) of 30%; the pregnancy rate was 32% and progression occurred in 15% of patients with EC [478]. The French analysis showed that after nine months of conservative treatment, further remissions were not expected. However, the probability of recurrence after initially successful conservative treatment increased continuously [478].

Another meta-analysis by this group found that the remission rate was higher with conservative therapy when specimen collection for diagnosis had been performed by operative hysteroscopy (OR for remission = 2.31; 95%-CI=1.10-4.84) [497].

No data are available on the dependence of the success rate of conservative therapy for early EC in childbearing on p53 and L1CAM -expression. However, it is logical to advise against fertility-preserving procedures in early EC that have a p53 mutation or L1CAM -overexpression, given the unfavorable prognosis. Immunohistochemical determination of L1CAM, which is generally recommended with a recommendation grade of 0, should be performed generously if fertility-preserving therapy is planned.

In a recent meta-analysis, estrogen and/or progesterone receptor expression had no predictive value regarding the response of endometrial hyperplasia with atypia or early EC to conservative therapy with oral progestogens. For therapy with a levonorgestrel IUP, ER and or PR expression had significant predictive value. However, the accuracy was too low to recommend clinical use [498]. The aforementioned meta-

analysis by Guillon et al. also found no significant predictive value for expression of either steroid receptor [497].

In the studies that were analyzed, widely varying progestin doses were used. Therefore, a definite dose recommendation cannot be made. It seems logical to the Guideline group to apply doses that are effective in the therapy of advanced EC (medroxyprogesterone acetate 200–250 mg/d orally; megestrol acetate 160–200 mg/d orally) [499], [500].

The statements, recommendations and background texts on fertility preservation in endometrial cancer have been adopted one-to-one in the S2k Guideline “Fertility preservation in oncological diseases” (AWMF register number: 015-082, http://www.awmf.org/leitlinien/detail/anmeldung/1/ll/015-082.html) after the consensus conference of this Guideline had agreed on them again. This resulted in 100% agreement between the experts of the S3 Guideline on endometrial cancer and the S2k Guideline on fertility preservation.

6 Surgical therapy of endometrial carcinoma

6.1 Basics of surgical therapy

The basis of surgical therapy for endometrial carcinoma is total hysterectomy and bilateral adnexal extirpation (see above Chapter 5). In exceptional cases, surgical removal of the ovaries may be omitted (Chapter 5; Recommendations 5.12).

6.1.1 Parametrial resection

6.1	Evidence-based recommendation	modified 2022
GoR **A**	In endometrial carcinoma cT2 or pT2 (with histologic evidence of involvement of the cervical stroma) without clinical suspicion of parametrial infiltration, radical hysterectomy (parametrial resection) shall not be performed.	
LoE **3**	[501]	
	Strong Consensus	

Background

Traditionally, radical hysterectomy (resection of the parametria) was recommended for stage pT2 endometrial carcinoma (involvement of the cervical stroma) [502]. This recommendation was based on small case series, such as Tamussino et al. [503], who found continuous progression of carcinoma from the cervical stroma into the parametria in 2 of 16 patients with cervical involvement. The Japanese GOTIC study group [313] retrospectively analyzed data from 300 EC patients with suspected macroscopic cervical involvement. Seventy-four women had received radical, 112 modified radical, and 114 simple hysterectomy. The type of hysterectomy did not affect the rate of local recurrence, progression-free survival or overall survival, even when clear cervical involvement was demonstrated on the hysterectomy specimen. Intraoperative complications and postoperative voiding dysfunction were found significantly more often in the groups with radical or modified radical hysterectomy.

A recent meta-analysis of 10 retrospective cohort studies involving 2,866 patients showed no significant advantage of radical hysterectomy for overall survival (HR 0.92; 95%-CI 0.72-1.16; P = 0.484) or progression-free survival (HR 0.75; 95%-CI 0.39-1.42; P = 0.378). Even after adjuvant radiotherapy was considered, there was no advantage of radical hysterectomy [501]. In case of parametrial involvement, stage pT3b is present, which should be treated with radical hysterectomy under the aspect of R0 resection.

6.2 Lymphonodectomy

6.2	Consensus-based recommendation	modified 2022
EC	In patients with endometrial carcinoma (all stages and histologies), the lymph nodes that appear enlarged on laparoscopic or open inspection of the abdominal cavity and/or are susspicuous on palpation (“bulky nodes”) shall be removed.	
	Strong Consensus	

6.3	Consensus-based recommendation	checked 2022
EC	Lymph node sampling of inconspicuous lymph nodes shall not be performed.	
	Consensus	

6.4	Consensus-based recommendation	new 2022
EC	When surgical lymph node staging is performed in patients with endometrial cancer, it shall be performed as a systematic LNE or sentinel node biopsy rather than sampling.	
	Strong Consensus	

6.5	Evidence-based recommendation	modified 2022
GoR A	In low-risk type I endometrial carcinoma pT1a, G1/2, no bulky nodes, systematic lymphadenectomy shall not be performed.	
LoE 1	[504]	
	Consensus	

6.6	Consensus-based recommendation	new 2022
EC	If pT1a (without myometrial infiltration), G1/G2, a p53 mutation (intermediate risk), or L1CAM overexpression (high-intermediate risk) is present in a type I endometrial carcinoma, a sentinel node biopsy can be performed, followed by systematic LNE if necessary.	
	Consensus	

6.7	Consensus-based recommendation	new 2022
EC	If a type I endometrial carcinoma cT1a, G3, or cT1b, G1/2 and no p53 mutation (i.e., at least an intermediate risk endometrial carcinoma) is present preoperatively, sentinel node biopsy can be performed, followed by systematic LNE if necessary. Primary systematic LNE should be omitted.	
	Strong Consensus	

6.8	Consensus-based recommendation	new 2022
EC	In endometrial cancer type I, cT1b, G3 (high-intermediate risk group), surgical lymph node staging - sentinel LNE or (sentinel-assisted) systematic LNE - should be performed.	
	Strong Consensus	

6.9	Consensus-based recommendation	new 2022
EC	If type I endometrial carcinoma cT1a, G3, or cT1b, G1/2 and a p53 mutation (high risk) are present preoperatively, surgical lymph node staging -sentinel LNE and/or (sentinel-assisted) systematic LNE- should be performed.	
	Strong Consensus	

Background

The staging of patients with endometrial carcinoma is based on the result of the staging operation (FIGO 2020), see Chapter 4.5.9, in particular the table “The new FIGO/TNM classification” regarding FIGO/TNM stages. The removal of lymph nodes from the lymph drainage area of the tumor serves the detection of tumor-involved lymph nodes for the purpose of a) determining the prognosis, b) identifying patients

in an advanced stage who require adjuvant systemic therapy, c) possibly therapeutic purposes through the removal of occult metastases and micrometastases.

Across all stages, there is approximately a 15% chance of having lymph node metastasis at diagnosis of endometrial cancer [505]. However, this frequency varies from approximately 0% to 31% depending on the extent of myometrial infiltration and grading [506]. Lymph node metastasis is a prognostic factor, with increasing absolute number of lymph node metastases, ratio of positive lymph nodes to total number of lymph nodes removed, and location of lymph node metastases correlating with prognosis [507], [508]. Approximately 22% of patients with preoperatively presumed stage I show higher tumor stage after surgical staging [509].

A recent Cochrane analysis summarizes, in terms of a meta-analysis, the results of the only two published prospective randomized trials on the performance of lymphadenectomy for early endometrial carcinoma [510]: the ASTEC trial investigated the survival of standard surgery (HE plus BSO) versus standard surgery plus lymphadenectomy in patients with endometrial carcinoma limited to the corpus in the preoperative diagnosis [511]. A total of 1,408 patients were randomized to a standard surgery arm (n = 704) and a lymphadenectomy arm (n = 704).

In the standard arm, abdominal hysterectomy was performed with bilateral salpingo-oophorectomy (BSO), peritoneal lavage and palpation of para-aortic lymph nodes with removal of suspicious lymph nodes. In the lymphadenectomy arm, the iliac lymph nodes and obturator fossa lymph nodes were also systematically removed. Postoperatively, risk-adapted (low, intermediate-risk, high) randomization was performed regarding the implementation of adjuvant radiotherapy versus nihil. The 5-year overall survival (OS) rate was 81% (95%-CI 77%–85%) for the standard arm and 80% (95%-CI 76%–84%) for the lymphadenectomy arm. The 5-year relapse-free survival (RFS) was higher in the standard arm (79% (95%-CI 75%–83%)) than in the lymphadenectomy group (73% [95%-CI 69%–77%], but was not significantly different. Risk stratified (low, intermediate or high-risk), the relative effect of additional lymphadenectomy versus standard surgery alone was determined, showing no advantage in favor of lymphadenectomy (OS p = 0.55; RFS p = 0.35). There was a higher rate of lymphedema in the lymphadenectomy arm (moderate to severe) compared to the standard arm.

Benedetti Panici et al. [512] studied in their RCT 514 patients with endometrioid or adenosquamous endometrial carcinoma in preoperative FIGO (1988) stage I. They were randomized into a lymphadenectomy (n = 264) and a control arm without lymphadenectomy (n = 250). Standard therapy in both arms was hysterectomy with bilateral salpingo-oophorectomy.

In the lymphadenectomy group, the external iliac lymph nodes and obturator including interiliac lymph nodes were removed. Lymphadenectomy was completed with resection of lymph nodes located above and lateral to “usual iliac lymph nodes”. Patients with FIGO (1988) stage IB grade 1 were excluded from participation. The 5-year OS was lower in the lymphadenectomy group than in the no lymphadenectomy group (85.9% versus 90.0%), but the difference between the two groups was not significant (risk of death 1.16; 95%-CI 0.67–2.02; p = 0.59). The 5-year DFS showed no significant difference between the two groups, 81.0% and 81.7%, respectively (difference between both groups risk of death 1.20; 95%-CI 0.75–1.91; p = 0.41).

Both early and late postoperative complications were significantly more common in patients who underwent lymphadenectomy (81 patients in the lymphadenectomy group and 34 patients in the no lymphadenectomy group, p = 0.001).

Surgery with pelvic systematic lymphadenectomy resulted in more accurate surgical staging because significantly more patients with lymph node metastases were found in the lymphadenectomy group than in the no lymphadenectomy group (13.3% versus 3.2%; difference = 10.1%; 95%-CI = 5.3%–14.9%; p < 0.001). In the lymphadenectomy group, approximately 10% of patients were classified as stage FIGO IIIC after surgery. The authors conclude that systematic pelvic lymphadenectomy results in more accurate surgical staging but not improvement in DFS or OS.

Consistent with the results of the two included studies, the authors of the Cochrane review concluded that for presumed stage I disease, there is no evidence that performing lymphadenectomy can reduce the risk of death or recurrence compared with not performing lymphadenectomy [513]. Additionally, when lymphadenectomy is performed, there is increased surgery-related morbidity with increased lymphocele formation. The authors also note that there is currently no evidence from RCTs for patients with advanced tumor stage or high risk of recurrence.

In addition to the two prospective randomized studies, three other studies showed excellent overall survival (96–98.9%) without performing lymphadenectomy [514], [515], [516], in a total of 936 low-risk stage I, G1, and G2 patients (and according to Mayo criteria, additional endometrioid histology and tumor diameter < 2 cm). The same results are found in a SEER analysis with over 50,000 patients [517].

In both RCTs, only pelvic LNE was performed. In a paper from the Mayo Clinic, Podratz's group [518], who performed a qualified systematic LNE, showed that in patients with stage pT1c or G3 or with diameter of the tumor >2 cm, 63 of 281 (22%) patients had lymph node metastases. Of these, 51% had both pelvic and para-aortic lymph nodes involved, and another 16% had only para-aortic lymph nodes. Only 33% had isolated involvement of the pelvic lymph nodes.

Many authors understand para-aortic LNE to mean removal of lymph nodes up to the inferior mesenteric artery and have significantly lower rates of positive para-aortic lymph nodes. All authors who lymphadenectomize to the renal pedicle have similar numbers to Podratz's group [518], as the majority of para-aortic lymph node metastases are located in the area of the renal pedicle. Based on this premise, only one-third of nodal-positive patients in both randomized trials probably underwent complete lymphadenectomy. In the Italian trial, a mean of 30 pelvic lymph nodes were removed [512]. In the ASTEC trial, fewer than 15 lymph nodes were removed in 60% of surgeries and fewer than 10 in 35% of cases. Both trials found numerous patients with low-risk tumors (49% in the non-LNE arm of the UK trial).

These tumors are expected to have only a minimal percentage of affected lymph nodes, and thus the potential benefit of LNE is very small. In the Italian study, high-risk carcinomas (serous, clear cell) were less than 1%, and in the UK study, 7%. In the UK study, there is a clustering of lower-risk patients in the non-LNE group [511]. In the Italian study, adjuvant therapy was completely optional. In the non-LNE group, 25% of women underwent postoperative radiation, compared with only 17% in the LNE group [512]. In the British study even a second randomization (± teletherapy) was performed after surgery. The indication for brachytherapy was again optional and this occurred in 52% [511]. One could calculate that in the British study only one third of

the subjects had a sufficient probability of positive lymph nodes. Of these, only one-third would have been treated correctly with a pelvic-only LNE. And of those, in turn, only one-third had a sufficient number of lymph nodes removed. This means that less than 4% of patients in the LNE arm can contribute to answering the question.

A conclusion of the authors of the Italian study should also be viewed critically. Here, the authors point out that two RCTs appeared during the trial that showed that adjuvant therapy was not associated with survival, so the effect of adjuvant radiotherapy has a limited effect on the primary outcome of this trial (overall survival). This contrasts with the results of a more recent Cochrane review, which found a benefit in overall survival when adjuvant platinum-containing chemotherapy was performed – regardless of whether adjuvant radiotherapy was performed [519].

This suggests that measures that contribute to a more precise determination of nodal status translate into improved prognosis.

This must be contrasted with the repeatedly documented lymphadenectomy-associated higher morbidity and the possible overtreatment of many patients, who have a high surgical risk profile due to obesity and co-morbidities.

In this respect, it makes sense to adapt the performance, technique and extent of lymphadenectomy to the expected probability of lymph node metastasis with the aim of improving prognosis by identifying patients with an indication for adjuvant therapy. The technique used in this context is to differentiate between a pelvic (starting from the junction of the circumflex ilium profunda vein with the external iliac artery up to half of the common iliac artery) or pelvic and para-aortic (from half of the common iliac artery up to the junction of the inferior mesenteric artery) lymph node metastasis. [inframesenteric] or to the level of the orifice of the left renal vein [infrarenal]). Extent refers to the number of lymph nodes actually removed in a given drainage area.

Another meta-analysis, which included 7 observational studies in addition to the RCTs discussed above, showed that performing systematic lymphadenectomy (non-systematic lymphadenectomy defined as the removal of ≤ 10–11 lymph nodes, systematic lymphadenectomy ≥ 10–11 lymph nodes) improved OS in patients with intermediate- and high-risk tumors [520]. Critically, the meta-analysis is quite significantly influenced by the non-prospectively collected SEER data [463], which indeed contribute between 62% to 72% of patients according to sub-evaluation in this paper and have a strong unilateral, indeed dominant effect.

Another evaluation of the same SEER database [521] documents a very obvious, undetected selection bias. In an attempt to balance this imbalance in the SEER data, Bendifallah et al. [517], arrive at a more restrictive conclusion regarding the benefit of LNE after propensity score matching (which leaves only 22,800 of nearly 51,000 patients for further evaluation).

In summary, given the current trial evidence found by the systematic literature search and assessment, there are currently no reliable data from randomized trials indicating an advantage of systematic lymphadenectomy or sentinel-assisted lymphadenectomy or sentinel lymphadenectomy alone in terms of recurrence-free or overall survival in patients with FIGO stage I EC.

Therefore, recommendations 6.5 to 6.11 recommending systematic lymphadenectomy or sentinel-assisted lymphadenectomy are not based on convincing

clinical evidence and should be considered as expert opinion only. There is also no reliable study evidence for the selection of patients to undergo systematic lymphadenectomy or sentinel-assisted lymphadenectomy based on molecular or immunohistochemical markers such as p53 (see recommendations 6.6, 6.8, and 6.9). Therefore, these recommendations should also be considered as expert opinion only and are based on the prognosis being considered unfavorable and the assumption of a higher probability of benefit from possible adjuvant therapy.

6.2.1 Lymphatic vessel invasion

6.10	Consensus-based recommendation	modified 2022
EC	If extensive lymphatic vessel invasion (at least high-intermediate risk group) is present in endometrial carcinoma type I stage I, pT1a G1-G3, pT1b G1/G2, a systematic LNE should be performed, even if no other risk factors are present. If a negative sentinel is present, LNE can be omitted.	
	Strong Consensus	

Background
No data clarifying the value of lymphadenectomy for proven lymphatic vessel invasion (L1) were found in the literature search. However, increased lymph node metastases are to be expected in L1 (see Chapter 4: Pathology).

6.2.2 Lymphonodectomy for advanced endometrial cancer

6.11	Consensus-based recommendation	modified 2022
EC	In endometrial carcinoma type I, pT2 to pT4, M0, G1–3, (sentinel-assisted) systematic lymphadenectomy should be performed if macroscopic tumor resection can be achieved.	
	Strong Consensus	

6.12	Evidence-based statement	new 2022
LoE **4**	If bulky nodes are present in patients with endometrial cancer (all stages, all histologies), sentinel node biopsy is no longer informative.	
	[522]	
	Strong Consensus	

Background

There are no published studies explicitly addressing the role of lymphadenectomy in advanced endometrial cancer. Multiple retrospective studies address the benefits of “optimal” cytoreductive surgery in patients with stage III and IV endometrial cancer [523], [524]. Each study was able to show a statistically significant benefit in terms of PFS and OS when optimal cytoreduction could be achieved.

No direct evidence exists in the literature for the recommendation of sentinel-assisted systematic lymphadenectomy in patients with EC type I, pT2 to pT4, M0, G1-3. The recommendation is based on the estimated unfavorable prognosis and the assumption of a higher detection rate of lymph node metastases and an associated higher probability of benefit from adjuvant therapy.

6.2.3 Lymphonodectomy for endometrial carcinoma type II

6.13	Consensus-based recommendation	modified 2022
EC	In endometrial carcinoma type II, (sentinel-assisted) systematic lymphadenectomy should be performed if complete tumor resection can be achieved macroscopically.	
	Strong Consensus	

Background

Type II carcinomas are more poorly differentiated and have a worse prognosis than type I tumors. Relative to the proportion of all endometrial cancers (10–20% of cases), they have a disproportionate share of endometrial cancer-related deaths (40%) [525].

No study separately reports the effect of systematic LNE versus no lymphadenectomy in patients with type II endometrial carcinoma, as they are mostly included in the so-called “high-risk” group of advanced or metastatic endometrioid carcinomas. In the SEPAL study alone, type II carcinomas (n = 55) were classified into an intermediate-risk (FIGO I and II) or high-risk (FIGO III u. IV) group based on stage. As will be shown below, pelvic and para-aortic LNE in intermediate and high-risk compared with pelvic LNE alone showed a reduction in the risk of death [526]. In addition, patients with type II carcinomas and proven pelvic metastasis (FIGO IIIC1) had more frequent occult metastases on ultrastaging of the para-aortic lymph nodes than patients with type I carcinomas [526].

No evidence from randomized trials exists in the retrieved literature for the recommendation of sentinel-assisted systematic lymphadenectomy in patients with EC type II. The recommendation is based on the prognosis being considered unfavorable and the assumption of a higher detection rate of lymph node metastases and an associated higher probability of benefit from adjuvant therapy.

6.2.4 Systematic lymphonodectomy

6.14	Evidence-based recommendation	checked 2022
GoR **B**	If systematic LNE is indicated, it should be performed pelvic and infrarenal-para-aortic.	
LoE **3**	[527], [528], [529], [438], [439], [530]	
	Strong Consensus	

Background

The effect of performing para-aortic lymphadenectomy on survival in endometrial cancer was investigated in a retrospective cohort analysis, the so-called SEPAL study [526].

Retrospectively, 671 patients with endometrial cancer treated at two tertiary centers with complete systematic pelvic (n = 325 patients) or combined pelvic and para-aortic lymphadenectomy were studied (n = 346) (January 1986 to June 2004). Patients at intermediate or high risk of recurrence were offered adjuvant radio- or chemotherapy. The primary outcome was OS. Here, OS was significantly better in the pelvic and para-aortic than in the pelvic LNE group (HR = 0.53, 95%-CI 0.38–0.76; p = 0.0005). Combined pelvic and para-aortic LNE had a positive effect in 407 patients at intermediate or high risk of recurrence (p = 0.0009), but not in low-risk patients. In multivariate analysis, pelvic and para-aortic LNE in intermediate and high-risk compared with pelvic LNE alone reduced the risk of death (0.44, 0.30–0.64; p < 0.0001). Analysis of 328 intermediate- or high-risk patients treated with adjuvant radio- or chemotherapy showed that both pelvic and para-aortic LNE (0.48, 0.29–0.83; p = 0.0049) and adjuvant chemotherapy each independently resulted in longer survival (0.59, 0.37–1.00; p = 0.0465).

It should be critically noted that the difference between pelvic only versus pelvic + para-aortic LNE in terms of HRs was substantially greater in the SEPAL trial than in the studies that examined LNE versus no LNE. The study is characterized by the risk of substantial bias [526].

Odagiri et al. [531] performed a systematic LNE from the femoral annulus to the renal vein in 266 patients with EC. A mean of 62.5 lymph nodes were removed (range 40–119). Forty-two women (15.8%) had lymph node metastases, of which 16 (38%) were exclusively pelvic, 7 (16.7%) were exclusively para-aortic and 19 (45.2%) were pelvic plus para-aortic. That is, para-aortic lymph nodes were involved in approximately 60% of women with lymph node metastases. 11% of positive lymph nodes were found above the inferior mesenteric artery [531].

Alay et al. [532] performed systematic pelvic plus para-aortic lymphadenectomy to the renal pedicle in 204 EC patients. A mean of 69.1 lymph nodes were removed (range 33–122). 44 patients (21.6%) had lymph node metastases, 27 of which were para-aortic. 11 of these women had exclusively para-aortic metastases above the

inferior mesenteric artery, 4 exclusively below this vessel and 12 in both locations [532].

The above and other retrospective analyses [531] show that in EC with lymph node metastases, the para-aortic lymph nodes are affected in at least 50%. In accordance with the lymphatic drainage of the corpus uteri, which is not insignificantly along the ovarian vessels, the lymph nodes between the inferior mesenteric artery and the renal pedicle are affected in relevant frequency in cases of lymph node involvement.

A recent systematic review with meta-analysis including eight studies and 2,793 patients showed that para-aortic plus pelvic LNE resulted in prolonged overall survival compared with pelvic LNE alone in patients with intermediate and high risk EC (HR= 0.52 ¸ 95%-CI = 0.39-0.69, P < 0.001) [530]. In patients with low risk EC, additional para-aortic LNE to the renal pedicle did not significantly improve overall survival. However, given the inherent limitations of retrospective studies, the authors of the meta-analysis call for validation of the results with sufficiently large RCTs [530].

A recent analysis of 3,650 women with lymph node-positive EC from the SEER database showed that compared with patients with pelvic LNE alone, those with additional para-aortic LNE had lower overall (HR= 0.74;95%-CI= 0.63-0.88) and EC-specific mortality (HR= 0.79; 95%-CI = 0.66-0.95) [533].

6.2.5 Lymphonodectomy for carcinosarcoma of the uterus.

6.15	Consensus-based recommendation	modified 2022
EC	For carcinosarcomas of the uterus, (sentinel-assisted) systematic LNE should be performed.	
	Strong Consensus	

Background

Surgical therapy for uterine carcinosarcoma has traditionally been similar to other endometrial cancer therapy and should include hysterectomy and bilateral adnexal extirpation [534].

In 2008, Nemani et al. [535] analyzed the courses of 1,855 operated patients with stage I (n = 1,099), II (n = 245), and III (n = 353) uterine carcinosarcoma from the SEER database; 965 women (57%) had received lymphadenectomy. A median of 12 lymph nodes had been removed. 119 (14%) of lymphadenectomized patients had positive lymph nodes. The 5-year overall survival was significantly better in patients with LNE than in those who did not have lymphadenectomy (49% versus 35%). Median survival was 54 months (CI 44–72) versus 25 months (CI 22–29). Adjuvant radiotherapy did not improve overall survival [535].

The study, like many retrospective analyses in the SEER database (see above), is at considerable risk of bias. For example, the finding that the number of lymph nodes removed (< 12 versus > 12) had no effect on improving survival is not plausible. The patients with positive lymph nodes were scored as stage IIIC, resulting in stage migration (improvement in both stage I by removal of the pN1 patients and stage III by inclusion of the patients who were putatively stage I but had pN1 microscopically).

However, since lymph node metastases are found in more than 10% of uterine carcinosarcoma, systematic lymphadenectomy seems a reasonable measure.

A retrospective analysis of 1,140 women with uterine carcinosarcoma from Dutch databases showed an improvement in overall survival when more than 10 lymph nodes had been removed (HR = 0.67; 95%-CI = 0.50-0.89; P= 0.006 in multivariate analysis). Additional adjuvant radiotherapy and/or chemotherapy improved overall survival in nodal-positive patients or those without LNE, but not in nodal-negative women with carcinosarcoma [536].

No evidence from randomized trials exists in the retrieved literature to recommend sentinel-assisted systematic lymphadenectomy in patients with carcinosarcoma of the uterus. The recommendation is based on the estimated unfavorable prognosis and the assumption of a higher detection rate of lymph node metastases and an associated higher probability of benefit from adjuvant therapy.

6.2.6 Sentinel lymph node biopsy

6.16	Consensus-based statement	modified 2022
EC	The combination of systematic LNE and sentinel biopsy (that is, sentinel-assisted LNE) may improve the detection of positive lymph nodes.	
	Consensus	

Background

Sentinel node biopsy (SNB) is an established concept in many tumors for the safe detection of tumor-involved lymph nodes and has advantages over conventional systematic lymphonodectomy due to less trauma. Studies have investigated SNB as an alternative and also additive to systematic LND.

Various labeling procedures and injection techniques for intraoperative identification of sentinel lymph nodes have been evaluated so far in endometrial cancer mainly in single-center studies; see for example [537], [538]. The Sentiendo study [539], [540], [541], [542] is the most important multicenter study. Detection rates achieved with intrauterine or cervical injection varied between 35 and 100%. A meta-analysis including 1,385 patients showed a sensitivity of the method of 81% and a false-negative rate of 19% [543]. Algorithms involving complete pelvic lymphadenectomy of the respective hemi-pelvis in the absence of unilateral detection increased the sensitivity to 95% and decreased the false-negative rate to 5%.

The FIRES trial is a multicenter prospective cohort study of the use of the sentinel lymph node procedure in early endometrial cancer [438]. At the 10 participating U.S. hospitals, 385 clinical stage 1 patients were labeled by cervical injection with indocyanine green. In subsequent surgery, accumulating SNL-lymph nodes were detected, removed, and pelvic +/- para-aortic lymphonodectomy was performed. SNL mapping with complete pelvic lymphonodectomy was performed in 340 and additional para-aortic lymphonodectomy in 196 (58%) patients. At least one SNL-lymph node was visualized in 293 (86%) of the patients. Forty-one (12%) patients had affected LK, of which 36 had at least one labeled SNL lymph node. Metastases in SNL-

lymph nodes were detected in 35 (97%) of the 36 labeled patients resulting in a sensitivity of 97.2% (95%-CI 85.0-100), and a negative predictive value of 99.6% (97·9-100) for the detection of LK metastasis. The authors concluded that because of its diagnostic accuracy in detecting invaded lymph node, SNL-LND is a safe alternative to systematic LND in endometrial cancer.

Approximately 4.1 to 5.6% of all unselected patients with low-risk endometrial cancer have lymph node metastases [506].

In the retrospective analysis by J. Mueller and N. R. Abu-Rustum et al. [544], 959 patients with clinical stage I endometrial carcinoma were evaluated: no positive (macro- or micrometastases) SLNs were found among the 510 patients with non-invasive FIGO grade 1/2 endometrial carcinoma.

In grade 1 and pT1a, 4.5% (9/202) and in grade 1 and pT1b, 10% (6/62) had positive SLNs.

For grade 2 and pT1a, it was 4% (3/76) and for grade 2 and pT1b, 20% (8/41).

For grade 3: 5% (1/20) with non-invasive endometrial cancer, 3% (1/31) with invasion of the inner myometrial layer and 24% (4/17) with invasion of the outer myometrial layer had positive SLNs.

The PORTEC-II study (Wortmann et al. 2018) investigated the impact of lymphatic vessel invasion (LVSI) risk factors, p53 mutation, and L1CAM expression on the likelihood of recurrence in women with high-intermediate risk EC. Extensive LVSI (see Chapter 4.5) was found to be a strong and independent risk factor for pelvic and distant recurrences (hazard ratio 8.73 ($p = 0.005$) and 5.36 ($p = 0.001$), respectively) and also for disease-related survival (HR 7.16, $p < 0.001$).

Sentinel lymphadenectomy is associated with low morbidity and mortality, but also allows better staging in the low-risk endometrial cancer group [438]; [545].

A retrospective study recently demonstrated a potential benefit of sentinel lymphadenectomy in these endometrial carcinomas. 279 patients with endometrial carcinoma at low risk of recurrence (FIGO stage 1, endometrioid histology, grades 1 and 2) were divided into three groups: 103 (36.9%) had no lymphadenectomy, 118 (42.3%) had SLN removal, and 58 (20.8%) patients had pelvic and/or para-aortic lymphadenectomy. After a median follow-up of 33 months, the SLN group, compared with the group in which no lymphadenectomy was performed, showed a trend toward better recurrence-free and overall survival. However, when comparing peri-operative morbidities, no significant differences were found between the group without lymphadenectomy and that with SLN removal [545]. Thus, in endometrial cancer with low risk of recurrence, SLN removal allows identification of the low percentage of patients who may benefit from adjuvant therapy.

A recent analysis of the SEER database showed in 11,603 patients with stage IA G1 endometrial cancer G1– G3 that neither systematic LNE nor sentinel node biopsy improved survival [546].

Ultrastaging allows intensive pathologic workup of identified sentinel lymph nodes. As a result, lymph node metastases are detected in up to 5% in the low-risk population that would not be identified by conventional pathologic evaluation. However, the significance of micrometastases and single-cell metastases identified in

this manner is unclear. Performing SNL lymphodectomy appears safe even in early stages (FIGO I, G1/G2), where the likelihood of lymphogenic metastasis is low, does not lead to higher surgical morbidity and may influence adjuvant therapy. There may be an improvement in oncologic prognosis for cases with LVSI [545].

Especially in low and intermediate risk endometrial carcinomas, ultrastaging detects more positive sentinel nodes [436], [438], [439]. In a good half of the cases of positive sentinel nodes, these are based on isolated tumor cells (ITC) or micrometastases [436], [438], [439], whose relevance for prognosis is at least unclear, possibly even irrelevant [436], [439]. Therefore, the generous performance of sentinel node biopsy with ultrastaging may also lead to unnecessary upstaging and initiation of adjuvant therapies that only increase morbidity without improving prognosis [436], [439]. Micrometastases (> 0.2 mm to ≤2 mm, pN1 (mi)) are considered by most experts to be metastatic disease indicating adjuvant therapy [435], [236].

In a retrospective study, patients with micrometastases were shown to have the same DFS as nodal-negative women when the micrometastases considered nodal-positive were treated adjuvantly [435]. Whether this is due to a therapeutic effect or lack of relevance of micrometastases cannot be clarified by this study.

The prognostic value of ITCs (pN0 (i+)) is unclear [236]. Adjuvant therapy is recommended only if additional risk factors (e.g. LVSI, p53 mutation, type II carcinoma) are present [522], [236], [436], [439], [528].

The definitive classification of an endometrial carcinoma into the “low-risk group” is made postoperatively after receipt of the definitive pathology report. A proportion of endometrial carcinomas are accordingly classified postoperatively into a “high-risk group”, with a risk of lymph node metastases of up to 40% [547]. The lack of information about lymph node status often leads to generously indicated adjuvant radiotherapy in these patients, which would have been omitted if appropriate knowledge about lymph node status had been available [548]; [549]; Sharma et al. 2011; [550]. Therefore, among others, Sinno et al. have suggested that if sentinel lymph nodes are identified bilaterally, a frozen section of the uterus to determine the depth of infiltration should be omitted [551]; [545].

A multi-institutional retrospective study compared long-term outcomes after LND, LND plus SNL, and SNL alone [528]. Using a propensity score matching algorithm, 180 patients with SNL-LND (90 SNL alone, 90 SNL plus LND) were identified and compared with 180 patients with lymphonodectomy. 10% of all patients had metastatically affected lymph nodes. Comparison of DFS and OS showed no significant difference between the three groups, even when the cohort was divided into low-, intermediate-, and high-risk cancers. The addition of SNL lymphonodectomy allowed better detection of nodal-positive patients than systematic LND alone. In the cohort with SNL plus lymphonodectomy (17% lymph node-positive patients), 16% were diagnosed in an SNL lymph node and only 1% in lymph nodes removed by systematic lymphonodectomy.

A similar result was found in a prospective multicenter cohort study (SENTOR study) of patients with intermediate- to high-grade carcinomas [552]. 156 patients, including 126 with high-grade endometrial cancer, were included. All underwent SNLB and pelvic LND, and 101 patients (80%) with high-grade endometrial carcinomas also underwent para-aortic LND. SNL detection rates were 97.4% per patient (95%-CI,

93.6%-99.3%), 87.5% per hemipelvis (95%-CI, 83.3%-91.0%) and 77.6% bilaterally (95%-CI, 70.2%-83.8%).

Of the 27 patients (17%) with lymph node metastases, 26 were correctly identified by the SNLB algorithm, resulting in a sensitivity of 96% (95%-CI, 81%-100%), a false-negative rate of 4% (95%-CI, 0%-19%), and a negative predictive value of 99% (95%-CI, 96%-100%). Only one patient (0.6%) was misclassified by the SNL algorithm. Seven of the 27 nodal-positive patients (26%) were found outside the usual lymphonodectomy areas or only by immunohistochemistry, so as a conclusion, the use of the SNL method may improve the detection of lymph node metastases in high-grade carcinomas.

However, it should be considered that up to more than 50% of positive sentinel nodes are due to micrometastases or isolated tumor cells (ITC), the clinical relevance of which is unclear or questionable [436], [437], [439][436], [529], [552], [528]). Moreover, in the studies showing higher sensitivity of sentinel node biopsy, systematic LNE according to US standards was performed in the comparison groups (11–20 lymph nodes, no presacral LNE, no LNE above the inferior mesenteric artery). It is therefore not surprising that positive sentinel nodes were found in these regions, which would have been missed in the “systematic” LNE [438], [529] [439], [552].

A retrospective cohort study in patients with type 2 EC sought to answer the question of whether SNL LND may also be an alternative to systematic pelvic and para-aortic LND in clear cell or serous EC (type II) at high risk for lymphogenic metastasis [553]. Lymph node staging was performed by SNL-LND in patents operated on at Memorial Sloan Kettering between 2006 and 2013 (n = 118) and by systematic lymphonodectomy in patients at the Mayo Clinic between 2004 and 2008 (n = 96). Although overall survival was not significantly different, the nodal-negative SNL group had worse DFS than the systematic lymphonodectomized nodal-negative group.

In conclusion, therefore, there is currently no direct evidence of an advantage of sentinel lymphadenectomy or sentinel-assisted lymphadenectomy over systematic lymphadenectomy in terms of recurrence-free or overall survival in patients with EC. Study data are also lacking for the therapeutic consequences of diagnosing micrometastases and isolated tumor cells in sentinel lymph nodes. Prospective randomized trials have not established whether adjuvant chemotherapy, radiotherapy or combined chemoradiation therapy is beneficial in the presence of micrometastases or isolated tumor cells in sentinel lymph nodes with respect to recurrence-free or overall survival.

6.17	Consensus-based recommendation	new 2022
EC	If sentinel node biopsy is performed, it should be done according to the following algorithm: • Laparoscopy and visualization of the situs (adhesiolysis if necessary) • Intracervical injection of ICG • a Rel injection of ICG, if necessary • If only unilateral visualization of a sentinel is possible despite Re-injection of ICG, a systematic pelvic LNE should be performed on the ICG-negative side (except in pT1a/G1-2) • Work-up of the sentinel lymph node by ultrastaging (details see background text)	
	Strong Consensus	

Background

The procedure should start with laparoscopy. Only after any adhesions or other pathologies have been removed should ICG be injected.

If the LSK reveals suspicion for “bulky nodes”, the injection of ICG is no longer useful.

The ICG powder (25 mg/ampoule) is dissolved in 10 ml of aqua for injection, this gives a solution of 2.5 mg/ml. Cervical injection is superior to hysteroscopic peritumoral injection [554]. Various injection techniques have been described in the literature. Injection of 1ml each (0.5 ml submucosal and 0.5 ml stromal) at 2 (at 3 and 9 o'clock) or 4 (2, 4, 8, 10 o'clock) sites in the cervical region has proven effective. Pelvic spread of ICG along the lymphatic vessels is clearly identifiable after 6 to 10 minutes. If bilateral spread of ICG does not occur and the SLN cannot be identified on one side of the pelvis, ICG may be re-injected. However, the total daily dose should be less than 5 mg/kg bw.

If there is only unilateral visualization of the sentinel even with repeated injections, a systematic pelvic LNE is recommended on the ICG-negative side (except for low-risk Ia, G1-2).

Various labeling procedures and injection techniques for intraoperative identification of sentinel lymph nodes have been evaluated so far in endometrial carcinoma, mainly in single-center studies; see for example [537], [538]. For the most important multicenter study on this, the Sentiendo study (ClinicalTrials.gov, number NCT00987051), see [539], [540], [541], [542]. Detection rates obtained with intrauterine or cervical injection varied from 35 to 100%. A meta-analysis including 1,385 patients showed a sensitivity of the method of 81% and a false-negative rate of 19% [543]. Algorithms involving complete pelvic lymphadenectomy of the respective hemi-pelvis in the absence of unilateral detection increased the sensitivity to 95% and decreased the false-negative rate to 5%. In the Swedish prospective SHREC study of 257 patients with high-risk EC, intracervical injection of ICG achieved a sensitivity of 98% and a negative predictive value of 99.5%. The bilateral staining rate was 95% [555]. The Canadian prospective SENTOR study found a sensitivity of 96% and a

negative predictive value of 99% in 156 patients with intermediate and high-risk EC after intracervical injection of ICG [552].

6.3 Laparoscopic surgery

6.18	Evidence-based recommendation	checked 2022
GoR **B**	For endometrioid adenocarcinoma of the endometrium at a presumed early stage, hysterectomy and bilateral adnexal extirpation should be performed by a laparoscopic or laparoscopically assisted vaginal procedure.	
LoE **1**	[556], [557], [558]	
	Strong Consensus	

Background

The US Gynecologic Oncology Group (GOG) conducted a large prospective randomized controlled trial (LAP 2) [559], in which 1,682 patients with clinical stage I and IIA endometrial cancer underwent laparoscopic surgery and 909 underwent laparotomy. Extrafascial hysterectomy, bilateral adnexal extirpation and pelvic and para-aortic lymphadenectomy were performed.

According to the rules of the GOG, the pelvic lymph nodes were removed ventral to the obturator nerve and the para-aortic lymph nodes were removed up to the inferior mesenteric artery. In 246 cases (14.6%), conversion from laparoscopy to laparotomy occurred because of exposure problems (57% of total converts). Laparoscopy had fewer moderate to severe postoperative complications (14% versus 21%; $p < 0.001$) but comparable rates of intraoperative complications. There was a significant difference in postoperative complications only in the aggregate but not in individual complications [559]. The study was designed as a non-inferiority trial, which was intended to show that the risk of recurrence was a maximum of 40% higher with laparoscopy than with open surgery.

After a follow-up period of 59 months, 229 of the 1,682 patients in the laparoscopy group and 121 of the 909 EC patients who had undergone open surgery had died. The hazard ratio for recurrence was 1.14 in disadvantage of laparoscopy. The confidence interval ranged from 0.92 to 1.46, indicating the option of a 46% worse recurrence-free survival after laparoscopy and thus laparoscopy was not “non inferior”. Thus, the study was formally negative.

The recurrence rate at 3 years was 11.4% after laparoscopy and 10.2% after laparotomy. The 5-year survival was approximately 89.8% in both arms. About 69% of patients had stage IA and 12.5% had stage IB, so predominantly low-risk endometrial cancer patients had been studied [560].

The Cochrane Collaboration performed a meta-analysis with this and several other much smaller RCTs that also studied almost only early endometrial cancer at low risk

of recurrence [556]. They found no significant differences in overall and progression-free survival.

Laparoscopy had less operative morbidity and resulted in shorter hospital stays. No significant differences were found in terms of severe postoperative morbidity. The authors explicitly note that oncologic safety appears to be present only for patients with early endometrial cancer [558].

A recent meta-analysis [557], shows a non-inferiority in terms of disease-free and overall survival of laparoscopic hysterectomy compared to total abdominal hysterectomy for early stage endometrial cancer. Intraoperative complications showed no differences, and postoperative complications were significantly lower after laparoscopy. With few exceptions, endometrial carcinoma patients with stage I endometrial carcinoma were analyzed. Few received para-aortic LNE and if so, only to the inferior mesenteric artery. Studies examining the oncologic safety of laparoscopy for endometrial cancer at higher risk of recurrence have not been performed [561].

A retrospective analysis of 494 patients with high-intermediate risk endometrial cancer who had received brachytherapy postoperatively showed that the women in the minimally invasive surgery group (n = 363) had a significantly increased risk of recurrence (HR = 2.29; 95%-CI = 1.07-4.92; P = 0.034) compared with those operated on via laparotomy [562]. The risk of locoregional recurrence was four times higher in women operated via minimally invasive surgery (HR= 4.18; 95%-CI= 1.44-12.1; P = 0.008).

Conventional laparoscopy is the standard procedure for hysterectomy and bilateral adnexal extirpation in clinical stage I (early stage). Unexpected intraoperative metastatic endometrial cancer, high BMI and age older than 63 years were risk factors for conversion to laparotomy in the LAP-2 study. Because morcellement in the free abdominal cavity is prohibited, laparotomy is required in patients with a uterus that cannot be retrieved vaginally because of its size until procedures for laparoscopic morcellement of malignantly altered uterus in pouches are validated. Basic contraindications to laparoscopy should be ruled out; otherwise, vaginal or abdominal hysterectomy with bilateral adnexal extirpation or nonsurgical procedures should be considered.

A retrospective analysis of 2,661 women with stage I and II endometrial cancer showed that when a uterine manipulator was used (n = 1756), the risk of recurrence was significantly higher than when this tool was not used (n = 905) (HR = 2.31; 95%-CI01.27-4.20; P = 0.006). Disease-free survival was significantly shortened, and the risk of death was significantly increased [563].

6.4 Robot-assisted surgical procedures

6.19	Evidence-based recommendation	modified 2022
GoR **0**	Robot-assisted laparoscopic procedures can be used in the same manner as conventional laparoscopy for endometrial cancer surgery. They may offer advantages in morbidly obese patients.	
LoE **3**	[564], [565], [566]	
	Strong Consensus	

Background

Already in the learning phase, robot-assisted laparoscopy showed comparable good results to non-robot-assisted laparoscopy in the perioperative as well as immediate postoperative phase [567]. A study published in 2015 of 16,980 patients who underwent endometrial cancer surgery by laparotomy or robotic-assisted laparoscopy in the United States between 2008 and 2010 also showed a reduction in perioperative complications by more than half (20.5% versus 8.3%) and a reduction in perioperative mortality from 0.8% to 0%. A more recent meta-analysis from 2014 [568] included 22 prospective and retrospective cohort studies of 4,420 patients who received either robotic-assisted versus unassisted laparoscopy (n = 3,403) or robot-assisted laparoscopy versus laparotomy (n = 1017). Compared with laparotomy, complication rates, inpatient length of stay, blood loss and transfusion frequency were significantly lower. Compared with unassisted laparoscopy, complication rate, blood loss and conversion rate were also significantly lower for robot-assisted surgery. The reduction in complication rate compared with non-robot-assisted laparoscopy was particularly marked in very obese patients (8% robot-assisted, 13% laparoscopic [23% laparotomy]) [569].

Regarding oncologic outcomes, there are numerous analyses, all of which show no disadvantage compared with laparoscopy or laparotomy, but no prospectively randomized data as for non-robot-assisted laparoscopy [570].

A recent meta-analysis of 36 studies (33 of which were retrospective) compared robot-assisted with conventional laparoscopic surgery for endometrial carcinoma and found no differences in operative time. However, hospital stay after robot-assisted surgery was shorter, blood loss was less, conversion to laparotomy and general complications were less frequent. [566].

A meta-analysis of 51 observational studies with a total of 10,800 obese EC patients showed that robot-assisted and conventional laparoscopic hysterectomies did not differ with respect to intraoperative complications. The conversion rate to laparotomy also did not differ between the two surgical procedures. However, intolerance to Trendelenburg positioning was the cause of conversion to the surgical technique in 31% for conventional laparoscopic surgery and in 6% for robot-assisted surgery. [564].

Because robot-assisted laparoscopy is a technically assisted “easier” laparoscopy, it is not reasonable to assume a worse oncologic outcome than for the technically more difficult laparoscopy. Therefore, consistently, robot-assisted laparoscopy is considered equal to unassisted laparoscopy in terms of indication for endometrial cancer [571].

6.5 Tumor reduction in advanced endometrial cancer

6.20	Evidence-based recommendation	checked 2022
GoR **0**	In advanced endometrial cancer (including carcinosarcoma), surgical tumor reduction can be performed with the goal of macroscopic complete tumor resection	
LoE **4**	[572], [573], [574]	
	Strong Consensus	

6.21	Evidence-based recommendation	new 2022
GoR **0**	For advanced endometrial cancer that cannot be primarily resected, neoadjuvant platinum-containing chemotherapy followed by cytoreductive surgery may be considered.	
LoE **4**	[572]	
	Strong Consensus	

Background

Barlin et al. [574] analyzed data from 14 retrospective case series involving 672 patients with advanced or recurrent (n = 157) endometrial cancer. They found that complete cytoreduction significantly improved survival (per 10% more patients with optimal cytoreduction improvement in overall survival by 9.3 months p = 0.04).

Postoperative radiotherapy also improved survival (per 10% more patients than with radiotherapy 11 months; improvement p = 0.004). Chemotherapy, on the other hand, worsened survival (per 10% more patients with chemotherapy decrease in survival by 10.4 months; p = 0.007). The authors already speculate themselves that the patients who received chemotherapy probably had a worse prognosis a priori [574].

Of course, the risk for strong bias of the retrospective case series is high: those patients were operated on who were fit and in whom complete resection could be achieved. If such an operation was successful, postoperative radiation was performed.

If this was not successful or if it was hopeless from the outset, chemotherapy was administered.

A later case series of 58 patients with stage IV endometrial cancer included 9 patients who underwent complete cytoreductive surgery, 32 who underwent surgery but had residual tumor >1 cm, and 6 in whom no cytoreduction was attempted.

Median overall survival was 42.2 months (CI not calculable) for the tumor-free patients, 18 months (CI = 13.9–24.1) for patients with residual tumor and 2.2 months (CI = 0.1–42) for those women in whom surgery was not even attempted. Of the 9 who underwent complete cytoreductive surgery, 7 had macroscopic omental metastases that could be completely removed by omentectomy. One patient had a metastasis in the sigmoid mesentery, which was removed by anterior resection. One patient had a singular lymphatic metastasis [524]. It is now evident here that the patients were operated tumor-free in whom this was easily possible.

The same group published a similar retrospective case series on stage III (n = 14) and IVB (n = 30) uterine carcinosarcomas. Macroscopic completetumor resection was achieved in 57%. These patients had an overall median survival of 52.3 months, whereas those with residual macroscopic tumor lived only 8.6 months.

Patients who were able to receive adjuvant therapy (chemotherapy ± radiation) had an overall survival of 30 months versus 4.7 months (without adjuvant therapy). Again, strong biases are evident.

A group of authors from the Netherlands, Belgium and Canada retrospectively analyzed data from 102 patients with endometrial cancer that had progressed primarily to the point where it was inoperable. They received neoadjuvant chemotherapy and, if they responded, secondary cytoreductive surgery. Forty-four patients (43%) had endometrioid carcinoma, 44 (43%) had serous carcinoma and the remainder had other type II endometrial carcinoma. Of the patients with endometrioid endometrial carcinomas, three had complete radiological remission and 28 (63.6%) had partial radiological remission. The women with serous endometrial carcinomas had 1 complete and 35 (79.5%) partial remissions. Complete interval debulking was achieved in 62% of women with endometrioid EC and in 56% of women with serous EC. A tumor residue <1 cm (optimal debulking) was achieved in an additional 31% and 28% of secondary-operated cases, respectively. In the completely and optimally operated patients, recurrences occurred in 56% and 67%, respectively. Progression-free survival was 18 months (endometrioid endometrial cancer) and 13 months (serous EC). Median overall survival was 41 months after complete and optimal debulking,16 months with incomplete debulking, and 13 months in patients who did not undergo secondary surgery. No differences were found between endometrioid and serous endometrial carcinomas with respect to survival data [572].

7 Radiotherapy of endometrial carcinoma

7.1 Postoperative adjuvant radiotherapy of endometrial carcinoma type I, stage I-II

7.1	Evidence-based recommendation	new 2022
GoR **0**	In all stage I and II endometrial carcinomas with POLE mutation, adjuvant radiotherapy and/or chemotherapy can be omitted in R0 situation, even if risk factors are present.	
LoE **3**	[378]	
	Strong Consensus	

7.2	Consensus-based recommendation	modified 2022
EC	In stage pT1a, pNX/0, G1 or G2, endometrioid endometrial carcinoma (type I), p53-wt and L1CAM negative, no extensive LVSI after hysterectomy with or without lymph node dissection, neither brachytherapy nor percutaneous irradiation should be performed.	
	Strong Consensus	

Background

The role of external pelvic irradiation in stage I endometrial cancer (endometrioid histology) has been repeatedly assessed in meta-analyses of randomized trials by Kong et al. [575]. The most recent version of the meta-analysis is from 2012 [576]. The evidence assessment by the Guideline group was based on the ASTRO Guideline published in 2014 [577], which was based on the systematic literature search from 1980 to 2011, and a supplementary update search. As this most recent version of the meta-analysis by Kong et al. 2012 [576] could therefore not yet be included in the ASTRO Guideline used for adaptation, although both have a very similar basis of primary studies, it is now given special consideration.

The meta-analysis considered 8 studies involving 4,273 patients with stage I endometrial cancer. When considering subgroups, it should be noted that in the primary studies as well as in meta-analyses, older TNM and FIGO stage classifications were used in some cases; in the recommendations and background texts of this Guideline, the corresponding current stages according to the TNM 7 classification of 2010/11 [578] are always mentioned. In the TNM 8 classification [579], valid since 2017, no changes have occurred for endometrial cancer. In the comparison of external beam radiotherapy vs. no external beam radiotherapy (with balanced distribution of the use of vaginal brachytherapy), there was no effect on overall

survival (primary endpoint of the meta-analysis), disease-specific survival, or distant metastasis for the overall stage I group, but there was a significant decrease in locoregional recurrence rate (HR = 0.36, 95%-CI = 0.25–0.52; p < 0.001).

In the stage I "low risk" subgroup (defined for meta-analysis as stage IA, i.e., maximal myometrial infiltration inner half, and G 1–2), the primary endpoint overall survival was not analyzed.

In the stage I "intermediate risk" subgroup (defined for meta-analysis as stage IB, i.e., infiltration of the outer half of the myometrium or G3, only one of the two factors present or as defined by the respective study), no significant effects of external beam radiotherapy on overall survival or disease-specific survival were found.

For the stage I "high risk" subgroup (defined for meta-analysis as stage IB, i.e., infiltration of the outer half of the myometrium, and G3 or as defined by individual studies), there was no significant effect of external beam radiotherapy on overall survival (HR = 0.91, 95%-CI = 0.60–1.39; I2 = 0%; p = 0.67) or disease-specific survival (HR = 0.84, 95%-CI = 0.51–1.40; I2 = 0%; p = 0.51). In the meta-analysis, the delivery of external beam radiotherapy was associated with increased rates of acute toxicities (RR = 4.68, 95%-CI = 1.35–16.16; I2 = 0%; p = 0.01 for grades 3 and 4) and late toxicities (RR = 2.58, 95%-CI = 1.61–4.11; I2 = 0%; p < 0.001). Regarding quality of life, the meta-analysis refers to the evaluation on the randomized PORTEC-1 trial [580]; see below.

Regarding the results of external beam radiotherapy in stage I (endometrioid histology), the Dutch study PORTEC-1 is presented as an example for which 15-year data [581] have not yet been included in the ASTRO Guideline, but are included in the described meta-analysis [576]. In PORTEC-1, 714 patients in the treatment period 1990–1997 after hysterectomy without lymphadenectomy in stages IB, i.e. more than 50% myometrial infiltration with G1–2 or IA with myometrial infiltration (myometrial infiltration < 50%) with G2–3, were randomized to: external pelvic irradiation with 46 Gy (2-dimensional irradiation techniques) vs. observation alone.

At median follow-up of 13.3 years [581], a 15-year locoregional recurrence rate of 5.8% (with irradiation) vs. 15.5% (without) was found in the overall collective (HR = 3.46; 95%-CI 1.93–6.18; log-rank test p < 0.0001), and the vaginal recurrence rate was 2.5% (with pelvic irradiation) vs. 11% (without) (no p-value given). The 15-year overall survival was 52% (with radiation) vs. 60% (without) (HR = 0.84; 95%-CI 0.67–1.06; log-rank test, p = 0.14), and the 15-year recurrence-free survival was 50% (with radiation) vs. 54% (without) (p = 0.94).

In the "high-intermediate risk" subgroup of the PORTEC-1 trial (defined as the presence of at least two of the following: G3, age > 60 years, stage IB, i.e., myometrial infiltration > 50%), 15-year overall survival was 41% with radiation vs. 48% without (p = 0.35), and disease-specific mortality risk was 14% vs. 13% (p value not reported). In this risk group, external beam irradiation particularly reduced the 15-year locoregional recurrence rate, from 21% to 7% (percentages not given in text, read from Kaplan-Meier curve).

A cross-sectional quality of life analysis was performed on the PORTEC-1 study [580]. No baseline data were obtained at the start of therapy, but 351 patients were surveyed over the long-term (median 13.3 years after therapy) with quality-of-life questionnaires (SF-36 and individual questions on bladder and bowel symptoms and

sexual function from EORTC organ modules); the response rate was 70%. There was significantly increased symptomatology regarding urinary incontinence, diarrhea and fecal incontinence in the radiation arm vs. observation, as well as worsened quality of life in the areas of physical function and role function.

In the interpretation, it should be taken into account that the form of 2D radiotherapy used in the study (1990–1997) has been replaced in Germany since the mid-1990s by the gentler 3D conformal radiotherapy (CT-guided radiation planning with 3D contouring of target volumes and adjacent organs).

Also after data closure of the meta-analysis [576], as well as the ASTRO Guideline [577], the long-term evaluation of a Norwegian study based on previous publications [582] considered in both was published [583]: in the period 1968–1974, 568 patients in stage I in both arms received vaginal radium brachytherapy, with randomization to external pelvic irradiation (40 Gy, counter-field technique with partial block-out from 20 Gy, partly Cobalt-60) vs. no external irradiation. The overall collective showed identical overall survival of median 20.5 years, which also corresponds to the median follow-up time of this collective, in both arms in younger patients (< 60 years at diagnosis), but significantly better survival without external pelvic irradiation, which was attributed to an increased risk of second malignancy in the arm with pelvic irradiation (HR = 2.02; 95%-CI 1.30–3.15 in the younger subgroup).

Recent analyses of secondary tumor risk including the PORTEC-1 and PORTEC-2 endometrial cancer trials show no increased risk of secondary malignancies after external pelvic irradiation at median follow-up of 13.0 years [584].

A special position within stage I is occupied by the combination of stage IB with simultaneous presence of G3. This constellation of a “high-risk”-stage I was, among others, not included in the PORTEC-1 and PORTEC-2 studies. Parallel to the PORTEC-1 study, 104 consecutive patients with this constellation were included in a registry study between 1990 and 1997 and received postoperative pelvic irradiation with a mean total dose of 46 Gy, of which 99 patients were evaluable [585].

For the registry collective, the following 5-year results were reported (in parentheses, the comparative value for the subgroup of n = 137 with IC [old] but grading G2 from the arm with external pelvic irradiation of PORTEC-1): Overall survival 58% (85%), death from endometrial cancer 30% (6%), vaginal recurrence 5% (2%), pelvic recurrence 7% (0%), distant metastasis 23% (7%). These registry data document good pelvic tumor control in stage IB G3 patients receiving pelvic irradiation despite an unfavorable survival prognosis.

In the current meta-analysis [576], no survival benefit of pelvic irradiation is observed for the stage I “high risk” subgroup (defined as stage IB with G3 or as defined by the respective study) (two studies, total 334 patients, HR = 0.91; 95%-CI = 0.60–1.39; I2 = 0%; non-significant reduction in risk of death p = 0.67).

The two studies included in the current meta-analysis on this topic [586], [587] will be considered in detail. The GOG 99 study randomized 392 patients (endometrioid type only) with myometrial infiltration (i.e., stage IA with myometrial infiltration or stage IB) and stage II, each of any grade, postoperatively to postoperative pelvic irradiation alone at 50.4 Gy (2D irradiation technique, counterfield or 4-field technique, in some cases Cobalt-60) vs. observation [586].

During the course of the study, a subgroup “high-intermediate risk” (HIR) was identified and considered separately. This was defined as follows: age >70 years with at least one of the factors G2–3, lymphovascular invasion, infiltration of the outer third of myometrium, or age >50 with at least two of these factors, or any age with all three factors. For this HIR group, overall survival (HR = 0.73, 90% CI = 0.43–1.26) was not significantly improved in the arm with external pelvic irradiation (4-year overall survival 88% vs. 74%, p = 0.35). The rate of initial pelvic recurrence at four years was decreased by pelvic irradiation from 13% to 5% (HR = 0.37; 90% CI 0.12–1.11).

The ASTEC/EN.5 study represents the pooled analysis of two initially separately planned randomized trials from Europe and North America [587]. Between 1996 and 2005, 905 patients at 112 centers of stage I or IIA with “intermediate or high risk” (definition: IA with G3 or IB with any grading or papillary serous/clear cell) were randomized to external pelvic irradiation with 40–46 Gy vs. observation. Vaginal brachytherapy was performed according to center strategy (actual use in both arms equally frequent, 53% vs. 54%). For the overall group, 5-year overall survival was 83.5% with external pelvic irradiation and 83.9% with observation (HR = 1.05; 95%-CI 0.75–1.48; p = 0.77).

In a defined high-risk group (IB with G3 or II (endocervical glandular invasion only) with G3 or papillary serous/clear cell or II (cervical stromal invasion) (the latter outside the inclusion criteria but also evaluated), disease-specific 5-year recurrence-free survival (i.e., death from other causes not counted as an event) was 73.7% vs. 88.8% with intermediate risk. However, within the high-risk group, with the use of vaginal brachytherapy in approximately half of the cases in both arms, no effect of external pelvic irradiation was seen on overall survival (HR 1.07; 5-year rate = 3%, 95%-CI = –6% to 10%) or on disease-specific survival (HR 1.01; 5-year rate = 3%, 95%-CI = –5% to 9%).

In summary, the current meta-analysis shows that external pelvic irradiation for stage I endometrial cancer (endometrioid type) reduces the locoregional recurrence rate (including vaginal and other pelvic recurrences) to about one-third of the control group over the long-term, but thus does not positively affect endpoints of overall or disease-specific survival, even in the meta-analyzable subgroups. In the subgroup “high risk” it must be taken into account that the two studies included in the meta-analysis (see above) used significantly different risk definitions; in the larger study brachytherapy was used in equal proportions in both arms, and both studies tended to show contrasting results. Only in the GOG-99 study was a central reference pathological assessment performed, which is relevant in light of the massive downgrading in subsequent reference pathological assessment in the PORTEC-1 and PORTEC-2 studies [588].

Kong et al. [575] point out in their discussion of the meta-analysis that the number of high-risk patients in the reported studies of external pelvic irradiation is relatively small (n = 334 in two studies) and it cannot be ruled out that the meta-analysis has insufficient power to detect a survival benefit.

Recent analyses document a particular risk profile for the group with “substantial LVSI” (highest degree of lymphovascular vascular invasion in three-tiered system): in the PORTEC-1 and PORTEC-2 study collectives (no LK dissection there), 4.8% of patients had “extensive LVSI” [589], . After 5 years, the following pelvic recurrence rates were observed: no adjuvant therapy 30.7%, vaginal brachytherapy 27.1%, external pelvic irradiation 4.3%. Thus, in stage pT1pNx with “extensive LVSI” – there is

a strong reduction in the high pelvic recurrence risk with external pelvic irradiation, regardless of grading. However, a prospective evaluation of the significance of LVSI is not available to date.

7.3	Evidence-based recommendation	checked 2022
GoR 0	In stage pT1a, pNX/0 without involvement of the myometrium, G3, endometrioid endometrial cancer (type I), vaginal brachytherapy can be performed to reduce the risk of vaginal recurrence.	
LoE 4	[590], [591]	
	Strong Consensus	

7.4	Consensus-based recommendation	modified 2022
EC	In stage pT1a, pNX/0 without involvement of the myometrium, G1-3, p53-abn or L1CAM positive (each POLE wild type), endometrioid endometrial carcinoma (type I), adjuvant vaginal brachytherapy or percutaneous radiotherapy can be performed, if necessary in combination with chemotherapy.	
	Consensus	

7.5	Evidence-based recommendation	modified 2022
GoR A	In stage pT1b, G1 or G2 pNX/0 and in stage pT1a (with myometrial involvement), G3 pNX/0, endometrioid endometrial carcinoma (type I), p53-wt, L1CAM negative, no extensive LVSI, postoperative vaginal brachytherapy alone shall be performed.	
LoE 2	[592], [341], [288], [593], [594], [595]	
	Consensus	

7.6	Evidence-based recommendation	new 2022
GoR **A**	In stage pT1b, G1-3 pNX/0 and in stage pT1a (with myometrial involvement), G1-3 pNX/0, endometrioid endometrial carcinoma (type I), p53- abn and/or L1CAM positive and/or extensive LVSI, percutaneous irradiation shall be performed postoperatively.	
LoE **3**	[358], [341], [596], [597], [598], [288], [580], [599], [600]	
	Strong Consensus	

7.7	Consensus-based recommendation	new 2022
EC	Radiation should be given in combination with chemotherapy in this situation (7.6.). See the Chapter on System therapy.	
	Strong Consensus	

7.8	Evidence-based recommendation	new 2022
GoR **A**	In Patients with endometrioid endometrial carcinoma (type I) stage pT1b pN0 G3 (without LVSI and p53-wt and L1CAM negative) vaginal brachytherapy shall be performed.	
LoE **3**	[341], [601], [602], [288]	
	Strong Consensus	

7.9	Evidence-based recommendation	new 2022
GoR **A**	Patients with stage pT2 pNX with additional risk factors (G3 or >50% myometrial infiltration or LVSI) shall receive percutaneous radiotherapy.	
LoE **3**	[341], [601], [602], [288]	
	Strong Consensus	

7.10	Evidence-based recommendation	modified 2022
GoR A	For patients with stage pT1b pNX G3 (without LVSI, p53-wt, L1CAM negative), endometrioid endometrial cancer (type I), vaginal brachytherapy or percutaneous radiotherapy shall be performed.	
LoE 3	[341], [601], [602], [288]	
	Strong Consensus	

7.11	Evidence-based recommendation	modified 2022
GoR A	Patients with stage pT2 pNx, G1/G2, (less than 50% myometrial infiltration, without LVSI, p53-wt, L1CAM negative), endometrioid endometrial carcinoma (type I), shall receive vaginal brachytherapy or percutaneous radiotherapy.	
LoE 3	[341], [601], [602], [288]	
	Strong Consensus	

7.12	Evidence-based recommendation	new 2022
GoR A	Patients with endometrioid endometrial carcinoma (type 1) stage pT1b and pT2 p53-abn, POLE-wt shall receive percutaneous radiotherapy in combination with chemotherapy (PORTEC 3 regimen).	
LoE 3	[341], [601], [602], [597], [288]	
	Strong Consensus	

7.13	Consensus-based recommendation	modified 2022
EC	For patients with stage pT2 pNX G3 or >50% myometrial infiltration or LVSI, radiation can be given in combination with chemotherapy.	
	Strong Consensus	

7.14	Evidence-based recommendation	new 2022
GoR **A**	In patients with stage pT2 pN0 endometrioid endometrial carcinoma (type I) (without other risk factors such as G3, >50% myometrial infiltration or LVSI and p53-wt AND L1CAM negative), endometrioid endometrial carcinoma (type I), vaginal brachytherapy shall be performed.	
LoE **3**	[341], [601], [602], [288]	
	Strong Consensus	

7.15	Evidence-based recommendation	new 2022
GoR **B**	Patients with endometrioid endometrial carcinoma (type I) pT2 pN0 with risk factors (>50% myometrial infiltration or LVSI or L1CAM positive) should receive percutaneous pelvic radiotherapy.	
LoE **3**	[341], [601], [602], [288]	
	Strong Consensus	

Background

The recommendations of the guidelines suitable for adaptation are based on the results of randomized trials that investigated vaginal brachytherapy with external pelvic irradiation or with observation alone or different dose concepts of brachytherapy. The update search found only two other relevant studies: a population-based analysis of forgoing any radiotherapy [603] and a retrospective analysis of the feasibility of vaginal brachytherapy in parallel with chemotherapy [604]. In a European multicenter study [605], 645 low-risk patients (defined as stage IA by current classification with G1–2, endometrioid histology only) were randomized to HDR brachytherapy alone (Iridium-192 or Cobalt-60) of the upper two-thirds of the vagina with total doses of 18 to 24 Gy (single dose 3 to 8 Gy), with dose prescription to 5 mm tissue depth (one center of six: LDR technique cesium-137, 40 Gy) vs. observation. At a median follow-up of 5.7 years, recurrence rates were as follows: vaginal 3.1% vs. 1.2% with brachytherapy (p = 0.114), pelvic 0.9% without brachytherapy vs. 0.3% with brachytherapy (p = 0.326), and distant 0.6% without brachytherapy vs. 2.2% with brachytherapy (p = 0.087) (confidence intervals not shown).

Late side effects were assessed according to RTOG/EORTC classification (https://www.rtog.org/). Significantly more vaginal adverse events (mild atrophy, dryness, sporadic mucosal bleeding) occurred in the vaginal brachytherapy arm (p = 0.00004), but these were rare at 8.8% (vs. 1.5% in the observation arm) and

predominantly grade 1. There was a trend regarding more urogenital side effects in the brachytherapy arm (total 2.8% vs. 0.6%, p = 0.063), but no difference in intestinal sequelae (0.9% vs. 0.6%); side effects of grade 3 or higher did not occur at all.

The Dutch PORTEC-2 study [600] tested whether in stage I "high intermediate risk" vaginal brachytherapy alone can secure comparable good locoregional, especially vaginal, tumor control compared to external pelvic irradiation, with more favorable toxicity and quality of life profiles. Included were: age >60 years with stage IB and G1-2 or with stage IA and G3. Patients with combination IB and G3 were not included. Stage II (endocervical gland involvement only) was included unless the combination >50% myometrial infiltration and G3 was present. 427 patients were randomized to external pelvic irradiation alone (46 Gy in fractions of 2 Gy each, CT-guided 3D radiation planning) vs. vaginal brachytherapy alone to the upper half of the vagina (HDR 3 x 7 Gy, dose prescription to 5mm tissue depth, 1 x per week; or 30 Gy LDR or 28 Gy MDR in each session) between 2002 and 2006 after hysterectomy without routine lymphadenectomy. The following 5-year recurrence rates (external pelvic irradiation vs. vaginal brachytherapy, respectively) were reported: vaginal 1.6% vs. 1.8% (HR = 0.78, 95%-CI 0.17–3.49; p = 0.74), locoregional 2.1% vs. 5.1% (HR = 2.08, 95%-CI 0.71–6.09; p = 0.17), distant 5.7% vs. 8.3% (HR = 1.32, 95%-CI 0.63–2.74; p = 0.46).

The 5-year overall survival was 79.6% after external beam radiation and 84.8% after brachytherapy (HR = 1.17, 95%-CI 0.69–1.98; p = 0.57); disease-free survival was 78.1% vs. 82.7% (HR = 1.09, 95%-CI 0.66–1.78; p = 0.74). Gastrointestinal toxicities of grades 1 to 2 (RTOG/EORTC classification) were present at the end of therapy in 53.8% (external beam) vs. 12.6% (brachytherapy); significant differences existed in this regard until 24 months after therapy. From 6 months on, more vaginal atrophy (especially grade 2) was continuously detectable in the brachytherapy arm.

Recently, the 10-year data of the PORTEC-2 study were published [341]: while overall the approximate equivalence of vaginal brachytherapy to external pelvic irradiation was confirmed in the studied stage groups, histopathologically or molecularly defined subgroups benefiting from external irradiation could be elaborated. After 10 years, overall survival was 69.5% (vaginal brachytherapy) vs. 67.6% (external irradiation) (HR 0.94, 95%-CI 0.67-1.32; p=0.72), pelvic recurrence rate was 2.5% vs. 0.5% (HR 5.07, 95%-CI 0.59-43.41; p=0.1) and vaginal recurrence rate was 3.0% vs. 1.5% (HR 1.68, 95%-CI 0.40-7.03; p=0.47).

The PORTEC-2 trial demonstrated a significant decrease in pelvic recurrence rates compared to brachytherapy for the p53-positive or L1CAM-positive or LVSI-positive subgroups (defined as "extensive LVSI" in the three-stage system) after external pelvic irradiation. Pelvic recurrence rates after 5 years were approximately 30% (brachytherapy) vs. approximately 0% (external irradiation) in the p53-positive group (p< 0.001), and approximately 25% (brachytherapy) vs. approx. 0% (external irradiation) (p< 0.0.1) and in the group LVSI-positive approx. 30% (brachytherapy) and approx. 12% (external irradiation) (p< 0.001) (exact values not given, reading from graph). Thus, for the above groups, there is an increased risk of pelvic recurrence after postoperative vaginal brachytherapy alone, which is why postoperative external pelvic irradiation is now recommended as an alternative.

While the main benefit of postoperative vaginal brachytherapy has previously been seen in lowering the risk of vaginal recurrence, several recent registry studies consistently suggest a resulting benefit in overall survival as well. Al-Hili et al. looked

at overall survival in 132,393 stage patients from 2004 to 2013 (National Cancer Database: https://www.facs.org/quality-programs/cancer/ncdb) [592]. For group IB G1-2, vaginal brachytherapy showed the best 5-year survival at 89% with significant advantage over observation (83%; HR 0.64, 95%-CI0.56-0.73); p< 0.0001) and also over external pelvic irradiation (87%, p=0.0004). For group IA G3, vaginal brachytherapy achieved a 5-year survival of 87% (vs. observation 83%; HR 0.81, 95%-CI 0.64 -1.02;p=0.07). Similarly, in an analysis of 44,309 stage I patients with lymphadenectomy (National Cancer Database 2003-2011), Rydzewski et al. showed a significant benefit of vaginal brachytherapy in overall survival compared with observation (HR 0.62, 95%-CI 0.51-0.74, p< 0.001), which was not present for pelvic irradiation (HR 0.93, 95%-CI 0.77-1.11, p=0.409) [606]. Thus, it can be assumed that vaginal brachytherapy also has a demonstrable beneficial effect on overall survival in the stage groups in which it has been previously recommended for prophylaxis of vaginal recurrence due to a favorable benefit-risk profile.

The quality-of-life analysis of the PORTEC-2 study was conducted as a longitudinal study over the first 24 months after therapy using the EORTC QLQ-C30 questionnaire and individual questions from organ modules with an overall response rate of 81%, and 53% at the 2-year time point [599]. There was a statistically significant and clinically relevant advantage for the vaginal brachytherapy arm at different time points in the areas of diarrhea, impairment of daily life due to bowel symptoms, and social function. It is concluded that in the considered collective, vaginal brachytherapy can achieve excellent vaginal tumor control, locoregional control comparable to external pelvic irradiation and comparable recurrence-free and overall survival, with less gastrointestinal toxicity and better quality of life.

The results of generally foregoing any radiotherapy in stage I low-risk (defined here as <50% myometrial infiltration with G1–2) or intermediate-risk (>50% myometrial infiltration with G1–2 or <50% myometrial infiltration with G3) patients were prospectively studied nationwide in Denmark during the 1998 to 1999 treatment period (survival data in Bertelsen et al. [603]; recurrence data in Ortoft et al. [607]). At a median follow-up of 13.8 years, 6.3% recurrences (2.9% vaginal, 1.2% pelvic, 1.2% abdominal, and 1.0% distant) were observed at low risk. At intermediate risk, recurrences occurred without radiotherapy in 21.6% (9.5% vaginal, 4.8% pelvic, 2.2% abdominal, 5.2% distant). When this intermediate group was subdivided into “high-intermediate” (>50 years with G2 with >2/3-myometrial infiltration or >70 years with G2–3 with >2/3-myometrial infiltration) and “low-intermediate” (the remainder), the recurrence rates for “high-intermediate” vs. “low-intermediate”: total 25.8% vs. 16.2%, vaginal 11.4% vs. 7.0%, pelvic 6.1% vs. 3.0%, abdominal 3.0% vs. 1.0%, and distant 5.3% vs. 5.1%.

The investigators of this study [603] consider the recurrence rates in the intermediate-risk stage I group to be acceptable because the 5-year overall survival in this population of 78% is comparable to the 79% observed for this high-risk population in an earlier period (1986–1988) with even broader use of radiotherapy. However, this evaluation insufficiently accounts for the burden of salvage therapies and for trends in overall life expectancy relevant to the overall survival endpoint.

The randomized GOG 249 trial compared pelvic irradiation (45-50 Gy) with the combination of vaginal brachytherapy plus 3 cycles of paclitaxel 175 / carboplatin AUC 6 [608] in stage I endometrioid with risk factors (IB or G2-3 or LVSI, age-dependent 1-3 factors had to be present), stage II endometrioid, and stages I to II serous or clear cell (without positive peritoneal cytology). Of 601 patients

randomized, 75% were stage I, and the rate of lymphadenectomies performed was 89%. After 5-year recurrence-free survival was 76% in both arms (HR 0.92, 95%-CI 0.65 – 1.30; p=0.31), 5-year overall survival was 87% for pelvic irradiation and 85% for brachytherapy plus chemotherapy (HR 1.04, 95%-CI 0.66 – 1.63; p=0.57). While rates of vaginal recurrence (2.5%) and distant recurrence (18%) were the same in both arms, pelvic irradiation halved the rate of pelvic or para-aortic recurrence (4% vs. 9%, HR 0.47, 95%-CI 0.24 – 0.94). Since for the majority of included patients none of the study arms met the previous S3 Guideline recommendation, current recommendations for action can hardly be derived. From a radiotherapeutic perspective, the study demonstrates the value of external pelvic irradiation in reducing the locoregional risk of recurrence, even after lymphadenectomy and in comparison to brachytherapy plus chemotherapy.

Especially under the impression of equivalence of the two therapy arms with regard to oncological outcome in overall survival, acute and late toxicity are of particular relevance: acute toxicity was higher in the chemotherapy + brachytherapy arm and patient reported outcomes showed a maximum at 11 weeks in the FACIT fatigue subscale in the chemotherapy arm ($p < 0.001$) and it took 8 months to reach baseline again. In the percutaneous radiotherapy arm, fatigue had already subsided after 11 weeks. A similar picture was seen for neurotoxicity, which measured by FACT/GOG-Ntx subscale was still relevantly higher after 4, 11 weeks and even after 8 months and only returned to baseline after 14 months ($p< 0.001$). Especially probably under the aspect of toxicity, the authors concluded that percutaneous radiotherapy was the appropriate adjuvant therapy in this situation. Toxicity data from the PORTEC-3 study [596] also point to the risk of long-lasting neurotoxicity, which is highly relevant for quality of life. Measured with EORTC QLQ-C30 OV 28, late neurotoxicity was strongly increased in the chemotherapy arm with 27.8 vs. 13.2% ($p< 0.0001$).

Specifically for stage II, the value of vaginal brachytherapy and external pelvic irradiation (± vaginal brachytherapy) was considered in a recent meta-analysis of 15 cohort studies involving 1070 patients [602]. For the group of studies with performance of lymph node dissection or sampling in at least 90% of cases, the use of external pelvic irradiation (± vaginal brachytherapy) compared with brachytherapy alone showed a strong reduction in locoregional recurrence risk (HR 0.17, 95%-CI 0.05-0.49; p=0.0009) and also a significant improvement in overall survival (HR 0.41, 95%-CI 0.17-0.99; $p< 0.05$). The authors concluded that external pelvic irradiation should be considered in stage II if risk factors (G3, myometrial involvement > 50% or LVSI) are present.

Also for stage II, a Danish registry study (2005-2012) was able to document the effect of external beam irradiation when lymphadenectomy was performed area-wide, as external beam irradiation was not performed from 2010 and brachytherapy was not performed at all [601]. The 5-year overall survival with vs. without pelvic irradiation was 80.3% vs. 71.7% (HR 0.66, 95%-CI 0.39-1.11), the 5-year rate of vaginal recurrence 7.3% vs. 14.2% ($p< 0.05$), and the 5-year rate of other pelvic recurrence 2.8% vs. 12.7% ($p< 0.05$).

While these two analyses on stage II did not consider molecular subgroups, they demonstrate a potential of postoperative external pelvic irradiation to safeguard locoregional tumor control in a proportion of stage II patients – even if lymphadenectomy was performed.

Performance of vaginal brachytherapy

Vaginal brachytherapy is performed with a special cylindrical applicator. The diameter and length of the applicator are based on the anatomical conditions of the patient. The applicator is inserted in lithotomy position. The irradiation itself should be performed with the patient's legs extended. The length of the residual vagina should be measured and documented before insertion of the cylinder. The target volume is individualized and should generally include the proximal third of the vaginal stump. The dose specification for standardized plans is given in 5mm tissue depth. Ideally, imaging (vaginal ultrasound, CT or MRI) will be used to determine the thickness of the vaginal epithelium and the distance to the rectal wall and adjust the dose specification if necessary.

For vaginal brachytherapy, there are different dosing and fractionation regimens that are used. There are no phase 3 trials meeting current standards that have comparatively evaluated the dosing of vaginal brachytherapy. A randomized trial by Sorbe compared 6 x 2.5 Gy versus 6 x 5.0 Gy. This showed no significant differences in terms of local recurrence rate. The rate of vaginal shortening and bleeding was significantly increased in the 6 x 5 Gy arm at 5 years. In the study, the upper 2/3 of the vagina was irradiated in a short period of 8 days in all patients. Irradiation of 2/3 of the vagina should not be performed today. Therefore, the 6 x 2.5 Gy regimen can only be conditionally recommended.

For vaginal brachytherapy alone, doses between 15-25 Gy should be applied in 3-4 fractions using HDR – brachytherapy. In the Portec II study, a dosage of 3 x 7.0 Gy at 5mm tissue depth once weekly was used. This dosage is also recommended in the ESGO/ESTRO/ESP Guideline 2020/21. Equivalent dose schedules are 4 x 6.0 Gy or 5 x 5.0 Gy 1-2 weekly. For vaginal brachytherapy as boost after percutaneous radiotherapy, 8 – 11 Gy are applied in 2-3 fractions. In general, the regimen of 2 x 5.0 Gy is used. Vaginal brachytherapy as a boost should be performed at the end of percutaneous radiotherapy.

7.2 Postoperative radiotherapy for endometrial carcinoma type I, stage III-IVA

7.16	Evidence-based recommendation	modified 2022
GoR **B**	Patients with endometrioid endometrial carcinoma (type I) and positive lymph nodes, involvement of the uterine serosa, adnexa, vagina, bladder, or rectum (stages III-IVA) should receive adjuvant percutaneous radiotherapy followed by simultaneous chemotherapy or, alternatively, chemotherapy alone in combination with vaginal brachytherapy.	
LoE **3** **5**	[608], [598] 3: Percutaneous radiotherapy with simultaneous chemotherapy followed by chemotherapy (PORTEC III; GoG 258), or exclusive chemotherapy (GoG 258). 5: Chemotherapy plus vaginal brachytherapy.	
	Strong Consensus	

7.17	Consensus-based recommendation	modified 2022
EC	Patients with endometrioid EC (type I) and positive lymph nodes, involvement of the uterine serosa, adnexa, vagina, bladder, or rectum (stages III-IVA) can alternatively receive adjuvant chemotherapy followed by percutaneous radiotherapy.	
	Strong Consensus	

7.18	Consensus-based recommendation	new 2022
EC	If simultaneous radiochemotherapy followed by chemotherapy is chosen, the regimen used in the PORTEC-3 trial should be applied.	
	Strong Consensus	

7.19	Consensus-based recommendation	new 2022
EC	When chemotherapy is combined with vaginal brachytherapy alone, brachytherapy can be given after or between chemotherapy administrations.	
	Strong Consensus	

Background

Relevant studies on the value of radiotherapy for endometrioid endometrial carcinoma (type I) in stages III to IVA relate to its effectiveness compared with chemotherapy alone or as an element of combined (sequential or simultaneous) radiochemotherapy.

In a randomized Italian multicenter trial [609] from 1990 to 1997, 491 patients with stages IB with G3 or II with >50% myometrial infiltration with G3 or stage III, 65% of cases were in the latter) were randomized postoperatively to pelvic irradiation with 45–50 Gy vs. chemotherapy with five cycles of cisplatin 50/doxorubicin 45/cyclophosphamide 600. 5-year overall survival (69% vs. 66%, p = 0.85) and 5-year progression-free survival (63% vs. 63%, p = 0.64) (HR = 1.04 95%-CI 0.72–1.50) were nearly identical for radiotherapy vs. chemotherapy. The following recurrence rates were reported (radiotherapy vs. chemotherapy, respectively): distant (extra-abdominal or liver) 21%/16%, pelvic 7%/11%, distant and pelvic 5%/5%. The data indicate improved locoregional control in the radiotherapy arm and improved distant tumor control in the chemotherapy arm, suggesting the benefit of combining both elements.

In the GOG 122 [610] trial, 396 patients with stage III or IV disease after hysterectomy with surgical staging and leaving no more than 2 cm of residual tumor were randomized to whole-abdomen radiation with 30 Gy (single dose 1.5 Gy) followed by pelvic dose boost to 45 Gy vs. chemotherapy alone with seven cycles of doxorubicin 60/cisplatin 50 followed by one cycle of cisplatin.

Despite randomization, the stage distribution was unequal between arms, e.g., nodal positive 45.1% in the radiotherapy arm and 58.2% in the chemotherapy arm. The 5-year progression-free survival was 42% with chemotherapy and 38% with radiotherapy, and the 5-year overall survival was 53% vs. 42% (p-values not reported). Due to the imbalance in stage distribution, the authors performed a stage-adjusted analysis, which showed an advantage for the chemotherapy arm in 5-year overall survival (55% vs. 42%, HR = 0.68, 95%-CI 0.52–0.89; p = 0.004) and 5-year progression-free survival (50% vs. 38%, HR = 0.71, 95%-CI 0.55–0.91; p = 0.007).

The following recurrence rates were reported (radiotherapy vs. chemotherapy, respectively): total 54% vs. 50%, pelvic 13% vs. 18%, abdominal 16% vs. 14%, extra-abdominal or liver 22% vs. 18%. There were 4% therapy-associated deaths in the chemotherapy arm and 2% in the radiotherapy arm. The study has methodologic flaws regarding stage-adjusted evaluation after randomization and the use of whole-abdomen radiation, which is now obsolete.

The potential of combined sequential radiochemotherapy is documented by the pooled analysis of two randomized trials [611]. Here, 534 patients with stage I ("with risk profile requiring adjuvant therapy", unspecified) and, based on amendments, also stage II, IIIA (positive peritoneal cytology only), and IIIC (positive lymph nodes only, with no macroscopic residual) were randomized to postoperative external pelvic irradiation with at least 44 Gy and optional vaginal brachytherapy (this used in 38%, largely balanced in both arms) vs. same radiotherapy followed by chemotherapy with 4 cycles of doxorubicin 50/cisplatin 50 (amendment: also paclitaxel 175/epirubicin 60, doxorubicin 40/carboplatin AUC5, paclitaxel 175/carboplatin AUC 5–6). The treated collective consisted of stage IA (28%), IB (36%), II (14%), and III (20%), respectively, according to current FIGO classification, with non-endometrioid histologies present in 29% of cases. In the primary endpoint of progression-free survival, a benefit was seen for the sequential combination at 78% vs. 69% at five years (HR = 0.63, 95%-CI 0.44–0.89; p = 0.009), and in overall survival there was a

trend in favor of the combination at 82% vs. 75% (HR = 0.69, 95%-CI 0.46–1.03; p = 0.07). This benefit was predominantly due to effects in the endometrioid carcinoma subgroup, with 5-year overall survival 84% vs. 74% (HR = 0.60, 95%, CI 0.36–1.00; p = 0.05). No significant benefits of the combination were seen in the serous and clear cell carcinoma group.

In the current Guideline update, the results of the PORTEC-3 and GOG 258 randomized trials and several large registry studies can be included to evaluate the place value of radiotherapy in stage III to IVA.

In the PORTEC-3 trial, 660 patients with stage IA (with myometrial infiltration) G3 to IIIC were randomized to pelvic irradiation with 48.6 Gy (plus brachytherapy for cervical involvement) vs. the same radiotherapy with simultaneous chemotherapy with cisplatin 50 mg/m2 at weeks 1 and 4 and sequentially four cycles of paclitaxel 175 / carboplatin AUC5 [597]. Formally, then, this study tested the benefit of additional chemotherapy in relation to the standard of external pelvic irradiation. Approximately 30% in stage I, 25% in stage II, and 45% in stage III were included. The addition of chemotherapy improved 5-year overall survival from 76.1% to 81.4% (HR 0.70, 95%-CI 0.51-0.97;p adjusted=0.034), and 5-year recurrence-free survival from 69.1% to 76.5% (HR 0.70 (95%-CI 0.52-0.94; p adjusted=0.016). The effect was generated very predominantly in stage III, where there was improvement in 5-year overall survival from 68.5% to 78.5% (HR 0.63, 95%-CI 0.41-0.99; p adjusted=0.043) and 5-year recurrence-free survival from 58.4% to 70.9% (HR 0.61, 95%-CI 0.42 – 0.89; p adjusted=0.011). The addition of chemotherapy tended to reduce the rate of distant recurrences (22.1% vs. 29.4%, HR 0.75, 95%-CI 0.56 – 1.01; p=0.057), but there was virtually no improvement in pelvic (5.5% vs. 8.5%) or vaginal (2.1% in both arms) recurrence. Relative to defined molecular subgroups, the addition of chemotherapy to pelvic irradiation achieved an improvement in 5-year overall survival for p53 mutation (64.9% vs. 41.8%, HR 0.55, 95%-CI 0.30 – 1.00, p-adjusted = .0.49), but not for pole mutation (100% vs. 96%, HR 0.02, 95%-CI < 0.01 – 105, p adjusted 0.637), in MMR deficiency (78.6% radiochemotherapy vs. 84.0% radiotherapy, HR 1.33, 95%-CI 0.64 - 2.75, p adjusted 0.446) or without specific mutation (89.3% vs. 87.6%, 95%-CI 0.26 – 1.77, p adjusted = 0.434).

Thus, compared with the standard arm of pelvic radiotherapy (± brachytherapy), the PORTEC-3 trial defined simultaneous radiochemotherapy followed by sequential chemotherapy as a new standard with survival benefit, especially in stage III and in the group with p53 mutation.

The GOG 258 trial compared chemotherapy alone with 6 cycles of paclitaxel 175 / carboplatin AUC 6 against radiochemotherapy with 2 doses of cisplatin 50 simultaneously followed by 4 cycles of paclitaxel 175 / carboplatin AUC 5 [608] in stages III to IVA (with <2 cm residual tumor) of any type and stages I to II serous-clear cell. Data on overall survival are not yet available from this trial. However, no significant advantage for radiochemotherapy has yet been demonstrated in 5-year progression-free survival (after radiochemotherapy 59%, after chemotherapy 58%; HR 0.9 90% CI 0.74-1.10, p=0.20). Recurrence patterns were significantly different: lower 5-year rates of vaginal recurrence (2% vs. 7%, HR 0.36, 95%-CI 0.16 -0.82) and pelvic or para-aortic lymph node recurrence (11% vs. 20%, HR 0.43, 95%-CI 0.28 – 0.66), but higher rates of distant recurrence (27% vs. 21%, HR 1.36, 95%-CI 1.00-1.86) were seen in the radiochemotherapy arm.

As in the GOG 249 trial, with equivalence of the two treatment arms in terms of oncologic outcome based on the data to date, acute and late toxicity is of particular importance: acute grade 3, 4, and 5 toxicity was more favorable at 58% vs. 63% in the radiochemotherapy arm; in particular, grade 4 toxicity was much more pronounced at 14% vs. 30% in the chemotherapy arm, and grade 5 toxicity was present only in the chemotherapy arm. The rate of lymphedema was also more favorable in the radiochemotherapy arm at 7 vs. 15% ($p< 0.05$), which may be related to the lower rate of pelvic and para-aortic recurrence. In the evaluation, the sometimes massive symptomatology of pelvic as well as para-aortic tumor recurrences should also be considered. In this case, a therapeutic approach that includes radiotherapy is more advantageous, even independent of the other oncological outcomes. It remains to be seen whether the lower rate of distant metastases after chemotherapy alone leads to improved survival [608].

In the absence of recent data from randomized trials on the effect of radiotherapy on overall survival in stages III to IVA, a recent analysis from the National Cancer Database from 2004 to 2016 of 13,270 patients who received polychemotherapy can be considered [612]. In Cox-adjusted analysis of overall survival, for endometrioid carcinomas, the addition of external beam radiotherapy showed an improvement in stage III (HR 0.87, 95%-CI 0.79-0.96, p=0.004), which was most pronounced in stage IIIC when subgroups were considered (HR 0.84, 95%-CI 0.75 – 0.95, p=0.003). In stage IVA endometrioid the effect was not significant with small group size (HR 0.38, 95%-CI 0.10 – 1.41, p=0.15). In non-endometrioid carcinomas, the addition of external beam radiotherapy improved overall survival in stage III overall (HR 0.80, 95%-CI 0.72-0.88, $p< 0.0001$), particularly in subgroups IIIB (HR 0.52 95%-CI 0.32-0.86) and IIIC (HR 0.79, 95%-CI 0.70 – 0.88, $p< 0.0001$). Thus, registry data support a survival benefit of external beam radiotherapy in subgroups of the collective considered in GOG 258 (for which survival data are not yet available), particularly for stage IIIC endometrioid.

Provided that sequential (not simultaneous) chemotherapy and radiotherapy are performed postoperatively in stage III to IVA patients, the results of current registry studies favor the sequence chemotherapy followed by radiotherapy. An analysis of the US National Cancer Database (2004-2014, n=5795 stage III-IVA patients) looked at overall survival after chemotherapy followed by radiotherapy vs. the reverse sequence. This was significantly better at 5 years for initiation with chemotherapy (80.1%) compared to initiation with radiotherapy (73.3%, $p< 0.001$) [613].

7.3 Vaginal brachytherapy as a boost in postoperative percutaneous pelvic radiotherapy

7.20	Consensus-based recommendation	modified 2022
EC	In the presence of specific risk factors for vaginal recurrence (stage II or stage IIIB-vaginal or LSVI or close vaginal resection margin, additional vaginal brachytherapy can be performed as a boost after postoperative pelvic irradiation after hysterectomy due to endometrioid endometrial carcinoma.	
	Strong Consensus	

Background

When external pelvic irradiation is indicated, vaginal brachytherapy should not automatically be performed in addition. In the PORTEC-1 study, a vaginal recurrence rate of only 2.5% after 15 years was observed in the arm with external pelvic irradiation alone (without additional vaginal brachytherapy) [581].

In PORTEC-2, vaginal recurrence occurred in only 1.6% after 5 years following pelvic irradiation alone [600]. In the absence of randomized trials of pelvic irradiation ± vaginal brachytherapy, a recent review [614] considered retrospective studies on the topic. A recommendation of combination pelvic irradiation and brachytherapy was made for stage II and IIIB patients, each with close or positive incision margins.

7.4 Postoperative radiotherapy for endometrial carcinoma type II

7.21	Consensus-based recommendation	modified 2022
EC	Patients with serous endometrial carcinoma and patients with p53-mutated endometrial carcinoma of all stages should receive vaginal brachytherapy (stage I) or adjuvant percutaneous radiotherapy (stage II and above).	
	Consensus	

Background

Evidence regarding the effects of postoperative radiotherapy in type II carcinomas is scarce, as these have mostly been brought in as a smaller subgroup together with high-risk type I patients due to their rarity. However, recent adjuvant therapy trials have relevantly included patients with type II histology, especially with serous carcinomas (PORTEC-3: 16% serous, GOG-249: 15% serous, GOG-258: 18% serous; see above for detail of individual studies). In the PORTEC-3 trial, the addition of concurrent chemotherapy to the standard of percutaneous radiotherapy showed a significant advantage in overall survival for the serous carcinoma group (after 5 years 59.7% vs. 47.9%, HR 0.42, 95%-CI 0.22-0.80) [597]. For the GOG-249 trial comparing postoperative percutaneous radiotherapy and vaginal brachytherapy with three cycles

of chemotherapy, subgroup analysis for patients with serous or clear cell carcinoma did not identify a significant advantage for either strategy [615]. In the GOG-258 trial, which tested the addition of percutaneous radiotherapy to chemotherapy alone and for which evaluations of overall survival are not yet available, subgroup analysis of recurrence-free survival for serous carcinoma has not yet shown a clear signal in favor of either arm.

The effect of the therapeutic element radiotherapy in serous carcinomas was considered in a recent meta-analysis of retrospectively collected data [616], numerically dominated by large registry studies from SEER and NCDB. In 9,354 patients evaluated, a highly significant survival benefit (HR = 0.72, 95%-CI 0.63–0.84; $p < 0.0001$) was reported for combination radiotherapy plus chemotherapy versus chemotherapy alone, which was similar for both limited and advanced stages. Of the patients for whom the type of radiotherapy was known, most had been treated with percutaneous radiotherapy +/- vaginal brachytherapy [616]. This suggests a preference for percutaneous radiotherapy in the high-risk group of type II carcinomas.

7.5 Primary radiotherapy alone for internal medicine inoperability

For patients with endometrial carcinoma who are inoperable for medical reasons, radiotherapy alone represents a treatment approach with curative intent.

In the absence of randomized trials, the Gynecological Cancer Group of the European Organization for Research and Treatment of Cancer currently produced a systematic review describing the use of radiotherapy for this indication and the results [617].

A total of 2,694 patients from 25 case series were considered. These were treated with brachytherapy alone (51%) or the combination of brachytherapy plus percutaneous radiation (47%). At five years, disease-specific survival was 78.5%, local control 79.9%, and overall survival, reflecting pre-existing comorbidities, 53.2%. The risk of late sequelae ≥ grade 3 was 2.8% (brachytherapy only) and 3.7% (combination). Based on these data, brachytherapy alone is recommended for stage I grade 1 only, and the combination of percutaneous irradiation and brachytherapy is recommended for the remainder of stage I and for stages II to IV in cases of internal cancer inoperability.

7.6 Radiotherapy for carcinosarcoma

7.22	Evidence-based recommendation	modified 2022
GoR **B**	To improve local control, postoperative radiotherapy should be given in addition to chemotherapy for carcinosarcoma when stage FIGO I or II is present.	
LoE **3**	[618]	
	Strong Consensus	

7.23	Consensus-based recommendation	new 2022
EC	In the case of carcinosarcoma, an individualized radiation concept can be implemented if higher stages are present.	
	Strong Consensus	

Background

Data are available on the benefit of adjuvant pelvic irradiation compared with no adjuvant therapy for stage I or II carcinosarcoma from the EORTC trial 55874 [619]. Within a mixed cohort of 224 patients with uterine sarcomas, 92 women with carcinosarcoma were randomized to the pelvic irradiation arm with 50.4 Gy (single dose 1.8 Gy, starting within 8 weeks postoperatively) or to the observation arm. At a median follow-up of 6.8 years, improved local control with reduction of local recurrence rate from 47% to 24% was observed for the subgroup of patients with carcinosarcoma, but without significant survival benefit.

Whole-abdomen irradiation with 30 Gy, followed by pelvic dose boost up to 50 Gy (in each case partially with 2 x 1 Gy per day), did not achieve significant differences in overall survival or recurrence rate in the randomized GOG 150 trial (206 patients, of whom 31% were stage I, 45% stage III) compared with chemotherapy with cisplatin, ifosfamide, and mesna, so such an extended volume of irradiation is not recommended [620].

Retrospective evaluations of US registry data (National Oncology Database or Surveillance, Epidemiology and End Results Database) repeatedly show positive effects for adjuvant pelvic irradiation (± brachytherapy) in large collectives with carcinosarcoma on locoregional recurrence-free survival [621] and also on overall survival [521], [622]. Another US epidemiologic study examining the benefit of lymphadenectomy [623], showed a favorable effect on overall survival (HR = 0.64, 95%-CI 0.56–0.73), but pelvic radiotherapy showed only nonsignificant improvements in the group with lymphadenectomy (HR = 0.92, 95%-CI 0.76–1.11) and without lymphadenectomy (HR = 0.87, 95%-CI 0.72–1.05), respectively. The effect of radiotherapy in the overall collective was not reported.

Given the repeatedly confirmed beneficial effects of radiotherapy on local control, postoperative radiotherapy should usually be indicated for carcinosarcoma.

As part of the guideline revision, an update search on postoperative radiotherapy for carcinosarcoma was conducted in 2020, the results of which were published in a formal non-systematic review [624]. No new prospective data were found in the update search from 2010, but nine analyses of US or European registry data were found that provided results on overall survival in varying detail depending on stage and radiotherapy modality used (vaginal brachytherapy, external beam or combination).

From the stage-specific registry data, the following options were offered (+: recommended, 0: unclear, -: not recommended):

Table 13: Proposal for stage-adapted radiotherapy in uterine carcinosarcoma

Stage	external beam radiotherapy alone	vaginal brachytherapy alone	combination (external + brachytherapy)
IA	(+)	+	(+)
IB	+	+	+
II	(+)	(+)	+
III	(+)	(+)	+
IV	(+)	–	0

+: recommended, 0: unclear, -: not recommended

7.7 Supportive therapy

When carrying out radiotherapeutic measures, the recommendations of the S3 Guideline “Supportive therapy in oncological patients” [625] should be taken into account. See also Recommendation 9.9 in Chapter 9.

Supportive therapy is an integral part of the treatment concept. Side effects can occur as acute changes during or directly after therapy or as late effects.

7.7.1 Radiotherapy-induced nausea and vomiting

Patients receiving radiotherapy should also be assessed for emetogenic risk using the risk categories and guideline-based prophylaxis and therapy should be initiated.

Background

In patients receiving combined radio(chemo)therapy, the emetogenic risk is usually defined by the chemotherapy (see Chapter 8), with theexception that the risk of radiotherapy should be higher due to tumor location.

7.7.2 Locoregional side effects

7.7.2.1 Radiogenic proctitis

Drug prophylaxis of radiogenic proctitis is not known. 5-aminosalicylic acid (5-ASA) is contraindicated due to increased complication rates during radiation therapy in the abdomen. For acute proctitis, topical therapy with butyrates is possible (see the summary of product characteristics) [626]. Treatment of late radiogenic changes of the rectum is an interdisciplinary task. There are isolated data on endoscopic sclerotherapy. If therapy fails, local antiphlogistic treatments and enemas with sucralfate (2 x 2 g in 20 ml water suspension/day), sodium, pentosan polysulfate or metronidazole with cortisone can be given. These therapies are performed in an interdisciplinary approach (gynecologic oncology, radiation oncology, gastroenterology), for example in experienced centers.

7.7.2.2 Radiogenic cystitis

Acute radiotherapy-induced cystitis leads to symptoms such as dysuria, increasing micturition frequency and nocturia. The main focus is on symptomatic treatment of the symptoms by means of analgesia and spasmolysis (metamizole, centrally acting analgesics, butylscopolamine, oxybutynin). Alkalinization of the urine and iron substitution up to transfusions in case of recurrent micro- and macrohematuria complete the therapy. Bacterial superinfections require appropriate antibiotic therapy.

Preventive use of amifostine (= aminothiol) to reduce radiotherapy-related toxicity may be considered according to the ASCO Guideline [627]. Ethyol® (amifostine) is not approved in Germany for this indication. Critical consideration of the side effects and benefits of amifostine in this off-label use indication is necessary [627].

7.7.2.3 Radiogenic vulvovaginitis

Acute radiogenic vulvovaginitis occurs up to 90 days after the start of radiotherapy and is often reversible. Dexpanthenol, chamomile sitz baths, and sitz baths with synthetic tanning agents such as phenol-methanal-urea polycondensate are available for the therapy of vulvovaginitis. Suppositories containing freeze-dried cultures of L. acidophilus are used to restore the physiological pH of the vagina as a prerequisite for restoring the physiological vaginal flora. In addition, creams containing benzydamine are also used. For the use of estrogen-containing creams, gels, ovules, etc.; see Chapter 9.7.2.

7.7.2.4 Lymphedema

In lymphedema, the combination therapy of manual lymphatic drainage and compression therapy is performed in clinical practice. The frequency and duration of these combined measures depend on the lymphedema stage I–III. After contraindications have been ruled out, the treatment is performed after weighing the expected benefit (for further details, see Chapter 11.4.3).

7.7.2.5 Vaginal dryness, vaginal stenosis and vaginal fibrosis

The radiogenic and/or chemotherapy-induced dryness of the vagina in endometrial carcinoma can be reduced by the application of inert lubricants. In individual cases, local estrogen treatment can be performed in cases of high distress after careful risk assessment and appropriate patient education. Approximately 4–6 weeks after the end of radiotherapy that has involved the vaginal region, mechanical dilatation

(vaginal dilators, bepanthen tampons) is a suitable instrument for the prophylaxis of vaginal stenosis (see also Chapter 9).

7.7.2.6 Sexual dysfunction

Providing patients with sufficient information about the effects of the therapy on their sexual life and about the possibilities of prophylactic-therapeutic measures (e.g. vaginal dilatation) is an existential part of the therapy of patients with endometrial carcinoma (for further details, see Chapter 11.1.3).

8 Adjuvant drug therapy of endometrial carcinoma

8.1 Adjuvant drug therapy for endometrial carcinomas

8.1.1 Adjuvant progestogen therapy

8.1	Evidence-based recommendation	checked 2022
GoR **A**	Adjuvant progestin therapy after surgery for endometrial cancer shall not be performed.	
LoE **1**	[628]	
	Strong Consensus	

Background

In view of the comparatively low side effects, high-dose progestogens have been intensively studied as adjuvant therapy after surgical treatment and adjuvant radiotherapy of endometrial carcinoma. There are 7 RCTs involving 4,556 endometrial cancer patients that have been repeatedly analyzed by the Cochrane Collaboration [629].

The most recent meta-analysis (search by 04/2009) [629], like the previous ones, found no difference for overall survival at 4, 5, and 7 years. The risks of dying from endometrial cancer, cardiovascular and intercurrent disease were also not affected by adjuvant progestin therapy. In one study, the risk of recurrence of endometrial cancer was reduced. This was not confirmed in another study. Effects of adjuvant progestin therapy on patients' quality of life were not investigated in any study.

The authors of the meta-analysis conclude that there are now several RCTs showing that adjuvant progestin therapy after primary therapy for endometrial cancer has no benefit. Further studies on this question are probably not Justified.

8.1.2 Adjuvant chemotherapy

8.2	Consensus-based recommendation	modified 2022
EC	Patients with primary type I endometrial carcinoma stage pT1a/b G1 and G2 cN0/ pNsn0, p53-wt, shall not receive adjuvant chemotherapy.	
	Strong Consensus	

8.3	Evidence-based statement	modified 2022
LoE 2	For patients with endometrioid or other type I endometrial carcinoma at stage pT1a G3 cN0 or pN0, p53-wt, there are insufficient data on the benefit of adjuvant chemotherapy.	
	[519]	
	Strong Consensus	

8.4	Evidence-based recommendation	modified 2022
GoR 0	For patients with type I endometrial carcinoma G3 pT1b, without POLE mutation or stage pT2 (each pN0), adjuvant chemotherapy with 3 or 6 cycles (see Statement 8.13) may be considered as an adjunct to vaginal brachytherapy (see Radiation Therapy recommendation) or percutaneous radiotherapy alone without chemotherapy.	
LoE 2	[519], [630]	
	Strong Consensus	

8.5	Consensus-based recommendation	new 2022
EC	Patients with type I endometrial carcinoma G3 pT1b or stage pT2 (both pN0) with POLE mutation should not receive adjuvant chemotherapy.	
	Strong Consensus	

8.6	Evidence-based recommendation	new 2022
GoR B	Patients with serous endometrial carcinoma in FIGO stage I – III should receive adjuvant therapy according to the PORTEC-III regimen (= radiochemotherapy followed by chemotherapy). For stage III serous endometrial carcinoma, adjuvant chemotherapy alone can be given as an alternative (carboplatin AUC 6 / paclitaxel 175 mg/m2).	
LoE 2	[608], [631]	
	Strong Consensus	

8.7	Consensus-based recommendation	new 2022
EC	Patients with type 1 endometrial carcinoma and abnormal p53 status on immunohistochemistry (type I endometrial carcinoma stage 1a or higher, with infiltration into the myometrium, or clear cell endometrial carcinoma) should be treated like patients with serous endometrial carcinoma.	
	Consensus	

8.8	Evidence-based recommendation	modified 2022
GoR A	Patients with primary endometrial cancer stage pT3 and/or pN1 shall receive adjuvant chemotherapy or adjuvant therapy according to the PORTEC-3 regimen.	
LoE 2	[608], [596], [597], [598]	
	Strong Consensus	

8.9	Evidence-based recommendation	modified 2022
GoR B	Patients with stage pT4a or M1 endometrial cancer who have undergone macroscopic complete tumor resection or have a maximum postoperative residual tumor less than 2 cm should receive adjuvant chemotherapy, if applicable in combination with radiotherapy.	
LoE 1	[608], [519], [630]	
	Strong Consensus	

8.10	Evidence-based recommendation	modified 2022
GoR **A**	Adjuvant chemotherapy for endometrial cancer shall be given with carboplatin AUC 6 and paclitaxel 175 mg per square meter. After percutaneous radiotherapy, carboplatin AUC 5 should be dosed.	
LoE **2**	[608], [632], [633]	
	Strong Consensus	

8.11	Evidence-based recommendation	modified 2022
GoR **0**	If chemotherapy alone is indicated and paclitaxel or carboplatin are contraindicated, adriamycin and cisplatin may also be used.	
LoE **2**	[608], [632], [633]	
	Strong Consensus	

Background

The benefit of adjuvant chemotherapy as an alternative to or in addition to adjuvant radiotherapy after primary surgery for EC has been intensively studied and has been the subject of several large, randomized trials (PORTEC-3, GOG 258, and GOG 249).

In the international Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC)-3 trial, adjuvant concurrent radiochemotherapy followed by adjuvant chemotherapy resulted in a significant improvement in overall survival in women with high-risk EC compared with radiotherapy alone [631]. In this study, patients (n = 660) with high-risk EC were studied. Approximately 45% were stage III, 26% were stage IIIC, i.e., with lymph node metastases, 25% of patients had serous or clear cell (type 2) EC, and 32% had poorly differentiated (G3) endometrioid EC. In the overall population, 5-year overall survival was 81.4% (95%-CI 77.2–85.8) in the chemotherapy and radiotherapy group vs. 76.1% (71.6–80.9) in the radiotherapy alone group (HR: 0.7; 95%-CI = 0.51–0.97; p = 0.034) (median follow-up 72.6 months). The 5-year failure-free survival was 76.5% (95%-CI = 71.5–80.7) vs. 69.1% (63.8–73.8; HR 0.7; 95%-CI 0.52–0.94; p = 0.01). In most patients, distant metastases were the first manifestation of recurrence. They occurred in 21.4% of women in the chemo/radiotherapy group and in 29.1% of women in the radiotherapy alone group. In a subgroup analysis of patients with stage I and II EC, no significant differences in overall survival and failure-free survival were found with the addition of chemotherapy. However, in the subgroups of patients with stage III and serous EC, the addition of chemotherapy resulted in a significant improvement in 5-year overall survival: 78.5 vs. 68.5% (stage

III; p = 0.043) and 71.4 vs. 52.8% (serous EC; p = 0.037), respectively, and failure-free survival: 70.9 vs. 58.4% (stage III; p = 0.011) and 59.7 vs. 47% (serous EC; p = 0.008).

After 5 years, adverse event rates were similar in both groups. Only sensory neuropathies were more common in the chemo/radiotherapy arm. The authors conclude that combined chemo/radiotherapy consisting of pelvic irradiation with 2 simultaneous administrations of cisplatin followed by 4 cycles of carboplatin/paclitaxel should be recommended to patients with serous and/or stage III EC. This includes all patients with pelvic and/or para-aortic lymph node metastases, regardless of the local spread of the primary tumor.

The US GOG-258 trial assessed whether adjuvant radiochemotherapy with cisplatin followed by 4 cycles of adjuvant chemotherapy with carboplatin/paclitaxel results in a survival benefit over adjuvant chemotherapy alone (6 cycles of carboplatin/paclitaxel) in patients with high-risk EC [608]. This was not the case. 736 patients with high-risk EC, of whom > 97% were stage III (50% stage IIIC1, 25% stage IIIC2; 21% serous or clear cell) were treated adjuvantly after surgery with either chemotherapy alone or combined chemo/radiotherapy analogous to the PORTEC-3 trial. If the para-aortic lymph nodes were affected (IIIC2), this region was also irradiated. The median follow-up time was 47 months. The 5-year recurrence-free survival was 59% (95%-CI = 53–64%) in the chemo/radiotherapy group and 58% (53–64%) in the chemotherapy alone group (HR 0.9; 90% CI 0.74–1.10). According to the study hypothesis, additional radiotherapy resulted in both fewer vaginal recurrences (2 vs. 7%; HR: 0.36; 95%-CI = 0.16–0.82) and fewer pelvic recurrences and para-aortic lymph node recurrences (11 vs. 20%; HR: 0.43; 95%-CI = 0.28–0.66). However, distant metastases were more frequent in the chemo/radiotherapy group than in the chemotherapy alone group (27 vs. 21%; HR: 1.36; 95%-CI = 1.00–1.86). Side effects ≥ grade 3 were observed in 58% of the chemo/radiotherapy group and in 63% of patients with chemotherapy alone. The addition of radiotherapy to chemotherapy did not improve relapse-free survival. It remains to be seen whether in the further follow-up period the reduction in the incidence of distant metastases in the chemotherapy alone group will have an effect on overall survival.

Finally, data are available from the GOG 249 trial, which tested whether adjuvant vaginal brachytherapy followed by shortened chemotherapy (3 cycles) is more effective than percutaneous radiotherapy ± brachytherapy [610] in high/intermediate-risk and high-risk stage I and II EC. This was not the case. High/intermediate risk was defined as age of ≥ 70 years plus 1 uterine risk factor, age of ≥ 50 years plus 2 risk factors, or age ≥ 18 years plus 3 risk factors. Uterine risk factors were G2 and G3 tumors, pT1b, and lymphatic invasion. Pelvic and para-aortic lymphonodectomy were recommended and performed in 90% of patients. Alternatively, postoperative CT or MRI was used to exclude enlarged lymph nodes. 21% of patients had endometrioid EC, G3, 20% had serous or clear cell EC [Randall et al. 2019]. 75% of patients were stage I, 25% were stage II. Patients with stage I or II serous or clear cell EC and positive peritoneal cytology were not eligible for the GOG-249 trial but were recommended for participation in the GOG-258 trial.

After a median follow-up of 53 months, 5-year recurrence-free survival was 76% (95%-CI = 0.70–0.81) for the percutaneously irradiated group and 76% (0.70–0.81) for the brachytherapy/chemotherapy group. The hazard ratio was 0.92 (90% CI = 0.69–1.23). The 5-year overall survival was 87% (95%-CI = 83–91%) for the percutaneously irradiated patients and 85% (95%-CI: 81–90%) for the brachytherapy/chemotherapy group (HR: 1.04; 90% CI = 0.71–1.52). Vaginal recurrences and distant metastases

were similarly frequent in both groups; pelvic and para-aortic recurrences were more frequent in the brachytherapy/chemotherapy group (9 vs 4%) [Randall et al. 2019]. Acute toxicity was higher in the brachytherapy/chemotherapy group; late toxicities were comparable.

Interpretation of these 3 studies can be used to formulate clear recommendations for action. The GOG-249 trial addressed the question of whether "little" chemotherapy and vaginal brachytherapy is better than external pelvic irradiation combined with optional vaginal brachytherapy. The GOG-258 trial, on the other hand, investigated whether adding radiation to chemotherapy is beneficial in advanced disease. The PORTEC-3 trial, in contrast, was designed to investigate whether the addition of chemotherapy to radiation was associated with improved overall survival. The PORTEC-3 study clearly shows that the addition of chemotherapy to percutaneous radiation, especially in stage III or serous EC, provides a significant and, above all, clinically relevant improvement in overall survival compared to radiation therapy alone.

The PORTEC-3 study does not answer the question whether radiotherapy is still necessary at all in patients with high-risk EC who receive sufficient adjuvant chemotherapy. Answering this question was the goal of the U.S. GOG-258 trial. Although the additional radiotherapy improved locoregional control, distant metastases occurred more frequently than in the chemotherapy alone group. Reasons for this could be the reduction of full chemotherapy cycles from 6 to 4 or the delayed onset of combination chemotherapy. In any case, the additional radiotherapy did not improve recurrence-free survival. Overall survival has so far been the same in both groups.

Therefore, if a patient is treated with adjuvant chemotherapy according to the standard arm of the GOG-258 trial, additional brachytherapy may be discussed to reduce the rate of vaginal recurrences. In contrast, if a patient is treated according to the experimental arm of the GOG-258 trial, it should be discussed with the patient whether the reduction of pelvic and para-aortic recurrences by percutaneous radiotherapy justifies the acceptance of more distant metastases, since pelvic and/or para-aortic recurrences can also be irradiated secondarily with good results if percutaneous irradiation has not yet been performed.

Recent data from Nomura et al. and Miller et al. [632], [634] emphasize the value of adjuvant chemotherapy with carboplatin and paclitaxel over alternative regimens. Nomura et al. In a randomized trial of patients with high-risk stage I-IV EC demonstrated that the following 3 regimens: doxorubicin 60 mg/m2 plus cisplatin 50 mg/m2; docetaxel 70 mg/m2 plus cisplatin 60 mg/m2; and paclitaxel, 180 mg/m2 plus carboplatin AUC 6 were equivalent in terms of progression-free survival and overall survival. In a randomized trial (GOG 209) of patients with stage III and IV EC or recurrence, Miller et al., showed that 7 cycles of paclitaxel 175 mg/m2 plus carboplatin AUC 6 were non-inferior compared with doxorubicin 45 mg/m2 plus cisplatin 50 mg/m2 plus paclitaxel 160 mg/m2 (with GCSF support). Adjuvant chemotherapy in early or advanced EC stages should therefore be given with carboplatin AUC 6 and paclitaxel 175 mg/m2. When combined with percutaneous radiotherapy, carboplatin AUC 5 should be dosed. Adriamycin and cisplatin may also be used if contraindications exist.

Of particular interest for the recommendations included in this Guideline were the first retrospective evaluations of the PORTEC-2 study and the PORTEC-3 study

regarding the predictive value of molecular subtypes. Wortmann et al. were able to show by combined molecular and immunohistochemical profiling of the PORTEC-2 collective that patients with “high-intermediate risk”-EC (defined as FIGO [1988] 1C G1/2 > 60 years or FIGO [1988] 1B G3 > 60 years or FIGO [1988] 2A – except G3 with deep stromal invasion), who had evidence of a risk profile (p53-mutant or L1CAM+ or extensive LVSI) benefited from adjuvant pelvic irradiation [341]. According to this work, therefore, conversely, adjuvant vaginal brachytherapy alone should be given to patients with “high-intermediate risk” EC without evidence of a risk profile (p53-mutant or L1CAM+ or extensive LVSI).

Leon-Castillo et al. investigated the predictive value of the 4 molecular subtypes (p53 abnormal, POLE-ultramutant, MMR-deficient and no specific molecular profile) with respect to the therapeutic outcome of adjuvant radiochemotherapy followed by 4 x carboplatin/paclitaxel in the PORTEC-3 trial [358]. It was shown that only the group with p53-abnormal EC benefited from adjuvant radiochemotherapy followed by chemotherapy. Therefore, from these data it can be hypothesized that in patients with serous EC, stage FIGO III (including pN1/2) or with “high-risk” constellation (FIGO 1A G3 with LVSI, FIGO 1B G3, FIGO II, FIGO III, FIGO I-III with serous or clear cell histology), adjuvant radiochemotherapy with cisplatin followed by 4 cycles of carboplatin/paclitaxel should be performed only in case of detection of a p53-abnormal molecular subtype. However, the authors emphasize that due to the small numbers of cases in the subgroups, the incomplete coverage of tissue samples, and the retrospective nature of the analysis, it can only be considered hypothesis-generating.

Therefore, as a limitation, it should be considered that no prospective data are currently available on the question of the predictive value of molecular subtypes. The currently still recruiting prospective randomized PORTEC-4a study will show whether combined molecular and immunohistochemical risk profiling in patients with high-intermediate risk EC can improve the choice between foregoing adjuvant radiation, adjuvant brachytherapy and adjuvant percutaneous radiation [635]. Prospective studies that could define the predictive utility of molecular classification for treatment decisions in high-risk EC do not yet exist.

8.1.3 Adjuvant drug therapy for carcinosarcoma.

8.12	Evidence-based recommendation	modified 2022
GoR **0**	Patients with carcinosarcoma FIGO stage I or II may receive adjuvant chemotherapy with carboplatin/paclitaxel (at a dosage of paclitaxel 175 mg/m² day 1 carboplatin AUC 6 day 1) or cisplatin/ifosfamide (at a dosage of ifosfamide 1.6 g/m² day 1–4 and cisplatin 20 mg/m² day 1–4).	
LoE **4**	[636]	
	Strong Consensus	

8.13	Evidence-based statement	checked 2022
LoE **1**	For patients with stage FIGO III or IV carcinosarcoma, adjuvant chemotherapy with ifosfamide/paclitaxel or ifosfamide/cisplatin was shown to have a significant survival benefit over monotherapy with ifosfamide.	
	[637], [638], [639]	
	Strong Consensus	

8.14	Consensus-based recommendation	modified 2022
EC	Given the high toxicity of ifosfamide-containing combinations, the combination of carboplatin and paclitaxel can also be used as adjuvant chemotherapy in patients with stage FIGO III or IV carcinosarcoma at a dosage of paclitaxel 175 mg/m2 day 1 and carboplatin AUC 6 or cisplatin/ifosfamide at a dosage of ifosfamide 1.6 g/m2 i.v. Day 1–4 and cisplatin 20 mg/m2 i.v. Day 1–4.	
	Strong Consensus	

Background

Only one retrospective multicenter case series of 111 women exists regarding adjuvant therapy in stages I and II carcinosarcoma. Of these, 44 (40%) had received no adjuvant therapy, 23 (20%) had received adjuvant radiotherapy, 29 (26%) had received adjuvant chemotherapy and 15 women (14%) had received radiochemotherapy. Women who received chemotherapy had better PFS than those who received radiotherapy alone or were observed only (HR = 0.28; CI = 0.12–0.64 in multivariate Cox model). Sixteen patients had received the cisplatin/ifosfamide combination and 18 had received the carboplatin/paclitaxel combination [640]. On the question of “off-label use”, see above.

In patients with recurrent carcinosarcoma, the U.S. Gynecologic Oncology Group (GOG) demonstrated in a series of phase II trials that the highest objective response (OR) rates were achieved with ifosfamide (36%).

Paclitaxel (OR = 18%), cisplatin (OR = 18%), doxorubicin (OR = 9.8%) and topotecan (OR = 10%) were less effective [641].

The combination of ifosfamide and cisplatin improved recurrence-free survival compared with ifosfamide alone in stage III and IV carcinosarcomas (HR = 0.73; CI = 0.55–0.98); overall survival was not significantly improved by the combination (HR = 0.80; CI = 0.60–1.08) [642].

The combination of ifosfamide (ifosfamide 1.6 g/m2 d 1–3, or reduced to 1.2 mg/m2 if pre-radiation) and paclitaxel (135 mg/m2 over 3 hours d 1 i. v.) significantly improved progression-free (HR = 0.71; CI = 0.52–0.97) and overall survival (HR = 0.69; CI = 049–0.97) in stage III and IV carcinosarcomas [643].

In the Cochrane Collaboration meta-analysis [644], combination therapy of ifosfamide and cisplatin or paclitaxel significantly improved PFS (HR = 0.72; CI = 0.58–0.90) and OS (HR = 0.75; CI = 0.60–0.94) compared with ifosfamide monotherapy. Side effects, except for nausea and vomiting (HR = 3.53; CI = 1.33–9.37), were not significantly different in the combination group compared with those in the ifosfamide monotherapy group.

Specifically, the side effects were: diarrhea/other gastrointestinal toxicities (RR = 1.51, 95%-CI 0.31–7.52); hematologic toxicities (RR = 1.56, 95%-CI 0.84–2.90); genitourinary toxicities (RR = 1.68, 95%-CI 0.54–5.18); cardiovascular toxicities (RR = 0.63, 95%-CI 0.13–3.11); liver toxicities (RR = 2.05, 95%-CI 0.73–5.74); neuropathies (RR = 1.59, 95%-CI 0.99–2.55) [644].

The better tolerated combination of carboplatin and paclitaxel (PC) had similar efficacy to ifosfamide combinations in some phase II trials and in retrospective series, with significantly less toxicity. This combination is currently being compared to the combination of ifosfamide and paclitaxel (PI) by the GOG in a phase III trial. At the abstract level, PC was non-inferior to PI in terms of OS, with longer PFS and comparable QoL [645].

8.1.4 Supportive therapy

8.1.4.1 Supportive measures in connection with system therapy

The S3 Guideline on supportive therapy for oncology patients addresses the following topics in detail in the context of system therapy:

- Tumor therapy-induced anemia
- Prophylaxis of tumor therapy-induced neutropenia with granulopoietic growth factors
- Tumor therapy-induced nausea and vomiting
- Tumor therapy-induced diarrhea
- Oral mucositis induced by systemic tumor therapy
- Tumor therapy induced skin toxicity
- Neurotoxicity – chemotherapy-induced peripheral neuropathy (CIPN)
- Osseous complications

- Osseous manifestations
- Drug intervention
- Surgical intervention
- Radiotherapeutic intervention
- Radionuclide therapy
- Therapy associated osteoporosis
- Extravasation

(S3 Guideline Supportive therapy in oncology patients long version 1.3 – February 2020 AWMF register number: 032/054OL, https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.pdf)

9 Follow-up/recurrence/metastases of endometrial carcinoma

9.1 Approaches in follow-up

9.1	Evidence-based statement	checked 2022
LoE 4	There is no evidence that follow-up in women with EC results in prolonged survival.	
	[214], [646], [647], [648], [649], [650], [651], [652], [653], [654]	
	Strong Consensus	

9.2	Consensus-based recommendation	checked 2022
EC	A medical history with specific query of symptoms and clinical gynecological examination with speculum and rectovaginal palpation examination should be performed at 3- to 6-month intervals for the first 3 years after completion of primary therapy and semi-annually in years four and five.	
	Strong Consensus	

9.3	Evidence-based recommendation	checked 2022
GoR B	Imaging studies and tumor marker determinations should not be performed in asymptomatic patients.	
LoE 4	[214], [646], [647], [652]	
	Consensus	

Background

The follow-up of patients with EC serves the early detection of a recurrence, which can be treated with curative intention, e.g. in case of an isolated vaginal tumor manifestation. Furthermore, since patients with EC and their relatives face physical, psychological, sexual, social, and spiritual/religious stresses, the need for psychosocial, psycho-oncological, and sexual medicine counseling should be actively

sought during follow-up and, if necessary, provided by a multiprofessional team. See Chapter 11.

EC recurs in about 13% of all cases, and in low-risk cases even in only < 3% of cases [655]. Some retrospective studies show that more asymptomatic than symptomatic recurrences are detected by organized follow-up programs. This means that systematized follow-up can identify recurrences earlier than in women who present for medical evaluation only when they have symptoms such as vaginal bleeding or pain, independent of a follow-up program. For those patients who present for treatment with an asymptomatic recurrence, longer survival times have been reported in some cases [648], [649], [656]. These findings, obtained from retrospective analyses, are the rationale for regular follow-up at initially closer intervals after completion of primary therapy for EC, with a focus on detection of recurrence of the vagina, vulva or pelvis that is still amenable to curative treatment. However, it is not proven whether the longer survival in asymptomatic women in the aforementioned studies can be explained by the advance time of recurrence diagnosis (so-called “lead time bias”) or by earlier therapy after recurrence diagnosis.

In a review of the above retrospective cohort studies, Salani et al. [654] describe a detection rate for vaginal recurrence by gynecologic examination including rectovaginal palpation of 35% to 68%. Therefore, regular gynecologic examination including rectovaginal palpation may be performed as part of follow-up. Cytologic smear of the vaginal blind sac leads to the diagnosis of recurrence in only 0% to 13% of asymptomatic patients with recurrence [649] and therefore does not appear to be a useful measure. Furthermore, the use of cytological smear in the follow-up of women with EC is not cost-effective [653].

In the aforementioned review, Salani et al. [654] put the proportion of women with symptomatic recurrence at 41% to 83%. Depending on the study, 68% to 100% of recurrences occurred within the first three years after the end of primary therapy. Approximately half were either local recurrences (vagina and pelvis) or distant metastases. Yalamanchi et al. 2018 and Nomura et al. 2019 found the proportion of isolated vaginal recurrences to be 20% and 37%, respectively, in their study collectives [657]; [658]. Patients with isolated vaginal recurrence had a 3-year survival rate after isolated vaginal recurrence of 73% versus 14% in the case of pelvic recurrence and 8% in the case of distant metastasis in the prospective randomized PORTEC-1 trial (comparing adjuvant pelvic radiotherapy with no adjuvant therapy for early endometrial cancer) [651].

In a systematic review of 16 retrospective cohort studies, no advantage was found for the detection of recurrence by intensified imaging follow-up in terms of overall survival [655]. Therefore, Dutch and US guidelines do not recommend routine imaging in the follow-up of women with EC [214], [228], [654]. Along the same lines, a retrospective analysis of 149 women for asymptomatic recurrences, 80% of which were detected by imaging, showed no advantage in overall survival and recurrence-free survival over symptomatic recurrences [657].

Ultrasound has not been studied as a tool in the follow-up of endometrial cancer in the last 15 years. An older work has shown high detection rates for recurrences of gynecologic malignancies for the combination of a transvaginal and transabdominal ultrasound [659]. Abdominal ultrasonography also allows early diagnosis of urinary retention, which can occur as a complication of surgery or radiation therapy in addition to tumor recurrence. Ultrasound has numerous advantages due to its general

availability in gynecologic practices, ease and speed of use, low cost and lack of radiation exposure, so this examination method can be used in the follow-up of endometrial cancer.

The importance of tumor markers in the follow-up of women with EC is unclear. In an older work from 1995, the tumor marker CA 125 was elevated in only 6/23 asymptomatic recurrence cases, especially with non-endometrioid histology and after advanced tumor stage [652].

Current studies address the question of whether follow-up in high risk recurrence should be intensified and performed with regular imaging [660], or, conversely, whether follow-up in low risk EC can be patient-directed or designed by telephone interviews. Three randomized studies showed higher patient satisfaction when follow-up of stage I EC was performed by telephone interviews or when patients instructed on critical symptoms were able to initiate appropriate examinations themselves [661]; [662]; [663]. These studies are also potentially relevant in terms of cost savings for the health care system [663].

In a Cochrane review on the follow-up of different tumor entities, 20,832 cases of adult female patients were evaluated, including 4 studies with 770 cases after EC [664]. Different intensity follow-up modalities (e.g. follow-up by specialist vs. non-specialist or nursing, closer and more elaborate protocols vs. simple clinical examination and follow-up with or without additional educational programs) were compared with each other in terms of quality of life, cost, time interval between primary therapy and recurrence diagnosis, and overall survival. The authors saw no detectable effect on overall survival, quality of life and costs.

A scientific topic of interest in the follow-up of different tumor entities is the improvement or replacement of follow-up by so-called “cancer survivorship plans” (CSP), which aim to support patients in their physical, psychological, social and economic rehabilitation by providing concrete instructions. In a prospective study in 12 Dutch hospitals with 221 patients after EC, patients felt better informed during follow-up with CSP but were also more concerned and dissatisfied [665].

In summary, there are currently no convincing data to support the introduction of alternative follow-up strategies.

9.2 Procedure for locoregional recurrences

9.4	Consensus-based recommendation	checked 2022
EC	If local recurrence in the vagina or pelvis is suspected or if distant metastases are suspected, histological confirmation shall be sought.	
	Strong Consensus	

9.5	Evidence-based recommendation	checked 2022
GoR A	Cross-sectional imaging shall be performed if vaginal recurrence, pelvic recurrence or distant metastasis is suspected or after histologic confirmation of vaginal recurrence, pelvic recurrence or distant metastasis.	
LoE 3	[214], [215], [666]	
	Strong Consensus	

Background

At least half of all cases of women with EC recurrence are noticed by symptoms outside the follow-up examinations. If possible, histologic confirmation shall be sought in cases of suspected recurrence, and the most accurate diagnosis of spread should be pursued to protect the patient from unnecessary, burdensome therapy.

Reliable data from randomized trials on the value of different imaging modalities or other follow-up in symptomatic women with EC in terms of response rate, overall survival, survival duration or time to further progression after completion of recurrent therapy are not available.

In 2013, Kadkhodayan et al. [667] investigated the detection of EC recurrence by PET-CT in a meta-analysis: in 11 cohort studies with 541 symptomatic and asymptomatic patients, a sensitivity of 95.8% (95%-CI 92.2–98.1%) and a specificity of 92.5% (89.3–94.9%) were found for PET-CT. These parameters were verified by a so-called combined reference standard, i.e., partly by histological examination of lesions suspected of recurrence and partly by follow-up of lesions on imaging. An increase in size of a lesion was considered a confirmation of suspected malignancy, whereas a decrease in size without therapy or a lack of change in size during progression was considered tumor-negative. PET-CT results led to a change in treatment plan in 22–35% of patients.

Another meta-analysis confirmed the high sensitivity and specificity of 18F-FDG PET/CT (95% and 91%, respectively) for the diagnosis of EC recurrence, although the studies evaluated were predominantly retrospective and did not distinguish between symptomatic and asymptomatic recurrences. Not all cases were verified by histologic examination [668].

Transabdominal sonography is of limited use for recurrence detection in the lesser pelvis and retroperitoneum due to intestinal gas superimposition, among other reasons, whereas MRI and CT are examination methods free of superimposition.

In summary, the value of cross-sectional imaging and especially PET-CT lies primarily in the more accurate diagnosis of tumor spread when recurrence is confirmed. This may help to avoid unnecessary recurrence surgery or optimize the individual therapy plan. The ACR guideline calls sectional imaging by PET-CT, MRI and CT suitable ("usually appropriate") for recurrence diagnosis of EC [209].

9.2.1 Isolated vaginal or vaginal stump recurrence

9.6	Consensus-based recommendation	checked 2022
EC	Women with isolated vaginal or vaginal stump recurrence after endometrial cancer without prior radiation therapy as part of primary treatment should receive radiation therapy with curative intent, consisting of external pelvic radiation and brachytherapy with or without local tumor resection.	
	Strong Consensus	

9.7	Consensus-based recommendation	checked 2022
EC	Women with isolated vaginal or vaginal stump recurrence after endometrial cancer with adjuvant brachytherapy alone as part of primary treatment, radiotherapy with or without local tumor resection may be given with curative intent.	
	Strong Consensus	

9.8	Consensus-based recommendation	checked 2022
EC	Women with vaginal or vaginal stump recurrence in status post external pelvic irradiation with or without brachytherapy, should be evaluated to determine whether new radiotherapy as external irradiation or brachytherapy with or without local tumor resection in curative intention is possible.	
	Strong Consensus	

9.9	Consensus-based recommendation	checked 2022
EC	Local late effects of radiotherapy shall be treated according to the S3 Guideline "Supportive therapy in oncology patients" [669]. * * See also Chapter 8.1.4 "Supportive therapy".	
	Strong Consensus	

Background

Patients with isolated vaginal stump recurrence after EC without adjuvant radiotherapeutic pretreatment or at least without adjuvant percutaneous radiotherapy in the history can be treated by radiotherapy and/or by surgical tumor resection.

Randomized comparative studies on the superiority of either treatment option are not available. Provided that radiotherapy has not been administered previously in the adjuvant setting, radiotherapy may achieve durable remission.

In the PORTEC-1 trial, 32 of the previously non-radiated patients developed isolated vaginal stump recurrence [670]. Of these, 30 patients were treated with curative intent, and of these 24 were treated with radiotherapy alone, two with surgery alone, three with surgery and radiotherapy and one with radiotherapy and endocrine therapy. Details of radiotherapy (dose of external pelvic radiation, combination with brachytherapy) were not provided. The overall rate of complete remission after salvage radiotherapy and/or salvage tumor resection was 87% (26/30). The 5-year survival rate in this group of patients treated adjuvantly without radiation and for vaginal recurrence with curative intent was 65%.

In 2014, Vargo et al. [671] retrospectively studied an adjuvantly nonirradiated cohort with isolated vaginal stump recurrence treated with an external pelvic irradiation (median dose 45 Gy in IMRT technique) and image-guided brachytherapy (median 24 Gy in 5 fractions) approach. After a follow-up of 3 years, local control was 95% and recurrence-free survival was 68%. Hardarson et al. [672] studied a collective of 31 radiation-naive patients with isolated vaginal recurrence. In 26 patients who received radiotherapy, the 2-year progression rate was 40% versus 0% in 5 patients treated by tumor resection. Jereczek-Fossa et al. [673] put the 3-year survival rate of 73 radiation-naive patients with vaginal stump recurrence after salvage radiotherapy (predominantly combined brachytherapy and teletherapy) at 62% for recurrences confined to the vaginal epithelium and 53% for recurrences with subvaginal infiltration.

Ng et al. [674] report complete remission in 6/6 patients treated with re-radiation therapy (external only, brachytherapy only or combination) with or without tumor resection for isolated vaginal stump recurrence after adjuvant brachytherapy alone as part of primary therapy. Thus, according to the data of the aforementioned case series, irradiation of vaginal recurrence appears to be the first-line therapy, unless percutaneous radiotherapy has been performed previously. However, due to the retrospective nature of the studies and the small number of subjects, the evidence base is very low.

The combination of high-dose brachytherapy with teletherapy (mean EQD2 dose of 68.3 Gray) achieved a 5-year survival rate of 77% and a cancer-specific 5-year survival rate of 83% in 30 patients with isolated vaginal EC recurrence without prior adjuvant radiotherapy [675].

9.3 Surgical therapy of recurrence

9.10	Consensus-based recommendation	checked 2022
EC	Provided that complete resection of the recurrent tumor appears achievable and cross-sectional imaging has shown no evidence of distant metastasis, surgical therapy for endometrial cancer recurrence can be performed.	
	Strong Consensus	

9.11	Consensus-based statement	checked 2022
EC	Exenteration has not been shown to improve duration fof survival, survival rate or progression-free survival in women with recurrence after endometrial cancer compared with other therapies or best supportive care.	
	Consensus	

9.12	Consensus-based recommendation	checked 2022
EC	Exenteration may be considered in individual cases in women with recurrence after endometrial cancer.	
	Strong Consensus	

Background

Surgical therapy is also available for the treatment of EC recurrence, but this has never been investigated in prospective studies. In a 2010 retrospective study of 14 cohorts with advanced or recurrent EC (n = 672), Barlin et al. [574] demonstrated that, on univariate analysis, progression-free survival and overall survival are significantly improved when surgery achieves complete removal of the recurrent tumor. Comparing the cohorts studied, each 10% increase in recurrences operated on macroscopically free of tumor resulted in a 9.3-month improvement in overall survival (p = 0.04) [574].

The safety and efficacy of exenteration for recurrence after EC is poorly established. A 2014 systematic literature review by the Cochrane Collaboration did not identify a single controlled trial assessing the safety and effectiveness of exenteration in women with recurrence after gynecologic malignancies [676].

In retrospective case series, high success rates after exenteration were found in selected patients. For example, Andikyan et al. [677] reported a 100% rate of complete cytoreductions after anterior exenteration with complete colpectomy [677] in 11 patients from Memorial Sloan-Kettering Cancer Center with tumor persistence or recurrence after gynecologic malignancies (3 of whom had EC). However, in this

case series, the median tumor size was only 0.9 cm, suggesting a highly selected patient population.

Chiantera et al. [678] reported on 21 gynecologic patients treated with exenteration in a retrospective cohort study, reporting a perioperative mortality rate of 5% and a serious complication rate of 43% [678]. In another study of a larger collective of 230 patients with various locally advanced or recurrent gynecologic carcinomas, perioperative mortality after exenteration was 3% and the rate of serious complications was 21% [679] (Note: the aforementioned study examined only endometrial carcinomas; the latter examined various malignancies). In the subgroup of 28 patients with endometrial carcinomas operated on by exenteration, the 5-year survival was 40%, which increased to 53% if macroscopic complete tumor resection was achieved by surgery.

Brain metastases of EC are rare events with an incidence of < 1% of all recurrences. Two case series and a meta-analysis have recently been published [680], [681]. In the meta-analysis by Beucler, 87 cases were retrospectively studied. Median overall survival was significantly longer after combined surgical and radiotherapeutic treatment, 15 months, compared with radiotherapeutic or surgical treatment alone (5.2 and 4.8 months, respectively). Prognostic favorable factors were the presence of singular brain metastases and extracranially stable EC disease.

9.4 Endocrine therapy in recurrence

9.13	Consensus-based statement	checked 2022
EC	There is no evidence that endocrine therapy improves duration of survival or survival rate or progression-free survival in women with recurrence after endometrial cancer compared with other therapies or best supportive care.	
	Strong Consensus	

9.14	Evidence-based recommendation	modified 2022
GoR **0**	Endocrine therapy with MPA (200-250 mg/d) or MGA (160 mg/d) or tamoxifen (20 mg/d or 40 mg/d) or a combination of tamoxifen and MPA/MGA can be given to women with recurrence after endometrial cancer.	
LoE **3**	[682], [683], [684], [38], [685]	
	Strong Consensus	

9.15	Evidence-based statement	modified 2022
LoE **3**	In women with recurrence after endometrial cancer, endocrine therapy with MPA or tamoxifen results in higher response rates when progesterone receptor expression or estrogen receptor expression or well to-moderate tumor differentiation (G1/G2) is detectable.	
	[682], [684], [38], [686]	
	Strong Consensus	

Background

A commonly used therapy in women with EC recurrence and reduced general health or advanced age is endocrine therapy with progestogens (e.g., medroxyprogesterone acetate [MPA], megestrol acetate [MGA]) or tamoxifen. However, the efficacy of endocrine therapy for recurrence after EC versus chemotherapy or “Best Supportive Care” has not been established by controlled trials.

A 2010 systematic literature review by the Cochrane Collaboration identified 6 randomized trials assessing the safety and effectiveness of endocrine therapy in women with primary advanced EC or recurrence after EC [687]. None of the studies reviewed compared endocrine therapy with systemic chemotherapy or “Best Supportive Care”. High-dose MPA (1000 mg/d) was surprisingly associated with a significantly increased risk of mortality and a shortened progression-free interval compared with lower-dose MPA (200 mg/d). Hormone replacement therapy in addition to chemotherapy or radiotherapy provided no benefit. Similarly, a combination of tamoxifen and megestrol acetate resulted in no benefit over megestrol acetate alone.

A recent review reported response rates for tamoxifen ranging from 10% to 53%, and for combination therapy with tamoxifen and a progestin ranging from 19% to 58% [38]. The authors note that response rates can be increased by selecting patients with well- or moderately-differentiated endometrioid adenocarcinomas with progesterone and/or estrogen receptor expression.

In a systematic review with a meta-analysis of 39 retrospective studies of endocrine therapy for EC, Ethier et al. described a response rate (ORR) of recurrent EC to progestins and tamoxifen or to the combination thereof of 21% in first-line treatment. Aromatase inhibitors achieved an ORR of 8%. Response was significantly higher in EC with positive hormone receptors and in low-gradecarcinomas. A limitation of the meta-analysis is the lack of standardization of hormone receptor determination. Jerzak et al. refer to different response rates of EC to endocrine therapy depending on different isoforms of hormone receptors [683].

Since the biological characteristics of the tumor may change during progression, reassessment of receptors and grading on recurrent tissue seems reasonable.

Endocrine therapy is an alternative to chemotherapy worth considering in elderly and multimorbid EC patients because of the few side effects. Therefore, the decision to

perform endocrine therapy can be made considering individual decision criteria and with reference to the good tolerability.

Similar to hormone receptor-positive breast carcinoma, targeted therapies to inhibit the PI3K/AKT/mTOR pathway and cyclin-dependent kinases have been investigated in advanced EC [688].

9.5 Chemotherapy for recurrence

9.16	Evidence-based recommendation	modified 2022
GoR **0**	Chemotherapy can be given to women with locally non-treatable endometrial cancer recurrence or distant metastasis.	
LoE **1**	[214], [689]	
	Strong Consensus	

9.17	Evidence-based recommendation	modified 2022
GoR **A**	The superiority of a particular chemotherapy regimen in women with recurrence after endometrial carcinoma has not been established. The carboplatin/paclitaxel and doxorubicin/cisplatin/paclitaxel combinations have been shown to be equally effective agents for chemotherapeutic therapy of advanced or recurrent endometrial carcinoma. Because of better tolerability, carboplatin (AUC 6) shall be used with paclitaxel (175 mg/m2).	
LoE **2**	[689], [633]	
	Strong Consensus	

Background

The safety and efficacy of systemic chemotherapy for recurrence after EC, in contrast to surgical therapy and hormone replacement therapy, has been investigated in a large number of randomized trials. However, there are no studies comparing chemotherapy with best supportive care, endocrine treatment or other non-chemotherapy treatment interventions.

A 2012 systematic literature review by the Cochrane Collaboration identified 14 randomized trials assessing the safety and effectiveness of systemic chemotherapy in women with primary advanced EC or recurrence after EC [690]. Eight randomized trials including 1,519 patients compared combination chemotherapies (doublet and triplet combinations) with less intensive chemotherapy regimens. In a meta-analysis

of these eight trials, more intensive chemotherapy significantly increased overall survival and duration of progression-free survival. Specifically, more intensive chemotherapy reduced the relative risk of mortality by 14%. However, the difference in median survival was only 1.5 months in favor of combination chemotherapies. More intensive chemotherapy regimens also resulted in significantly higher toxicity, especially myelosuppression and gastrointestinal side effects.

The other randomized trials in this meta-analysis compared different chemotherapy doublets or different single-substance regimens. No differences were seen, so an optimal chemotherapy agent or chemotherapy combination cannot be recommended. Active agents are doxorubicin, cisplatin, carboplatin, cyclophosphamide, paclitaxel, docetaxel, methotrexate, vinblastine and ifosfamide.

In recent years, the combination of carboplatin and paclitaxel has been established in practice as a relatively well-tolerated and safe therapy.

A prospective randomized phase III trial of 1381 patients with primary advanced or recurrent EC compared the two regimens carboplatin (AUC 6) and paclitaxel (175 mg/m2) q1, d21 x 7 and doxorubicin (45 mg/m2; d1), cisplatin (50 mg/m2; d1), paclitaxel (160 mg/m2; d2) + granulocyte colony-stimulating factor (GCSF) [633]. Non-inferiority in terms of overall survival and progression-free survival and better tolerability for the carboplatin/paclitaxel regimen were shown.

In a retrospective analysis of 216 patients in the SGSG012/GOTIC004/INTERGROUP trial, Nagao et al. [691] reported that the sequence 1) platinum/taxane palliative after platinum/taxane adjuvant was more effective than the sequence 2) platinum/taxane palliative after anthracycline/platinum adjuvant or the sequence 3) anthracycline/platinum palliative after platinum/taxane adjuvant. Progression-free interval and overall survival were significantly longer after sequence 1) treatment at 10 and 48 months than after sequence 2) at 9 and 23 months and 3 and 12 months after sequence 3), respectively [691].

9.6 Immunotherapy for recurrence of EC

9.18	Evidence-based recommendation	new 2022
GoR **0**	In patients with locally advanced or recurrent serous endometrial cancer with her2/neu overexpression, systemic chemotherapy with carboplatin (AUC 5) and paclitaxel (175 mg/m2) combined with trastuzumab (8 mg/kg as initial dose, followed by 6 mg/kg as maintenance therapy) can be given.	
LoE **2**	[292]	
	Strong Consensus	

9.19	Evidence-based recommendation	new 2022
GoR **B**	Patients with recurrent or primary advanced endometrial cancer with microsatellite-stable/mismatch-repair functional tumor tissue and progression after at least one line of chemotherapy should receive combined immune and multikinase inhibitor therapy with pembrolizumab (200 mg i.v. d1, q21 or 400 mg i.v. d1, q42) and lenvatinib (20 mg p.o. 1 x daily). The high toxicity should be noted.	
LoE **2**	[692], [693]	
	Strong Consensus	

9.20	Evidence-based recommendation	new 2022
GoR **0**	In patients with recurrent or primary advanced endometrial cancer with microsatellite unstable/mismatch repair deficient tumor tissue (MSI-H or dMMR), immunotherapy with dostarlimab (4 cycles 500mg i.v. d1, q3w followed by 1000mg i.v. d1, q6w) or with pembrolizumab (200 mg i.v. d1, q21 or 400 mg i.v. d1, q42) can be performed after preceding platinum-based therapy.	
LoE **3**	[694], [695], [696], [362]	
	Strong Consensus	

Background

Approximately 30% of all serous EC overexpress her2/neu and thus exhibit an "actionable target" for targeted therapy with trastuzumab. In a randomized phase II trial of 61 subjects with serous EC (FIGO stage III/IV or recurrence) and her2/neu overexpression, therapy with trastuzumab during and after carboplatin/paclitaxel significantly improved progression-free survival (8.0 months vs. 12.9 months) and overall survival (24.4 months vs. 29.6 months) [292]. Subjects with FIGO stage III/IV benefited in terms of progression-free survival and overall survival, while subjects with recurrence benefited only in terms of progression-free survival.

EC, and particularly variants with mismatch repair deficiency (dMMR) and/or microsatellite instability (MSI-H), are "mutation-prone" tumors with increased expression of antigens, making them a target for immunotherapeutic approaches in general and immune checkpoint inhibitors in particular [694]. Approximately 13% to 30% of EC recurrences show mismatch repair deficiency (dMMR) and/or microsatellite instability [362].

In the KEYNOTE-158 trial of 49 patients with EC recurrence with dMMR or MSI-H, pembrolizumab monotherapy achieved a response rate of 57% and a complete response rate of 16% (8/49 patients) [695]. 3/49 patients showed grade 4 toxicity (Guillain-Barré syndrome, liver dysfunction, neutropenia). In the Garnet trial, another non-randomized phase 1 study with a PD-1 directed antibody, 71 patients were treated with dMMR/MSI-H EC. In the post-platinum chemotherapy condition, dostarlimab was given as intravenous monotherapy at 500 mg i.v. d1, q21 for 4 cycles, followed by 1000mg i.v. q42. In a preliminary analysis of efficacy and toxicity data, a response rate of 42% and complete remission of 13% were found after a median follow-up of 11.2 months [696]. The authors highlighted long-lasting efficacy in "responders" and acceptable toxicity with only 1.9% treatment discontinuations due to treatment-related serious adverse events. Another phase 2 trial evaluated the PD-L1 directed antibody avelumab in EC relapse and found virtually no clinical effect in tumors without microsatellite instability. Among the 15 cases with dMMR/MSI-H, 3 partial remissions and one complete remission were observed [697].

However, since the majority of EC recurrences do not have microsatellite instability and monotherapy with an immune checkpoint inhibitor has proven to be ineffective in these, new combinations are currently being tested. Combination therapy of pembrolizumab and lenvatinib, an oral multikinase inhibitor, was investigated in the KEYNOTE-146 trial [693]. In 94 patients with MMR-proficient (i.e. non-dMMR) EC relapse or primary advanced EC, combination therapy achieved a response rate of 36%. However, grade 3-/4 toxicities were observed in 69% of cases, and 2 deaths were classified as treatment-related.

The acceptable discontinuation rate of 17.7% could be achieved only by a high rate of dose reductions.

These results could be confirmed in the randomized phase III study KEYNOTE-775. Here, combination therapy of pembrolizumab and lenvatinib was evaluated versus investigator's choice of chemotherapy (doxorubicin or paclitaxel). Dual primary endpoints were defined as overall survival (OS) and progression-free survival (PFS).

For the combination therapy of pembrolizumab and lenvatinib, median overall survival was shown to be prolonged compared with chemotherapy in both the pMMR population (N=697) and the overall population (pMMR and dMMR populations,

N=827) [pMMR population: 17.4 vs. 12.0 months (HR=0.68; P< 0.001); overall population: 18.3 vs. 11.4 months (HR=0.62; P< 0.001)].

Median PFS also showed an advantage for combination therapy in both the pMMR [6.6 vs. 3.8 months (HR=0.60; P< 0.001)] and overall populations [7.2 vs. 3.8 months (HR = 0.56; P< 0.001)].

The safety profile of combination therapy was consistent with the known profile from prior studies [692].

Thus, immunotherapy has expanded the treatment spectrum of recurrent EC, for which there was no standard of second-line treatment until recently. Phase III data are available on combination therapy of pembrolizumab with lenvatinib (KEYNOTE-775). Additional phase III data on pembrolizumab, lenvatinib, dostarlimab and atezolizumab (LEAP-001, NRG-GY018, RUBY, AtTEND) are expected [692].

The use of trastuzumab and avelumab in women with EC recurrence is an off-label use. This must be taken into account in education and therapy implementation (case-by-case review by the medical service). Pembrolizumab, dostarlimab (each as monotherapy) and the combination of pembrolizumab with lenvatinib have been approved by the EMA.

For palliative chemotherapy of carcinosarcoma of the endometrium, see Chapter 8.

9.7 Post-actinic changes in the irradiation field

9.7.1 Vaginal atrophy

9.21	Evidence-based recommendation	checked 2022
GoR **A**	Symptoms of vaginal atrophy in patients after therapy for endometrial cancer shall be treated primarily with inert lubricating gels or creams.	
LoE **3**	[698]	
	Strong Consensus	

Background

Percutaneous radiotherapy of the lesser pelvis and brachytherapy in the treatment of EC can lead to acute (mucositis, ulceration, necrosis formation, cystitis, proctitis) and chronic post-actinic changes in the radiation field (atrophic vaginitis, telangiectasia, vaginal stenosis, shortening/obliteration of the vagina, fistula formation, urethral stricture) [699]. This can lead to significant dysfunction (vaginal dryness, dyspareunia, post-coital bleeding, urge and stress urinary incontinence), and thus impaired sexuality and quality of life. Therapeutic options include antiseptic vaginal irrigation, inert lubricating gels and creams, locally and systemically administered estrogens, vaginal dilators, hyperbaric oxygen treatments and surgical measures.

Because of inconclusive data in this regard, an increase in the risk of recurrence by local estrogen application after treated endometrial carcinoma cannot be excluded [700]; [701]; [702]; [703]. Therefore, for first-line treatment of symptoms of atrophic vaginitis, non-estrogen-containing lubricating gels (water-, glycerin-, silicone- or hyaluronic acid-based) and/or moisturizers are recommended [704]. PH-stabilized preparations with a pH of 4 to 4.5 (lactic acid) have proven particularly effective in treating atrophic vaginitis in breast cancer patients [705].

9.7.2 Local estrogen treatment

9.22	Consensus-based recommendation	checked 2022
EC	Local estrogen treatment after primary therapy for endometrial cancer may be considered, after unsatisfactory treatment with inert lubricating gels or creams.	
	Consensus	

Background

The beneficial effect of local estrogens on contact bleeding and dyspareunia after radiotherapy of the vagina was shown as early as 1971 by Pitkin et al. [706] in a study involving patients after cervical carcinoma. In a meta-analysis, the rehabilitation of sexual function after radiotherapy of the lesser pelvis by local and systemic estrogen application could be confirmed [707]. In contrast, Hintz et al. [708], demonstrated that locally administered estrogens can be reabsorbed by the irradiated vaginal skin and thus become systemically effective. In this context, transvaginal absorption of estrogens seems to occur much more slowly after radiotherapy [709].

In various retrospective cohort studies and case-control studies, an increased recurrence rate in EC of stages I and II could neither be demonstrated for the local (vaginal) use of estrogens [703] nor for systemic hormone replacement therapy (HRT) (compilation of studies at [710]; [711]; [702]. Nevertheless, the overall data situation appears to be too weak to pronounce a harmlessness with regard to the oncological risk for local and systemic hormone application. The authors of the Cochrane analysis on systemic HRT after EC recommended an individualized approach taking into account the patient's symptoms/preferences. This was due to insufficient evidence regarding the possible benefits or potential risks of estrogen treatment after primary therapy of EC in FIGO stage I. No information was found in the literature regarding the impact of HRT in patients after treatment of higher tumor stages of EC [712].

In patients after therapy of an EC with vaginal complaints caused by estrogen deficiency or postactinic complaints, the possibly increased risk of recurrence should be weighed against the advantages of hormone application before application of local estrogens and discussed with the patient in the sense of an “informed consent”. Legally sound documentation is recommended (see also S3 Guideline “Peri- and Postmenopause - Diagnostics and Interventions”, 01/2020, DGGG, OEGG, SGGG, AWMF register number 015/062, [German Society of Gynecology and Obstetrics, AWMF et al. 2009].). The NCCN panel also advises caution with HRT after primary therapy in patients with EC, recommending restriction to early stages with low risk of recurrence and treatment initiation only 6 to 12 months after the end of primary therapy [228].

9.7.3 Treatment and prophylaxis of vaginal stenosis

9.23	Consensus-based recommendation	checked 2022
EC	Vaginal dilators can be used for the treatment and prophylaxis of vaginal stenosis in patients with endometrial cancer after the end of radiotherapy and resolution of acute radiation sequelae.	
	Strong Consensus	

Background

Due to acute and chronic radiation sequelae (see above) in the area of the vagina and surrounding organs, bleeding after sexual intercourse, dyspareunia and limited clinical assessability of local findings at tumor follow-up due to synechiae of the vaginal wall may occur.

Postactinic vaginal discomfort occurred in 35% after brachytherapy and in 17% after percutaneous radiotherapy of the lesser pelvis in the PORTEC-2 study [713]. The risk for the occurrence of clinically relevant late toxicity (vaginal stenosis) depends on radiooncological factors (radiation dose, dose fractionation, irradiated volume) and on tumor-specific (tumor location, tumor volume) and patient-specific circumstances (age, nicotine abuse, concomitantly administered chemotherapy). In a literature review by Morris L. et al. the incidence of vaginal stenosis after radiation varied from 1.25 to 88% [699].

To prevent this complication, vaginal dilators are often used and recommended along with lubricant 2 to 4 weeks after radiotherapy as expert consensus [714]; [715]. However, there is limited evidence for the benefit of vaginal dilators. For example, in the Cochrane analysis published in 2014 on the treatment of women with vaginal dilators after pelvic radiotherapy, Miles T. et al. found no study that met the evaluability criteria for a meta-analysis on the topic [714]. Even in more recent work, the use of dilators after radiotherapy did not prevent functionally limiting vaginal stenosis in 2/3 of patients [716]; [717]; [718]; [719]. To objectify the efficacy of dilators, vaginal length and width, among other parameters, were measured and documented during follow-up. From 2 recent prospective studies, it is clear that lack of compliance for regular use of dilators is the limiting factor for the effectiveness of this preventive and therapeutic measure [718]; [719].

Laser therapy is a possible therapeutic option for vulvovaginal atrophy in postmenopause. It is postulated that laser stimulates increased synthesis of collagen and extracellular matrix as well as fibroblast proliferation, thereby increasing vaginal elasticity and hydration. Currently, laser therapy is being studied for the treatment of post-actinic change after radiotherapy for endometrial and cervical carcinoma [720]. There are no results of prospective randomized studies on this therapeutic approach.

9.8 Palliative radiotherapy

9.24	Consensus-based recommendation	checked 2022
EC	As a palliative measure for vaginal bleeding or pain from vaginal stump or pelvic wall recurrence, low total dose radiotherapy can be used even after previous radiotherapy.	
	Strong Consensus	

Background

The recommendations of the S3 Guideline “Supportive Therapy in Oncological Patients” [625] should be taken into account when performing medicinal and/or radiotherapeutic measures.

In the presence of an incurable disease situation as well as current and expected physical and psychosocial stress, the recommendations of the S3 Guideline “Palliative care for patients with a non-curable cancer” [721] as well as recommendations 11.12.1, 11.12.2, 11.12.3 should be considered.

10 Hereditary endometrial carcinomas

10.1 Introduction

Up to 5% of all endometrial carcinomas are based on a monogenic hereditary disposition (hereditary or hereditary endometrial carcinomas) and thus occur in the context of a hereditary tumor syndrome (ETS). Clinically or molecularly confirmed carriers of certain ETS and their related family members have a significantly increased lifetime risk of developing endometrial cancer.

The vast majority of hereditary endometrial carcinomas occur in the setting of Lynch syndrome (LS)/hereditary non-polyposis colorectal cancer (HNPCC). Cowden syndrome (CS) or PTEN hamartoma tumor syndrome (PHTS) is also known to have a significantly increased risk of endometrial cancer. Carriers of these ETS have a 6–20-fold increased risk of endometrial cancer in contrast to the general population (see Table 14). In addition, there are several other ETS that are very rare or for which the level of risk for endometrial carcinoma has not yet been conclusively determined. These include, in particular, MUTYH-associated polyposis (MAP), polymerase proofreading-associated polyposis (PPAP) and NTHL1-associated tumor syndrome.

Hereditary tumor syndromes are caused by mutations, particularly in tumor suppressor genes and especially in DNA repair genes. The mutations are present in all body cells (germline mutations, constitutional mutations), in contrast to sporadic tumors in which the relevant mutations occur only in the tumor itself (somatic mutations).

Most hereditary tumor syndromes are inherited in an autosomal dominant manner. As a result, first-degree relatives of affected persons (persons at risk) of hereditary endometrial carcinoma have an up to 50% risk of having inherited the genetic disposition and thus the increased tumor risk. Therefore, families often contain numerous at-risk individuals.

10.2 Hereditary tumor syndromes with increased risk of endometrial cancer

10.1	Evidence-based statement	checked 2022
LoE **3**	The hereditary tumor syndromes (ETS) with a confirmed, significantly increased risk of endometrial cancer are Lynch syndrome (hereditary colorectal cancer without polyposis, HNPCC) and Cowden syndrome (CS) or PTEN hamartoma tumor syndrome (PHTS). Congenital carriers of these ETS are also at increased risk for other syndrome-specific intestinal and extraintestinal benign and malignant tumors.	
	[722], [723], [724], [725], [726], [727], [728], [729], [730], [731]	
	Strong Consensus	

Background

Currently, at least two ETS (LS, CS) are thought to have an increased lifetime risk of endometrial cancer [732], [733], [734]. Details regarding tumor risks, causative genes and mutation detection rates are summarized in the table below.

Table 14: Tumor risks and mutation detection rates

	Lynch syndrome (LS)	Cowden syndrome (CS)
Mode of inheritance	Autosomal-dominant	Autosomal dominant
Causative genes	MLH1, MSH2, MSH6, PMS2, EPCAM	PTEN
Frequency General population	1:279-370 [735], [736]	1:200,000? [737]
Frequency in unselected endometrial cancer cohorts	Approximately 3% [738]	< 0.5%
Frequency in endometrial cancer < 50years	Approximately 10%	
Endometrial carcinoma lower uterine segment	14–30% [730]	
Mutation spectrum of LS-associated endometrial carcinoma	approx. 15, approx. 25%, approx. 50%, approx. 10% for MLH1, MSH2, MSH6, PMS2 [739]	
Lifetime risk of endometrial cancer up to 70 years of age (General population about 2.6%)	By 75 LY. MLH1 about 40%, MSH2 about 50%, MSH6 about 40%, PMS2 about 15%. [740],	By 70th YOL 20–30% [741], [742]
Mean age of onset of LS/CS-associated endometrial cancer (years)	Total: 50 years MLH1: 44 (29–54), MSH2: 50 (36–66) MSH6: 55 (26–69), PMS2: 57 (44–69) [743], [726], [386], [744],	48–53 [745]
Metachronous carcinoma after endometrial carcinoma diagnosis	10 years: 25%, 15 years: 50%, 20 years: > 50% [726], [724], [746]	
Endometrioid type	approx. 60–85%	approx. 85%
Other lead tumors/ tumor spectrum	Colorectal carcinoma, duodenal carcinoma, gastric carcinoma, ovarian carcinoma, brain tumors, urothelial carcinomas	Thyroid carcinoma, breast cancer, kidney cancer, brain tumors, skin tumors

Lynch syndrome (LS) caused by germline mutations in mismatch repair (MMR) genes is one of the most common hereditary tumor syndromes (ETS) [747], [748], [749]. In unselected case series of endometrial carcinoma, the proportion of LS-associated endometrial carcinoma is 2–4% [750], [751]; in women with endometrial carcinoma < 50 years the value is 9–10% [746], [752], [743], [380]. The terms HNPCC and LS are mostly used synonymously in this country. In the international literature, however, the preference is to refer to molecularly confirmed HNPCC as LS and to cases with fulfilled clinical criteria and typical changes in tumor tissue without detectable germline mutation as HNPCC.

Throughout this Guideline, the term LS is used.

Mutation carriers have, in addition to a very high lifetime risk of endometrial carcinoma or colorectal carcinoma [753], a high risk of metachronous carcinoma after initial endometrial carcinoma diagnosis [754], [755], [756]. Endometrial carcinoma occurs about as frequently or more frequently than colorectal carcinoma in LS carriers: in 50–70% even before colorectal carcinoma ("sentinel" carcinoma) [757], [758].

In Cowden syndrome (CS), only a few case series with limited number of patients have been published due to the low prevalence regarding tumor risks. A bias in the data regarding an overestimation as well as an underestimation of the risks is to be suspected (recruitment bias). A more precise estimate of cumulative and age-specific risks is still pending.

Because of the sometimes broad spectrum of tumors, patients and those at risk for these and some other very rare ETS require multidisciplinary care and syndrome-specific screening programs [365], [759], [760].

There are no data to suggest that manifest (symptomatic) endometrial cancer should be diagnosed in women with genetic predisposition using a different algorithm or procedures than in women without genetic predisposition [761], [762], [204], [763].

10.3 Risk assessment

10.2	Consensus-based statement	checked 2022
EC	An important tool for detecting a genetically determined increased risk of endometrial carcinoma is the personal and family history taken by a physician, taking into account specific clinical criteria (in Lynch syndrome: Amsterdam I/II, revised Bethesda criteria).	
	Strong Consensus	

Background

The risk assessment is usually based on the medical history and/or the molecular-pathological or histopathological tumor findings. In this context, the non-organ-centered recording of family history is relevant, since most ETS with an increased risk of endometrial carcinoma have a broad tumor spectrum.

The suspected clinical diagnosis of ETS is made on the basis of certain syndrome-specific clinical criteria (e.g. GeneReviews [764]). Specific clinical criteria have been defined for LS, the Amsterdam I/II criteria (AK) and the revised Bethesda criteria (BK) [765], [766], [767]; see Appendix Chapter 17.

Detection of at-risk individuals can be increased through the use of standardized questionnaires, for example as part of the check-up examination offered at 35 years of age and regular presentations for gynecologic cancer screening. A corresponding questionnaire or checklist has been developed for the certified gynecological cancer centers of the DKG (https://www.krebsgesellschaft.de/zertdokumente.html).

Alternatively, the presence of a HNPCC-typical molecular-pathological findings or histopathological findings is crucial: i.e. the failure of a DNA mismatch repair protein in the immunohistochemical expression analysis and/or the presence of a microsatellite instability (MSI) by microsatellite analysis as a functional correlate of an impaired DNA mismatch repair, if necessary, followed by examination of MLH1 promoter methylation (see below for diagnostic algorithm).

10.4 Procedure in case of suspected presence of a hereditary form of endometrial carcinoma

10.3	Consensus-based recommendation	modified 2022
EC	If a hereditary form of endometrial cancer is suspected, the patient should present to a certified gynecologic cancer center or a center for hereditary tumor diseases.	
	Strong Consensus	

Background

The diagnosis of ETS has significant consequences for patients and their families. Expertise regarding the specific features of each clinical picture (differential diagnosis, tumor spectrum, identification of at-risk individuals, predictive testing, specific therapy and screening) and multidisciplinary care exists particularly in centers that care for a larger number of patients and are familiar with the complex diagnostic algorithms and logistical requirements.

To improve the diagnostic and therapeutic situation, accompanying scientific research and therapy studies on sufficiently large patient collectives are important; these are often available only in specialized centers. Studies showed that the care and prognosis of families with ETS can be improved by linking them to specialized centers [768], [769], [770]. If there is suspicion of one of the above mentioned ETS, the patient and her first-degree relatives should therefore be offered presentation at a center for ETS [365].

10.5 Psychosocial counseling and support services

10.4	Consensus-based recommendation	modified 2022
EC	Already affected persons, carriers and not yet tested persons (risk persons) from families with a hereditary tumor syndrome should be informed about the possibility and benefit of psychosocial counseling and care.	
	Consensus	

Background

For the purpose of these recommendations, carriers are individuals with a confirmed pathogenic germline mutation in one of the causative genes. High-risk individuals are relatives of confirmed carriers until a familial mutation is excluded. In cases of clinically high suspicion of ETS, patients and their relatives should be considered at risk even if no causative germline mutation has been identified in the family to date.

The diagnosis of a manifest ETS, the knowledge of a significantly increased cancer risk or the definitive proof of the genetic carrier can be accompanied by a variety of psychosocial stress factors for the affected persons and their relatives. Corresponding investigations have been carried out, especially in case of LS [771], [772], [773], [774], [775], [776], [777], [778], [779]. Predictive testing of minors is additionally accompanied by specific challenges such as lack of own decision-making capacity and limited understanding of the meaning and consequences of testing [780], [781], [782].

Complementary to clinical and human genetic care, psychosocial counseling can support patients and at-risk individuals in the process of decision-making for or against predictive genetic testing and can be helpful in processing test results [365] (see also Chapter 11).

Persons who already have the disease, proven carriers of the disease and persons at risk should therefore be made aware of the offer of psychosocial counseling by the physician treating them.

10.6 Clarification of the suspected clinical diagnosis

10.5	Evidence-based recommendation	checked 2022
GoR **A**	If at least one revised Bethesda criterion is fulfilled, further (molecular) pathological examination shall be performed on the tumor tissue with regard to Lynch syndrome-typical changes. This includes the examination of the immunohistochemical expression of the DNA mismatch repair proteins, microsatellite analysis and, if necessary, the examination of the methylation of the MLH1 promoter.	
LoE **3**	[723], [726], [727], [728], [386]	
	Strong Consensus	

10.6	Evidence-based recommendation	modified 2022
GoR **A**	If a suspicious finding is raised during routine testing for MMR deficiency (immunohistochemical examination of MMR genes or microsatellite analysis), information and, if necessary, counseling under the Genetic Diagnostics Act shall be offered regarding diagnostic genetic testing for Lynch syndrome.	
LoE **3**	[723], [726], [727], [728], [386], [783]	
	Strong Consensus	

10.7	Consensus-based recommendation	modified 2022
EC	In patients from families in which the Amsterdam criteria are fulfilled and whose tumor tissue does not show Lynch syndrome-typical abnormalities, Lynch syndrome is not excluded. Therefore, for assessment and, if necessary, further diagnostics, education and, if necessary, genetic counseling for diagnostic genetic testing should be offered in a center for familial tumor diseases with appropriate expertise.	
	Strong Consensus	

Background

An algorithm for further work-up of the suspected clinical diagnosis of LS is shown in the figure below. The first indications for a DNA-MMR defect are the immunohistochemical examination (IHC) of the MMR proteins MLH1, MSH2, MSH6 and

PMS2 in the tumor tissue. This should already have been performed as part of the routine histopathological findings or represents the first step in clarifying heritability in the screening procedure if the clinical criteria (AK or revised BK) are fulfilled. In case of an inconspicuous or unclear finding, a microsatellite analysis (MSA) in the tumor DNA should be performed in addition if a familial burden is present [784], [785], S3 Guideline "Colorectal Carcinoma", long version 1.1, 2014, AWMF register number: 021/007OL, http://leitlinienprogramm-onkologie.de/Kolorektales-Karzinom.62.0.html [365].

In the presence of clinical criteria and an abnormal finding in the tumor tissue examination, there is still clinical suspicion of LS, even if no germline mutation is subsequently detected.

IHC failure or high microsatellite instability (MSI-H) and thus evidence of LS can be detected in 23–35% of unselected endometrial carcinomas. For endometrial carcinomas with an MLH1 and PMS2 failure in the IHC, methylation analysis of the MLH1 promoter should also be performed, but not BRAF analysis, to identify non-hereditary endometrial carcinomas [786], [750], [751], [758], [743], [744], [787], [788], [789], [790]. In unselected endometrial carcinomas with abnormal IHC and/or MSA findings and excluded MLH1 promoter methylation (in MLH1/PMS2 failure), an MMR mutation (mutation detection rate, PPV) is found in 36–42% [751], [750], [758], [744], with an age cut-off of < 60 or < 70 years in 46–70%. Thus, the positive molecular pathological finding of tumor tissue has a high PPV for the detection of LS-associated endometrial carcinoma.

The initiation of germline diagnostics in an already diseased person (diagnostic genetic testing) is carried out after the patient has been informed by and has given his or her consent to the attending physician in accordance with the requirements of the German Genetic Diagnostics Act (GenDG). Every licensed physician is allowed to perform this clarification.

In rare cases, endometrial carcinoma may be caused by other sometimes very rare hereditary forms (see above), which are based on germline mutations of other genes (in particular POLE, POLD1, MUTYH, NTHL1) [791]. Due to the rarity and the limited data available, a targeted germline analysis should currently be reserved for an indication in specialized centers on the basis of phenotypic characteristics in the case of a conspicuous personal or family history.

The best screening strategy and target group for the identification of LS-associated endometrial carcinomas has been investigated in five cohort studies during the last years [750], [751], [758], [743], [749], [744], [792], each of which included a larger number (118–702) of unselected endometrial carcinomas (1,715 cases in total).

It was consistently shown that a substantial proportion of LS-associated endometrial carcinomas (62% and 64% in the two largest studies) were diagnosed after the age of 50. A significant proportion of LS-associated endometrial carcinomas (mean 37%) did not meet clinical criteria – especially in LS-associated endometrial carcinomas diagnosed after the age of 50 (46%–67%) – and up to half of the cases were identified in the age group 50–59 years.

The data thus underscore the known insensitivity of the screening strategy based solely on a conspicuous self and family history and/or early manifestation (< 50 years of age). Many authors have therefore long called for universal screening for LS-typical

abnormalities in all colorectal and endometrial carcinomas or in all cases below a certain age limit (< 60 years or < 70 years) [750], [751], [758], [744].

According to the largest study, the mutation detection rate (positive predictive value, PPV) of MSA/IHC screening to identify LS-associated endometrial carcinoma is 46% when mutation search is performed in all unselected endometrial carcinoma cases < 60 years with conspicuous IHC and inconspicuous methylation in case of MLH1/PMS2 failure. The authors conclude that this screening strategy has the highest PPV in terms of number of mutation carriers identified with the lowest number of diagnostic tests, making it the most cost-effective approach among the strategies studied [750]. Therefore, in case of abnormal findings, clarification should be offered according to the requirements of the Gene Diagnostics Act.

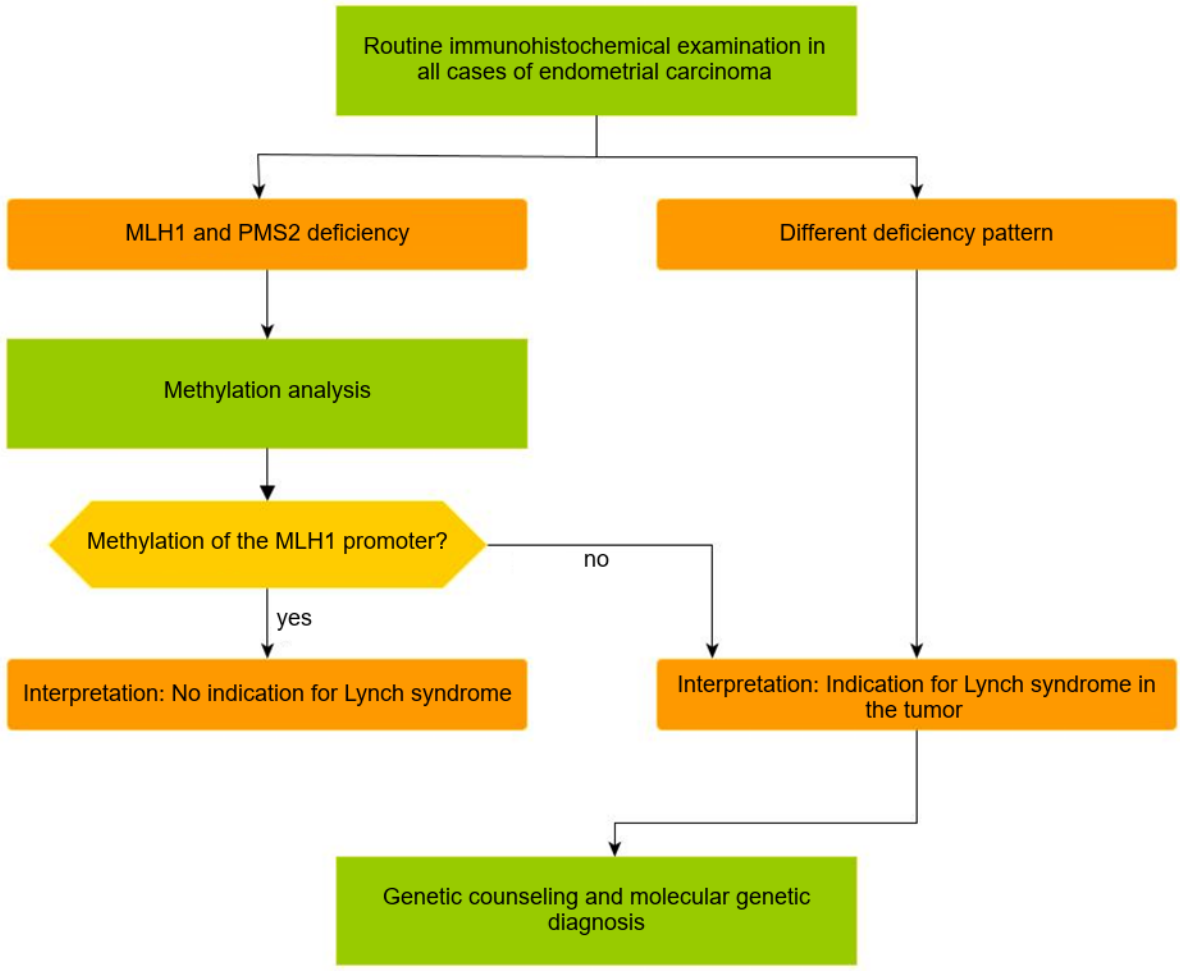


Figure 8: Procedure of MMR diagnostics in case of abnormal findings in the immunohistochemical or molecular-pathological examination

10.6.1 Search for germline mutations

10.8	Evidence-based recommendation	modified 2022
GoR **A**	If there is evidence of MMR deficiency and suspicion of Lynch syndrome based on abnormal immunohistochemistry or molecular pathology (failure of MMR proteins) or high microsatellite instability (MSI-H), the affected individual shall be offered education and, if appropriate, genetic counseling for germline mutation analysis in the likely affected MMR gene(s).	
LoE **3**	[723], [726], [728], [386]	
	Strong Consensus	

Background

The identification of a pathogenic germline mutation in a diseased patient (index patient of the family) serves to confirm the diagnosis and enables predictive genetic testing of family members (persons at risk). Genetic diagnostics should be performed in accordance with the Guidelines for the Diagnosis of Genetic Disposition to Cancer of the German Medical Association [793] and the Gene Diagnostics Act [780]. At the latest when a mutation is detected, the patient should be offered human genetic counseling by a specialist in human genetics or a specialist who is qualified for genetic counseling in his or her field.

Due to the low prevalence, a CS and some other ETS with an increased risk for endometrial cancer are very rarely found among unselected endometrial cancer cases (see HGT 8.7). Therefore, a targeted mutation search in the relevant genes should be performed only if there is a specific suspicion of one of these ETS in the personal and family history.

10.6.2 Procedure in case of missing or uncertain mutation detection

Background

Mutation detection is not always successful in the presence of a clinically established suspected diagnosis. This may be method-related or due to an inaccurate clinical diagnosis. Therefore, a suspected diagnosis cannot be excluded by a missing mutation detection [793].

In case of a clinically high-grade suspicion of ETS, the patients and their first-degree relatives are therefore to be considered at risk even in the absence of mutation detection. If a patient has molecularly confirmed ETS, the first-degree relatives are to be considered at risk until the familial mutation is excluded. In the case of autosomal recessive ETS, these are in particular the siblings of the index patient.

10.7 Procedure for individuals at risk for Lynch or Cowden syndrome

10.9	Consensus-based recommendation	modified 2022
EC	Once the causative mutation is known in the family, the patient shall be advised to inform family members of the increased risk and the options for genetic counseling and (predictive) genetic testing.	
	Strong Consensus	

10.10	Consensus-based statement	checked 2022
EC	Once the familial mutation has been ruled out in an at-risk individual, the general cancer screening measures apply.	
	Strong Consensus	

Background

Due to the mostly autosomal dominant mode of inheritance, first-degree relatives of affected persons have a 50% risk of having inherited the genetic disposition and thus also carrying the high tumor risk. Therefore, it is important to inform the family members who are considered as carriers due to the inheritance about this risk and the possibility of human genetic counseling and risk reduction through screening/early detection examinations (S3 Guideline “Colorectal carcinoma”, long version 1.1, 2014, AWMF register number: 021/007OL, http://leitlinienprogramm-onkologie.de/Kolorektales-Karzinom.62.0.html) [365], (S2k Guideline “Human genetic diagnostics and genetic counseling”, 2011 version, currently under revision, AWMF register number: 078/015, http://www.awmf.org/leitlinien/detail/ll/078-015.html) [794]. Since information can usually be conveyed to the patient's relatives only via the patient herself, it is important to inform her of the consequences of her findings for her relatives and the associated responsibility. This must be documented by the physician.

The genetic alteration identified in an index person should be evaluated according to the generally accepted standards for the classification of genetic findings [795]. A 5-class system is used, in which class 1-3 mutations have no clinical consequences. Class 3 findings, i.e. variants of unknown significance (VUS), are problematic as they currently cannot be classified with regard to their disease-causing relevance. Patients should be made aware that the significance of many unclear variants is likely to be clarified in the future by better data, and therefore re-consultation may be useful.

Predictive testing is usually possible only if an undoubtedly pathogenic germline mutation (familial mutation) has been detected in a family member who already has the disease (Class 4 or 5 mutation). According to the GenDG, predictive testing may be performed only after education and counseling by specialists in human genetics or other physicians who have qualified for genetic testing within the scope of their

specialty when acquiring their specialist, focus, or additional designation [Aretz 2006], S2k Guideline “Human genetic diagnostics and genetic counseling”, version 2011, currently under revision, AWMF register number: 078/015, [214298 et al. 2011] [794], [780].

If the causative mutation known in the family has been excluded in a person and there is no evidence of any other increase in risk for tumor disease, the general cancer screening/cancer early detection recommendations apply to this person, since an increased tumor risk is not to be assumed (S3 Guideline “Colorectal carcinoma”, long version 1.1, 2014, AWMF register number: 021/007OL, http://leitlinienprogramm-onkologie.de/Kolorektales-Karzinom.62.0.html) [365], [793].

10.8 Primary prevention of the risk group

10.11	Consensus-based statement	checked 2022
EC	A separate recommendation for primary prevention by dietary measures or chemoprevention compared to the general population cannot be given due to lack of data for the mentioned risk groups.	
	Strong Consensus	

Background

In general, the recommendations for primary prevention that apply to the general population (see Chapter 3 Statements 3.16 and 3.17) can also be adopted for members of the risk groups. A separate recommendation for primary prevention by dietary measures or chemoprevention compared to the normal population cannot be given due to lack of data.

In Lynch syndrome, a protective effect for the occurrence of colon carcinoma by taking acetylsalicylic acid (ASA) for several years has already been demonstrated in studies [796]. However, a study to determine the appropriate dose is currently ongoing. Long-term observations of patients currently provide evidence that the risk of other tumor entities (including endometrial carcinoma) may also be reduced by ASA use. At present, however, the data are not yet sufficient to formulate a corresponding recommendation.

10.9 Endometrial cancer screening in Lynch and Cowden syndrome patients

10.12	Evidence-based statement	checked 2022
LoE **4**	To date, no screening method for early detection of endometrial cancer has been shown to prolong life for Lynch syndrome and Cowden syndrome patients. Therefore, from the limited data, no recommendations can be made for or against specific screening for early detection of endometrial carcinoma in Lynch syndrome or Cowden syndrome patients.	
	[214], [797], [798], [154], [155]	
	Strong Consensus	

Background

Carriers of LS or CS have a significantly increased risk of endometrial cancer and develop the disease on average about 10 years earlier than patients with sporadic endometrial cancer (see Table 22). Approaches to early diagnosis of endometrial carcinoma are therefore being tested, particularly in LS patients – such as education about possible early symptoms and various screening strategies [799], [800].

Regarding the optimal screening method, a number of retrospective cohort studies have been conducted. These showed clear evidence that transvaginal ultrasound (TVU) is unsuitable as the sole screening examination for early detection of endometrial carcinoma in LS patients, especially pre- and perimenopausal [801], [802], [800]. In another study (175 LS patients, 759 person-years), using TVU and endometrial biopsy (EB), 4 of the 14 endometrial carcinomas diagnosed were found by TVU, 8 only by EB [803]. EB detected an additional 14 potentially premalignant endometrial hyperplasias.

The results of 3 prospective endometrial cancer screening studies vary; however, all studies have relatively small case numbers and short observation periods. In 58 LS patients, TVU and EB diagnosed 2 endometrial carcinomas detected by TVU [804]. In a study of 41 LS patients with annual TVU, outpatient hysteroscopy, and EB, half of the endometrial carcinomas or premalignant lesions were not detected by TVU, so the additional EB significantly increased sensitivity [805].

In a third study of 75 LS patients or persons at risk (300 person-years), 6 premalignant lesions and one endometrial carcinoma were found, all of which were diagnosed by TVU [806].

Thus, the value of endometrial cancer screening remains unclear, as improved survival under regular surveillance has not been demonstrated to date. Among other reasons, this is due to the already good prognosis (5-year survival rate 98% [807] and the need for long-term prospective data collection to demonstrate a survival benefit, the results of which are still pending. The fact that EB with the Pipelle method is still not very common in Germany and LS patients often opt for prophylactic hysterectomy also contributes to the poor data situation.

10.9.1 Syndrome-specific screening tests in patients or individuals at risk for Lynch or Cowden syndromes

10.13	Consensus-based recommendation	checked 2022
EC	Patients and persons at risk with Lynch syndrome or Cowden syndrome shall be recommended syndrome-specific screening examinations, especially colonoscopies, due to the broad tumor spectrum. Detailed guidance can be found in the relevant guidelines.	
	Strong Consensus	

Background

Regarding the complete screening recommendations, please refer to the corresponding guidelines: S3 Guideline “Colorectal Carcinoma”, long version 1.1, 2014, AWMF register number: 021/007OL, http://leitlinienprogramm-onkologie.de/Kolorektales-Karzinom.62.0.html [365], [759], [760].

10.10 Procedure for Lynch and Cowden syndrome carriers

10.14	Consensus-based recommendation	checked 2022
EC	Lynch syndrome and Cowden syndrome carriers shall be offered counseling on the advantages and disadvantages of prophylactic total hysterectomy after completion of family planning, and Lynch syndrome patients shall additionally be offered counseling on bilateral adnexal extirpation, if appropriate.	
	Strong Consensus	

Background

A retrospective study showed a significant decrease in endometrial cancer incidence in LS mutation carriers after prophylactic hysterectomy [808]. However, robust evidence from prospective studies on the benefits and harms of prophylactic hysterectomy is still lacking. Especially in case of an upcoming laparotomy or laparoscopy or abdominal surgery (e.g. colectomy or colon resection) due to other indications, a prophylactic hysterectomy should be discussed with the patient, as this may also avoid a later relaparotomy due to an endometrial carcinoma with corresponding risks. (S3 Guideline “Colorectal carcinoma”, long version 1.1, 2014, AWMF register number: 021/007OL, http://leitlinienprogramm-onkologie.de/Kolorektales-Karzinom.62.0.html [365], [208].

It is known from many studies of patients with hereditary breast and ovarian cancer that no effective early detection measures exist with regard to ovarian cancer. Thus, the only effective measure to improve survival is prophylactic adnexal extirpation. The risk of ovarian cancer is increased in LS, especially in the presence of an MSH2 / 15%-47%) or MLH1 (11%-38%) mutation. However, more favorable tumor stages are diagnosed: i.e., approximately 65% of tumors have a Figo I/II stage [809], [807].

The 5-year survival rate is 89% [807], [810], [Seppälä, T et al. 2017]. Also, the age of onset varies greatly depending on the gene affected, so no increased ovarian cancer incidence has been found in mutation carriers in the PMS2 gene [807], This is especially important to consider for family planning. Therefore, a general recommendation for prophylactic ovariectomy in LS cannot be given. Rather, the individual risk situation must be considered.

In order to enable individuals to make a non-directive decision for or against prophylactic surgery, or secondary prophylactic surgery in the case of tumor disease that has already occurred, it is important to provide information that enables such a decision or is a prerequisite for such a decision. This includes in particular the communication of age-dependent disease rates in a manageable period of time, the prognosis and treatment options, as well as, in the case of the presence of a tumor disease from the syndrome spectrum, the determination and communication of the competing risk caused by the initial disease and presentation of the evidence of prophylactic surgery including possible side effects.

11 Psycho-oncological aspects, patient education, palliative care, rehabilitation, physiotherapeutic treatment in the context of rehabilitation

11.1 Psycho-oncological aspects

This chapter was prepared following the already existing S3 Guidelines “Psycho-oncological diagnosis, counseling and treatment of adult cancer patients”, version 1.1, January 2014, AWMF register number: 032/051OL, http://www.leitlinienprogramm-onkologie.de/leitlinien/psychoonkologie/ [811] as well as “Diagnosis, therapy and follow-up of the patient with cervical carcinoma”, version 2.1, September 2021, AWMF register number: 032/033OL, http://www.leitlinienprogramm-onkologie.de/leitlinien/zervixkarzinom/) [219] created.

11.1	Consensus-based statement	checked 2022
EC	Patients with endometrial cancer and their families may face multiple physical, psychological, social and spiritual/religious stresses	
	Consensus	

Background
As a result of their tumor disease, patients with endometrial cancer and their families face a wide range of different physical, psychological, occupational, social and spiritual stresses that can impact all areas of their lives [812], [813], [814], [815], [816], [817]. As mortality decreases, the number of long-term survivors also increases, and they face the associated risk of increased chronic morbidity [818], [819] and possible limitations in their quality of life [818], [819], [820].

During and after treatment of endometrial cancer, physical complaints are predominantly the result of the therapies performed [821], [822], [823], [824]; in the foreground are: residual dysfunctions in the pelvis, such as urinary and fecal incontinence [821], pain [821], [825], vaginal dryness, pain during sexual intercourse (dyspareunia) [826], [827], but also menopausal complaints caused by the ovariectomy (and if necessary by anti-hormonal therapies, which, however, are used only in cases of far advanced endometrial carcinoma). Persistent postoperative pain leads to high subjective distress in the women affected by it, with a severe reduction in quality of life.

The frequently occurring psychological stress factors include emotional changes, limitations in previous role function, contact and interaction skills, problem solving and coping with the disease and the inability to mobilize social resources. Their effects show up primarily as impairments in everyday life, occupational and social contexts [828]. In the study on the four-week prevalence of psychological disorders

in different tumor diseases by Mehnert et al. [814], patients with gynecological tumors were in fifth place.

Across all tumor entities, a mean of 32.6% of all patients received a diagnosis of a comorbid mental disorder. Patients with gynecological tumors had a four-week prevalence of any mental disorder of 36%, which is slightly higher in direct comparison with other tumor diseases and significantly higher in comparison with the German general population (20%). Leading were adjustment disorders at approximately 13%, followed by anxiety disorders (ICD-10 F41.- [829]) at 12% and depressive disorders (ICD-10 F32.- [829]) at 7.5%. There is evidence that the presence of anxiety disorders or depression can lead to worsening of pain symptomatology. Improvements in psychological symptomatology, for example through (psycho)therapeutic interventions, may lead to improvements in subjectively perceived pain intensity [825]. A longitudinal study of patients with early-stage endometrial cancer demonstrated that the prevalence of anxiety or depression (HADS scores ≥ 11) around the time of surgery was approximately 16% [830]. Also in the longitudinal course the long-term survivors still showed elevated anxiety as well as depression scores compared to age-adjusted norm comparison group [831].

In some studies, the occurrence of psychological symptoms such as anxiety or depression proved to be independent of the stage of the disease, but dependent on the extent of therapy administered. With regard to the development of depression or anxiety disorders, an exclusively surgical therapy without additional irradiation showed positive results in the long-term follow-up [832], [833].

Although endometrial cancer is rare in women of childbearing age, fertility-preserving measures are becoming increasingly important in this group of patients, as more and more women are delaying their first pregnancy. In the future, therefore, there may also be an increase in the incidence of this condition in patients who have not yet completed family planning [813], [834]. However, not all patients with childbearing potential and endometrial cancer can be offered fertility-preserving measures [834]. Therefore, it is recommended that the issue of childbearing is addressed before starting treatment to allow patients and their partners to deal with their family planning in a timely and realistic manner.

In contrast, older female cancer patients are particularly susceptible to the development of physical as well as psychological stress, anxiety and depressive symptoms. Increasing frailty, functional limitations such as incontinence, disabilities in coping with everyday life and cognitive deficits should be mentioned here [835], [836], as well as the loss of social support due to an environment that is also aging. At the same time, older age may also have a positive effect on disease management and coping strategies due to the associated experience of life, illness and crisis [835].

Kornblith et al.[837] conducted telephone catamneses of American patients with breast or endometrial cancer one year after diagnosis of their tumor disease. They found that younger patients had significantly worse quality of life outcomes than older patients, particularly in dealing with psychological distress, tumor treatment and its physical consequences, sexual problems, and coping with difficult everyday situations.
Social dysfunction manifests as impairments in everyday life (e.g. real or feared limitations in mobility due to incontinence), in occupational limitations (performance, type and extent of employment, ability to make contact) or in family and social interactions [838], [833].

11.1.1 Psychosocial support

11.2	Consensus-based recommendation	checked 2022
EC	Cancer patients and their relatives shall be informed about psychosocial support, counseling and treatment services as early as possible in all phases of the disease and shall be given access to these services according to their individual needs.	
	Strong Consensus	

Background
Psychosocial counseling and psycho-oncological treatment of patients with endometrial cancer is an integral part of oncological treatment and diagnostics. It is a multiprofessional task that can be needed and realized by the affected women, as well as by their relatives, at any time of treatment, at diagnosis, during the treatment phases, in aftercare and during rehabilitation [839], [840], [813], [815]. Psycho-oncological care for patients is realized on the basis of an interdisciplinary approach between all professional groups involved in the treatment [839].

Psychosocial assistance includes patient-oriented information (including low-threshold through business cards and posters of the offering services), counseling, a qualified psychosocial diagnosis as well as targeted psychosocial support and, if necessary, treatment. It includes the processing of the disease, the treatment and the side effects and subsequent problems that occur, as well as dealing with persisting functional disorders and other restrictions associated with the disease or treatment, such as economic difficulties and questions about returning to working life.

In concrete terms, therefore, these measures can be provided in the form of psychological/psycho-oncological interventions, counseling by social workers, as part of oncological rehabilitation, or by other professional institutions (e.g. cancer counseling centers). These aids are directed at those affected and their relatives in the surrounding area and concern the entire phase of the disease from diagnosis, information, therapy, supportive treatment, rehabilitation, aftercare and, if necessary, palliative medical care [839].

Rowlands et al. [832], [841] conducted a catamnesis study of endometrial cancer patients whose tumor diagnosis was 3–5 years ago and asked about existing needs and possible needs for psychosocial support. The main issues mentioned by about a quarter of the women surveyed were the best possible medical treatment, the willingness of the treating physicians and the professional team to talk and good accessibility of medical facilities. About 16% wished for emotional support and help in dealing with fear of recurrence or progression, persistent consequences of therapy or everyday stress management. 12% wished for more understanding from those around them of the significance and continuing effects of the tumor disease, which in the eyes of unaffected persons was supposed to have been overcome, on the current attitude and organization of life of the affected women. In particular, about 10% of the respondents expressed a desire for support in better dealing with the uncertainty of making life decisions after the disease. Furthermore, they wished for help in better dealing with their own demands or expectations, especially from outsiders, after supposedly overcoming tumor disease (long-term survival) [838]. According to initial study results, survivorship plans are especially useful for patients with active

information-seeking processing strategies, while patients with distracting avoidance behavior benefit less from them [842]. Survivorship programs should therefore be tailored to the individual needs of the different patient groups.

Regarding psychosocial aspects, regardless of the underlying diagnosis, reference is made to the S3 Guideline “Psycho-oncological diagnosis, counseling and treatment of adult cancer patients”, version 1.1, January 2014, AWMF register number: 032/051OL, http://www.leitlinienprogramm-onkologie.de/leitlinien/psychoonkologie/ [839].

It is significant for the assessment of the subjective need for psychosocial counseling, support or treatment that the physical condition of the patients and the subjective condition correlate only poorly [819], [843], [844], [845]. Therefore, it is important to actively inquire about potentially stressful contextual factors, such as the family, financial, professional or partnership situation, in the (doctor-patient) discussion and to refer to further psychosocial services.

The recommendations were adapted from the S3 Guideline “Psycho-oncological diagnosis, counseling and treatment of adult cancer patients”, version 1.1, January 2014, AWMF register number: 032/051OL, http://www.leitlinienprogramm-onkologie.de/leitlinien/psychoonkologie/[839].

Standardized and validated screening procedures should be used to identify psychosocial distress as well as psycho-oncological treatment needs [846]. The use of a psycho-oncological screening instrument should be performed as early as possible and repeated at appropriate intervals if clinically indicated or if the patient's disease status changes (e.g. recurrence or progression of the disease).

According to the guidelines in the above-mentioned S3 Guideline “Psycho-oncological diagnosis, counseling and treatment of adult cancer patients” [839], the following procedures are recommended (LoE 1b): the Distress Thermometer, the Hospital Anxiety and Depression Scale (HADS), the Questionnaire on Burden of Cancer Patients* (FBK), the Depression Module of the Patient Health Questionnaire (PHQ-9) or the Generalized Anxiety Disorder Scale-7 (GAD-7) [818]. In case of a positive result of a screening, a diagnostic interview for further diagnostic clarification should take place. Further diagnostic clarification should then take place according to the individual problems in the psychological/social/somatic area identified in the interview.

Table 15: Recommendations of the S3 Guideline "Psycho-oncological diagnosis, counseling and treatment of adult cancer patients", version 1.1, update as of June 2021 [494]

11.3	Assessment of psychosocial distress and individual psycho-oncological treatment needs should occur as early as possible and then repeatedly during the course of the disease.
11.4	All patients shall receive screening for psychosocial distress. Psycho-oncological screening should be performed as early as possible at appropriate intervals, when clinically indicated or repeatedly during the course of the disease if there is a change in a patient's disease status (e.g., recurrence or progression), and in long-term survivors.
11.5	Validated and standardized screening instruments shall be used to assess psychosocial distress. The screening instruments to be used are the Distress Thermometer (DT), the Hospital Anxiety and Depression Scale (HADS), the Burden of Cancer Patients Questionnaire (Fragebogen zur Belastung von Krebspatienten, FBK), the depression module of the Patient Health Questionnaire (PHQ-9), or the Generalized Anxiety Disorder Scale-7 (GAD-7) (LoE 1b).
11.6	In addition to the stress screening, subjective psychosocial support needs shall be asked about (EC).
11.7	If the screening is positive and/or the patient requests it, a diagnostic interview to clarify psychosocial stress and psychological comorbidity shall take place.
11.8	Further diagnostic clarification should take place according to the individual problems in the psychological/social/somatic area identified in the interview.

11.1.2 Indication for psycho-oncological interventions

11.3	Consensus-based recommendation	checked 2022
EC	The indication for psycho-oncological interventions shall be made according to the identified individual need, the setting, and the patient's disease phase (initial diagnosis, surgery, adjuvant therapy, recurrence-free phase, relapse phase, palliative phase, long-term survival) and should take into account the patient's wishes.	
	Consensus	

Background

The recommendation was adapted from the already mentioned S3 Guideline “Psycho-oncological diagnosis, counseling and treatment of adult cancer patients” [839].

In the majority of patients, there are no psychological disorders in the narrower sense, but strong stresses as a result of a new and often unexpected (objectively or subjectively) life-threatening situation. The goals of psycho-oncological interventions are therefore the provision of information, education, reduction of psychological stress, preservation of psychological functioning and thus improvement in the quality of life of those affected and their relatives. Tailored to the respective individual needs [839], [847], advice, support and, if necessary, (psychotherapeutic) treatment are provided to the women concerned and their partners and relatives [836]. In a multiprofessional network [839], [813], [819], the aim is to support those affected in coming to terms with and processing the disease, and in doing so to structure and shape everyday life with the restrictions and the real threat posed by the tumor disease [818].

Psycho-oncological interventions are defined according to the S3 Guideline “Psycho-oncological diagnosis, counseling and treatment of adult cancer patients” [839] as a non-pharmacological intervention in which psychological methods, such as psychoeducation, stress management training, psychotherapy, relaxation methods alone or in combination are carried out by a professional therapist in a face-to-face interaction with cancer patients in order to reduce their psychological and social distress and increase their quality of life. Psycho-oncology interventions include:

- Relaxation techniques,
- Psychoeducation,
- Psychotherapy (individual, group, couple therapy),
- Psychosocial counseling,
- Artistic therapy.

These psycho-oncological interventions are indicated for severe psychological distress, couple conflicts as well as for psychological disorders, especially depressive disorders and anxiety disorders [839], [848]. A systematic review with meta-analysis demonstrated that psycho-oncological interventions are effective in cancer patients with various diagnoses, although few intervention studies were available in patients with endometrial cancer [849]. A randomized intervention trial for patients with gynecologic diseases (psychoeducational intervention for targeted improvement of

illness processing and communication) including patients with endometrial cancer showed significant effects in terms of improvement of depression, distress and general psychological well-being compared to a general counseling intervention and control condition (care as usual) [850].

A systematic literature review of non-pharmacological interventions in patients with endometrial cancer [851] examined the efficacy of specific interventions on lifestyle changes (diet, weight reduction, exercise) (n = 10 studies) with different outcome measures (quality of life, self-efficacy, attitude change, anxiety, depression). Nine studies examined quality of life as a primary endpoint and six studies examined quality of life as a secondary endpoint. Significant improvements for global quality of life were found in two studies and for domain-specific quality of life in three studies with small to moderate effect sizes. Very few studies examined psycho-oncology interventions or specific interventions to improve sexual function, social function or psychological function. The authors see a high need for high-quality studies in the area of psychological interventions for this target group.

Diagnostic workup as well as indication for psycho-oncological interventions should be done according to the S3 Guideline "Psycho-oncological Diagnosis, Counseling and Treatment of Adult Cancer Patients" [839]. The S3 Guideline Psycho-oncology formulates a graded clinical care algorithm for psychosocial care of patients and their relatives based on the results of psychosocial screening, identified need for intervention, diagnostic workup, clinical evidence, setting, disease phase and patient preference [839].

11.1.3 Sexuality and endometrial cancer

11.4	Consensus-based recommendation	checked 2022
EC	The topic of sexuality shall be actively addressed in the various phases of the treatment process and follow-up care for patients with endometrial cancer, in order to assess the need for support and to be able to initiate appropriate assistance.	
	Consensus	

Background

The recommendation was adapted from the S3 Guideline "Diagnostics, therapy and follow-up of patients with cervical carcinoma".
(Version 2.1, September 2021, AWMF registry number: 032/033OL, http://www.leitlinienprogrammonkologie.de/leitlinien/zervixkarzinom/) [840])

It is not through the diagnosis of endometrial carcinoma itself, but through the treatment and its consequences that body perception, body image, enjoyment ability as well as the body-related psychological experience of the affected women change [833], [844]. In addition, extensive surgical procedures affect the libido of female patients. Anxiety and depression also affect self-esteem as well as subjectively perceived sexual attractiveness [818], [819]. Symptoms such as postoperative pain [828], fecal or urinary incontinence [821], fatigue and feelings of shame can also

affect libido and sexual activity [820], [852], [853]. Sexual difficulties are associated with lower quality of life and higher emotional distress [820].

Questions about libido changes, impairments in sexual intercourse as well as problems of sexual identity are repeatedly named as significant in different studies, but are still too little actively addressed in everyday care, both in the practice or in the hospital, even today [813], [819], [820]. In a study by Sporn et al. [820] with 800 interviewed male and female tumor patients, 59% of the interviewed women, among them also endometrial cancer patients, wished to be able to talk about sexual topics with the treating physicians.

Treating physicians themselves report that they very rarely ask their patients about sexual concerns or difficulties [822], [827]. Possible obstacles that were named included: time pressure during patient contacts, lack of knowledge about and insufficient training in the diagnosis and treatment of sexual disorders and uncertainty, subjective discomfort and lack of information about sexual desires and activities of their patients [820], [827]. Another barrier identified was that only about 63% saw a way to successfully refer affected patients to further counseling services or offer treatment options after such a conversation [827].

Patients and their relatives rarely address their questions or difficulties with the topic of sexuality on their own initiative. It is therefore all the more important that the impulse to actively address these issues or to pick up on corresponding signals in an encouraging manner comes from the professional team [819].

With regard to the “right time”, different and very individual aspects and phases of disease processing play a role. Professional support at the time of diagnosis or during primary therapy is initially informative for some patients [813], [819]. Side effects or follow-up problems, for example for sexuality, may initially appear to be of lower priority, but then gain importance after completion of treatment or during follow-up [820], [832], [854]. Addressing sexual health is also an important part of programs for long-term survivors [855].

Evidence suggests that single women at an earlier stage of treatment, such as immediately after surgery, want to talk about intimacy and sexuality more often than women who are married or in a committed partnership [819]. After completion of treatment, during the follow-up phase and also in the long term, psychological, socio-demographic factors such as age, school education, social support and relationships, as well as the type of treatment carried out (surgery, radiation, chemotherapy, anti-hormonal treatment) are important with regard to psychological as well as sexual well-being [822], [832].

The more naturally and openly possible problems are proactively addressed in the conversation between the patient and the physician, the easier it will be for the patient to verbalize her difficulties or fears [813], [854]. Ongoing communication between patients, family members and the treatment team is important to identify who needs what and who needs more or different information or support [813].

A number of tools are available for diagnosing sexual problems in endometrial cancer patients; these can be used to identify the problem and prepare for the medical interview [856]. Although no gold standard is available for this topic area, the Female Sexual Function Index (FSFI) can be recommended as a method [857], [858]. The questionnaire is also available in a German validated version [859].

11.2 Patient education

This chapter was prepared in close accordance with the following national and international guidelines:

- “Diagnosis, therapy and follow-up of breast carcinoma.” [860]
- “Diagnosis, therapy and follow-up of malignant ovarian tumors” [528], “Diagnosis, therapy and follow-up of patients with cervical carcinoma” [840]
- “Psycho-oncological diagnosis, counseling and treatment of adult cancer patients” [839]
- “Early detection, diagnosis and therapy of the different stages of prostate carcinoma” [861]
- “American Society of Clinical Oncology Consensus Guideline 2017” [862]

11.2.1 Patient information and educational content

11.2.1.1 Information materials

11.5	Consensus-based recommendation	checked 2022
EC	Qualified and relevant information materials (print or internet media, e.g. the patient guideline on uterine cancer), which have been prepared according to defined quality criteria for health information, shall be made available to patients in order to support them in their self-determined decision for or against medical measures through generally understandable risk communication (e.g. indication of absolute risk reductions).	
	Strong Consensus	

Background

Due to the use of new information technologies, such as the Internet, and the increasing need of patients for information and co-determination in the treatment of their disease, the comprehensible provision of information and differentiated education of the patient is becoming increasingly important. Its importance for the doctor-patient relationship, the course of the disease and the achievement of the therapeutic goal has been proven by numerous studies [863], [864], [865]. An open-ended patient education in combination with a joint (participative) decision-making enables a trustful cooperation. According to the established model of Beauchamp and Childress, four ethical principles operate in these interactions:
1. Respect for patient autonomy
2. Non-harm (non-maleficence)
3. Caring (beneficence)
4. Equality and justice [865].

Two of these principles are often in tension with each other: the patient's self-determination (autonomy) and the physician's care [Horton]. The goal is the farthest possible respect for the autonomy of the patient, as it justifies the principles in the “informed consent”. Patients can speak out for or against medical measures in diagnostics and therapy or also decide for a “not-knowing-wanting”.

In order for patients to be able to make a decision in the sense of effective consent ("informed consent"), potential information deficits must be evaluated and compensated for by physicians. Personal discussions between patients and physicians are of particular importance as a basis for trusting and respectful communication.

11.2.1.2 Communication of diagnosis

11.6	Consensus-based recommendation	checked 2022
EC	The patient shall be offered to include her partner or relatives/trustworthy persons in the conversation(s) for the purpose of communicating the diagnosis and in further conversations during therapy and for follow-up care.	
	Consensus	

11.7	Consensus-based recommendation	checked 2022
EC	During the medical consultation, the patient's individual preferences, needs, concerns and fears shall be determined and taken into account. If a patient requires more than one consultation, the offer of further consultations should be made.	
	Strong Consensus	

Background

The information and education obligations towards patients have been regulated since 2013 in the new "Act on the Improvement of Patients' Rights" (PatRechte G (entered into force on February 26, 2013) [866]. The following aspects are the subject of the law:

- Information obligations between practitioner and patient,
- Consent,
- Obligations to provide information,
- Documentation of treatment,
- Inspection of the patient's file,
- Burden of proof for liability in the event of treatment and information errors.

This legal regulation is associated with obligations of a statutory nature that go beyond the scope of recommendations in a guideline [866].

The participatory decision making thereby has a high value ("shared decision making") [860]. The prerequisite for this is the patient-centered discussion. The information provided by the physician should be comprehensive, truthful, complete with regard to the type of measure, purpose, benefits and risks and, in particular, comprehensible (including information on frequencies instead of relative percentages) [867], [868]. The patient's individual somatic, psychological and social situation, age and comorbidities must be taken into account during the discussion. In

this context, the patient's fears and concerns, specific burdens, and in particular her need for information, her treatment expectations and her preferences must be addressed directly by the physician [860], [869], [870], [871], [872].

The patient's medical education should include the following aspects: information about the disease, examination results obtained, the course of treatment to date, diagnostic and therapeutic options including the side effects to be expected, as well as assessments of the associated prognoses and the impact on the patient's life planning [860], [873], [874]. Accompanying, supporting and helpful for decision-making by a patient is the provision of and access to written information [873], [875]. This includes professional and competent, comprehensibly prepared and quality-assured information materials [860], [873], [874].

11.2.1.3 Information dissemination and education

11.8	Consensus-based recommendation	modified 2022
EC	The communication of information and education of the patient shall take place at an early stage and according to the basic principles of patient-centered communication, which enables participatory decision-making. This should include the following aspects: • Expression of empathy and active listening, • Addressing difficult issues directly and empathetically, • Avoidance of technical medical vocabulary, explanation of technical terms when appropriate, • Strategies to improve understanding (repetition, summarizing important information, use of graphics, etc.), • Encouragement to ask questions, • Permission and encouragement to express feelings, • Offering further help.	
	Consensus	

11.9	Consensus-based recommendation	new 2022
EC	To improve patient education, physicians should complete quality-assured training on communication with patients.	
	Strong Consensus	

Background

Receiving a cancer diagnosis causes anxiety and helplessness in the patient and her relatives. The complex treatment is also difficult for them to understand. The treating physicians must be able to deal with these feelings in order to have a successful conversation for both sides [862].

11.2.1.4 Information about self-help organizations

11.10	Consensus-based recommendation	checked 2022
EC	The patient shall be made aware of self-help options and given contact information for self-help organizations.	
	Consensus	

Background

As soon as the histopathological diagnosis of endometrial carcinoma is confirmed, the patient should be informed by her treating physician according to the criteria described [860]. Basic patient education is usually already provided by the general practitioner or the physician who made the initial diagnosis or who diagnosed recurrence or metastasis. Since the period between and during the diagnosis and the start of therapy is often very difficult for patients, the possibilities of self-help, psycho-oncological care or psychosocial cancer counseling should be pointed out at this early stage depending on the situation (see [839]). Contact details for self-help organizations can be obtained from the National Contact and Information Center for the Initiation and Support of Self-Help Groups (NAKOS), e-mail: selbsthilfe@nakos.de, Internet: www.nakos.de.

Contact information for counseling services and contact points for patients with endometrial cancer will also be available in the accompanying Patient Guideline. This is freely available on the Internet, e.g., on the pages of the German Guideline Program in Oncology (http://www.leitlinienprogramm-onkologie.de/home/) and the pages of the AWMF (http://www.awmf.org/leitlinien/patienteninformation.html). The final therapy recommendation, its alternatives and the respective effects will then be discussed, if necessary, in a renewed conversation with the doctors who will ultimately treat the patient (e.g. treatment within the framework of studies, is surgery possible, etc.), because often not all information about the disease (staging, etc.) is available at the time of initial diagnosis. It is at the patient's discretion whether her partner or relatives or persons she trusts should be included in the discussion(s). The conversation should take place in a form and setting that is understandable and appropriate for the patient [876].

The physician must inform the patient truthfully without diminishing the content. The patient should not be deprived of hope for a cure or relief, depending on the stage of the disease. The physician providing the information must ensure that the information provided is in line with the current state of medical knowledge and takes medical progress into account [860]. The patient should always be given time to think about the decision on the type of therapy. Only then will the patient sign the informed consent.

11.2.1.5 Information about therapy options

11.11	Consensus-based recommendation	checked 2022
EC	Patients with endometrial cancer shall be informed about the treatment options described in this Guideline that are relevant for them, their prospects of success and their possible effects. In particular, the impact on their physical appearance, sexual life, urinary and fecal control (incontinence) and aspects of female self-image (self-image, fertility, menopausal symptoms) shall be addressed.	
	Strong Consensus	

Background

In addition to his or her duty to inform (§ 630c), the attending physician is required by § 630d of the "Gesetz[es] zur Verbesserung der Rechte von Patientinnen und Patienten" [Act Improving the Rights of Patients] (PatRechte G) [877], to inform the patient orally, in person and in good time "[…] of all circumstances essential to consent. This includes in particular the nature, scope, implementation, expected consequences and risks of the measure as well as its necessity, urgency, suitability and prospects of success with regard to the diagnosis or therapy. The information must also refer to alternatives to the measure if several medically equally indicated and customary methods can lead to substantially different burdens, risks or chances of recovery."
https://www.bundesaerztekammer.de/fileadmin/user_upload/downloads/Patientenrechtegesetz_BGBl.pdf.

Specifically, this is education about treatment recommendations, especially if they are consented to in a case-based, interdisciplinary conference. The principles of treatment and potential expected benefit(s) or risk(s) should be presented. Alternative forms of treatment that may be considered for the patient, for example in the context of participation in a clinical trial, should be explained. The effects on the patient's lifestyle and quality of life should be discussed.

11.3 Palliative care

More detailed information on this topic can be found in the S3 Guideline Palliative Medicine (S3-Leitlinie Palliativmedizin).

Selected key recommendations from the S3 Guideline Palliative Medicine

11.12	Evidence-based recommendation	modified 2022
GoR **A**	All patients shall be offered palliative care (APV or SPV) after diagnosis of non-curable endometrial cancer, regardless of whether tumor-specific therapy is used.	
LoE **1-**	1-: LoE from S3 palliative care.	
	Strong Consensus	

11.13	Consensus-based recommendation	new 2022
EC	For patients with non-curable endometrial cancer, the complexity of the palliative situation shall be repeatedly assessed; this includes: the needs of the patient and her family, the patient's functional status and the disease phase.	
	Strong Consensus	

11.14	Evidence-based recommendation	new 2022
GoR **A**	Patients with non-curable endometrial cancer and high complexity of their situation shall receive specialized palliative care. S3 Guideline Palliative Care.	
LoE **3**	[721] 3: LoE from S3 Palliative Care.	
	Strong Consensus	

Background (as of 2021)
Palliative medicine or palliative care (synonym: palliative care) is defined as a multiprofessional approach to improving the quality of life of patients and their families facing problems associated with a life-threatening illness. This is done by preventing and relieving suffering, by early recognition, careful assessment and treatment of pain and other problems of a physical, psychosocial and spiritual nature (Expanded S3 Guideline Palliative Care for Patients with Non-curable Cancer Long

version 2.2 – September 2020 AWMF Register Number: 128/001OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/, S3 Guideline Diagnosis, Therapy and Follow-up of the Patient with Cervical Carcinoma Long Version 2.1 – May 2021 AWMF Register Number: 032/033OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/zervixkarzinom/.

From the WHO definition of palliative care derives a holistic approach taking into account all four dimensions of the person. This is also the basis for the inclusion of the family in therapeutic efforts, which does not end with the patient's death but includes the mourning phase. Palliative care requires a multiprofessional and interdisciplinary team approach. Early integration (principle of involving (specialized) palliative care as systematically as possible in parallel with tumor-modifying treatment) has been shown to be relevant to quality of life and, in individual cases, survival, and is now considered the standard of care. Palliative care affirms life and recognizes dying as a normal process and thus does not aim to delay or hasten dying.

Patients who are not curatively treatable by surgery, radiochemotherapy or postoperative adjuvant radiochemotherapy and have advanced endometrial cancer with or without distant metastases (M1b, c) can usually be assumed to have incurable disease.

Needs of the patients

The most important/overriding palliative medical therapy goal – the individual quality of life – can only be evaluated and defined together with the patient. Burdens of the patient can be physical, psychosocial, spiritual and existential. The need for support should be regularly determined together with the patient using suitable, validated and multidimensional instruments.

A prerequisite for the treatment of patients and a component of palliative medical basic values is the high appreciation of patient autonomy and participation (patient guideline S3-guideline palliative medicine). In addition to the above-mentioned routine recording of the patient's self-assessment of quality of life and symptom burden, this also includes the monitoring of therapy decisions in compliance with the medical ethics principles of benefit, harm, patient autonomy and appropriateness (justice). Discussions about possible therapy options should also include palliative care services. The patient guideline on palliative care contains valuable suggestions for preparing for discussions with physicians, which patients can use as a checklist. Relatives or other trusted persons named by the patient should be included in the discussions. In order to enable the patient to ensure that her confidants can represent the patient's will as well as possible, even in the event of disorders of consciousness that may occur in the course of the illness, they should be involved in determining the patient's treatment wishes and goals, and, if necessary, in drawing up a health care proxy and a living will. The living will should be drafted as specifically as possible and contain plans for probable or possible emergency situations in the course of the disease (S3 Guideline on palliative), [878].

Care structures

Palliative care includes medical symptom control, palliative care, and psychosocial support from the onset of non-curable tumor disease until death. In the palliative

situation, all necessary measures are oriented to the patient's individual therapeutic and life goals. The S3 Guideline presents a two-stage concept of palliative care: patients with low-to-moderate and less complex symptoms receive palliative care (general palliative care, (Allgemeine Palliativversorgung, APV)) through the primary care teams, (gynecologists, family physicians, social services). For patients who continue to suffer from a high level of physical, psychosocial or spiritual stress despite qualified palliative medical measures, specialized palliative medical (co-) treatment is advisable (spezialisierte palliativmedizinische (Mit)behandlung SPV)). This is provided in the outpatient setting by the palliative care teams of SAPV and by hospice services; in hospitals, treatment is provided by the palliative care service or in specialized palliative care units [879].

Through legislation, the following options for outpatient palliative care and palliative care in facilities are regulated and refinanced:

1. Outpatient care by specially qualified contract physicians is possible, billing of palliative care with the introduction of fee schedule figures in the EBM:

This includes “coordination of palliative medical and nursing care in cooperation with other specialized service providers such as contract physicians, psychotherapists, nursing services, psychosocial care services, hospices, as well as guidance and counseling of the care and reference persons”.

[Source: § 87 para. 1b SGB V, Bundesmantelvertrag (BMV-Ä): Annex 27 and 30, EBM Chap. 37 “Particularly qualified and coordinated palliative medical care”, EBM chap. 33 general care by contract physicians without an additional designation in palliative medicine].

2. Additional services such as the individual palliative care measures that can be provided by home health care such as wound care and other individual measures, and a complex code introduced in 2017. The name of the complex service 24a is “Symptom control in palliative patients”. This includes all treatment care services that become necessary in case of need in a complex symptom event and also includes crisis intervention in close consultation with the prescribed contract physician.

[Source: Guideline of the Joint Federal Committee on Home Nursing (HKP Guideline), § 37 SGB V] .

3. SAPV (spezialisierte ambulante Palliativversorgung) as specialized outpatient palliative care, which is intended for patients who require particularly complex care if there are indications of a complex symptom occurrence, the treatment of which requires specific palliative medical and/or palliative nursing knowledge and experience as well as an interdisciplinary coordinated concept. SAPV is provided by a specially designated SAPV team [Sources: Framework recommendations SAPV for adults (as of 2021), SAPV guideline of the Federal Joint Committee, § 37b SGB V, § 132d SGB V)].

4. Outpatient hospice work and inpatient hospice care [Source: § 39a SGB V, framework recommendations of the health insurance funds and service providers].

5. Special offers for female patients in licensed nursing homes and facilities of integration assistance for disabled people concern “health care planning for the last phase of life”. This includes an extensive consultation of the patient and the relatives in relation to the medical and nursing care and care in the last phase of life;

possibilities of the assistance and offers are to be pointed out in the context of one or more case discussions. The patient's wish for end-of-life care should also be addressed and emergency situations discussed in advance. The attending physician is to be involved.

[Source: § 132 g SGB V, Hospice and Palliative Act].

Treatment of special symptoms
Patients with endometrial carcinoma often have a high symptom burden even in the locally advanced stage. Bowel obstruction/constipation, urinary retention, fistula formation, vaginal discharge and/or genital bleeding, cloacal formation and depression and fatigue are common [880].

Constipation and Malignant Intestinal Obstruction (MIO)
Regarding specific therapeutic procedures, please refer to the article “Palliative Concepts in Ovarian Cancer” [880], and to Chapters 13 and 14 of the expanded S3 Guideline “Palliative Care with a Non-curable Cancer” of the Oncology Guideline Program (S3 Guideline Palliative Care).

Fistula formation
Fistula tracts can develop especially between the vagina and the intestine (enterovaginal fistula) and between the vagina and the urinary bladder (vesicovaginal fistula). They are either tumor-related due to invasive growth, but can also be therapy-related, e.g. postoperative or after radiation therapy [880]. Fistulas to the bladder or into the bowel are particularly distressing for patients because of the incontinence for urine or stool they cause. Surgical repair by means of fistula closure is not possible in most cases or is not advisable because of the high risk of recurrence. In patients with a life expectancy of days to weeks, symptom-based care with pads, incontinence pants or catheters is reasonable [880]. If a longer life expectancy of months to years is anticipated, permanent diversion through an anus praeter or urinary diversion should be discussed with patients. In view of the foreseeable negative effects of long-term incontinence as a result of the fistula, patients should be empathetically relieved of the fear of the expected limitations on quality of life caused by artificial urinary or fecal diversion. The reference to the modern, odorless and securely connectable systems is decisive for acceptance.

Vascular erosion
Bleeding due to tumor ingrowth into adjacent vessels is potentially life-threatening for the patient. In the acute situation, usually only local compression with immediate vascular surgery is possible. In cases of insidious onset with permanent oozing bleeding, both local radiation and targeted angiographic embolization may be considered. Both approaches are equivalent in terms of local control, but usually of short efficacy without additional antineoplastic therapy, which is usually not indicated in the advanced palliative situation [880]. In patients in good general condition with sufficiently assessed life expectancy, targeted surgical coverage should also be considered.

Genital bleeding
Genital bleeding may be an expression of local recurrence, metastasis or – more rarely – due to tumor penetration into the vagina. Small foci of bleeding can be well controlled in the short term with local application of silver nitrate or Monsel solution. Tight tamponade may also be useful, as well as local radiation therapy as brachytherapy, or small-volume percutaneous if necessary. In some circumstances,

the use of a laser for coagulation may also be useful. If life expectancy is prolonged, palliative hysterectomy or colpectomy may also be offered to control bleeding [880].

Vaginal discharge
Permanent foul-smelling vaginal discharge is mostly caused by tumor necrosis and/or infection and means an immense restriction of the patient's quality of life. Even a small amount of discharge affects the well-being and partnership. If the symptoms are pronounced, shame, disgust and also odor-related environmental reactions such as exclusion or rejection are added. With longer life expectancy – if not already done – simple hysterectomy is the treatment of choice. Radiation is a good alternative to the purely symptom-oriented approach. In mild manifestations, local sitz baths with antiseptic substances for local cleansing are also helpful and possible ([880]. Since colonization with anaerobes is mostly responsible for the odor, low doses of metronidazole can also be used intermittently to reduce the odor ([880], [Guidelines Program Oncology (German Cancer Society, German Cancer Aid, AWMF) et al. 2020]).

Since resistance and resistance developments must also be taken into account in the palliative situation; antibiotic therapy should be calculated, i.e., the selection of the antibiotic is based on the most probable pathogens. Systemic antibiotic administration, for example with metronidazole (* off-label use), reduces the number of anaerobic germs, especially in the deeper wound layers, which cannot be reached with germ-reducing products. The recommendation is three times daily 400 mg orally or 500 mg i. v. (for 14 days). If necessary, treatment can be longer (“low-dose antibiotic therapy” 200 mg 2 times daily), depending on the patient's current situation, remaining lifespan and the burden of odor on the patient and his relatives ([Guidelines Program Oncology (German Cancer Society, German Cancer Aid, AWMF) et al. 2020]).

Urinary retention
Compression of one or both ureters up to complete obstruction is also a frequently encountered symptom in endometrial carcinoma [880]. Due to the outflow obstructing compression, infections of the urinary tract occur frequently. In the course of the disease, the retention parameters increase up to uremia in case of complete obstruction. Death from uremia is painless and in the vast majority of cases means peaceful sleep. In patients with a very short prognosis, the indication for urinary diversion should therefore be very strict, since death from a cloaca usually means a much more symptom-laden course of death. If life expectancy is longer, urinary diversion is a highly effective and efficient measure. With existing patency of the ureters, the double J catheter is available. Apart from occasional pressure or foreign body sensation and the need for regular checks and changes with appropriate visits to the doctor, no restrictions are to be expected. The risk of infection is only marginally increased; there is no indication for antibiotic prophylaxis.

In case of a complete occlusion of the ureters or tumor-related locally increased risk of bleeding, percutaneous nephrostomy is a good option. This can be performed unilaterally or bilaterally. Similar to fistula treatment, empathic education and guidance is essential for acceptance. The modern odor-proof and tightly adherent drainage bags, if handled well, usually mean hardly any restrictions on the quality of life [880].

Tumor-related cloacal formation
Cloaca is the most serious specific palliative care problem. Tumor-related infiltration of the bladder and rectum creates a common excretory tract with no possibility of

voluntary control of excretion. Constant urinary and fecal incontinence as well as additional infectious or necrotic foetid discharge massively limit the quality of life. In addition to the physical problems, the patients also suffer massive psychological problems, since in many cases this situation causes complete exclusion from the personal and nursing environment. Early phases of cloacal formation are to be treated in the same way as fistula treatment. Artificial stool and urine diversion, if necessary in combination with palliative radiotherapy, can provide relief. These measures are also often suitable in the presence of distant metastases to alleviate the stressful effects of cloacal formation and to achieve a significant short-term improvement in the quality of life for patients. Nursing measures such as pads, incontinence pants or catheters inevitably quickly reach their limits. Helpful advice can be found in Chapter 15 “Wound care” of the extended S3 Guideline “Palliative care with a non-curable cancer” of the German Guideline Program in Oncology (AWMF register number 128/001OL, version 2.1 - January 2020 (S3 Guideline palliative care).

Depending on the overall situation, exenteration with palliative intent for symptom control may also be reasonable. The usefulness and feasibility of such a measure should be carefully discussed and weighed with the patient, especially in the palliative situation. In individual cases, such operations may even lead to a prolongation of life and provide a better starting point for other palliative therapy options. In the discussion, the patient's level of suffering is the decisive factor and an individual consideration of the lethality of the operation and the massive burden of cloacal formation is necessary [880].

11.4 Rehabilitation

11.15	Consensus-based recommendation	checked 2022
EC	Medical-oncological rehabilitation serves the specific treatment of disease and therapy sequelae. All patients with endometrial carcinoma shall be informed and advised about the legal options for applying for and receiving rehabilitation services.	
	Strong Consensus	

11.16	Consensus-based recommendation	checked 2022
EC	Therapy-related disorders, such as abdominal wall and adhesion discomfort, sexual dysfunction, pain during intercourse, vaginal dryness, urinary bladder and bowel dysfunction shall be inquired about and treated not only during primary therapy but also during rehabilitation and follow-up.	
	Strong Consensus	

Before rehabilitation

All patients are to be informed and advised in detail about the legal options for follow-up rehabilitation, curative treatment and outpatient rehabilitation offers. For this purpose, the respective attending physician and social worker are to work together. The rehabilitation ability results from a positive motivation of the patient and the physical and psychological ability to use the offered rehabilitation programs in a goal-oriented way.

The need for rehabilitation in the somatic and psychosocial area results from the determination of the disease and treatment sequelae with orientation to classification principles of the ICF classification of the WHO (2001). These can be differentiated in more detail into functional disorders, ability disorders, impairments as well as context and risk factors and can also be coded.

Accordingly, the assessment of the need for rehabilitation (e.g., in the application process) requires consideration of bio-psycho-social impairments in addition to bio-medical health problems.

Rehabilitation is carried out on an inpatient or outpatient basis, if necessary as a mixed form, but always in an interdisciplinary and multimodal approach.

Aims of rehabilitation

Oncological rehabilitation is the next therapeutic step for patients with endometrial carcinoma after completion of primary therapy in order to return to everyday family, social and professional normality.

The overall global goal of oncological rehabilitation is the regaining of physical, mental and social well-being. In the case of chronic disease sequelae, support and

care are provided to help patients accept or compensate for unavoidable disabilities and discomforts, and to help them lead their lives again to their own satisfaction.

The aim of oncological rehabilitation is to significantly improve or restore a significantly endangered or already reduced ability to work, or at least to prevent a deterioration.

The aim of oncological rehabilitation is to avoid the need for care or to postpone the need for care.

Overcoming physical, psychological and social consequences
Oncological rehabilitation is carried out in a multidisciplinary setting based on ICF and a bio-psycho-social model:

- Diagnosis of the sequelae of cancer and therapy
- Preparation of an individual rehabilitation plan
- Multidisciplinary treatment of specific sequelae, e.g. local sequelae due to surgery or radiotherapy or due to estrogen deficiency, dyspareunia, lower urinary tract or bowel disorders, lymphedema or chronic tumor-associated fatigue syndrome
- Sports and physical therapy training program to increase strength and conditioning and to overcome or compensate for specific sequelae
- Physical therapy, provision of aids
- Occupational therapy
- Psycho-oncological services with individual and group sessions, relaxation techniques, creative therapies
- Social counseling on professional, domestic, family or social situation
- Provision of information on the disease and on healthy lifestyles
- Motivation and training for a healthy lifestyle and for dealing with illness and health independently

Professional assistance
Sequelae caused by endometrial carcinoma and the antitumor therapies carried out can have an adverse effect on occupational performance. After cancer, there is a higher risk of unemployment, job change, reduction in hours and lower pay.
An important task of oncological rehabilitation is to help compensate for these disadvantages and risks:

- Is the rehabilitant's performance capacity sufficient to meet the demands of the workplace in the medium term?
- Can the rehabilitant continue to perform her job to the same extent as before?
- Does the rehabilitant need equipment for the workplace that is appropriate to her condition?
- Is it necessary to change jobs within the company?
- Does the rehabilitant need services for participation (e.g. further vocational training)?
- Is the rehabilitant's ability to perform at work suspended?

Oncological rehabilitation is suitable to competently support patients on their way back to working life. In doing so, it does justice to the mandate from the Basic Law

"No one may be disadvantaged because of their disability" (Art. 3 Para. 3 Sentence 2 GG) and the Social Code IX "Right to participation".

In the medical discharge report of the rehabilitation clinic, a socio-medical performance assessment is prepared for patients who are of working age, which, in addition to assessing the previous activity profile, also refers to the capacity for the general labor market.

Evidence

Many therapeutic measures in oncological rehabilitation are provided on the basis of scientifically proven effectiveness. For methodological reasons, corresponding studies are usually conducted with the frequent diagnoses of breast cancer, prostate cancer and colorectal cancer. Evidence has been described for the effects described below; we consider the analogy to patients with endometrial carcinoma to be appropriate:

- Exercise therapy: improve fatigue symptoms, increase exercise capacity and physical functionality, improve body image, decrease depression, improve quality of life (a)
- Patient education: reduction in physical symptoms, improvement in quality of life, improvement in mood (b)
- Health education: decrease uncertainty, increase quality of life, improve well-being (c)
- Nutrition education practical: intentional weight loss through practical intervention (d)
- Psychological counseling and therapy: improvement quality of life, improvement fatigue and stress, improvement anxiety and depression (f)
- Relaxation training: reduction of pain, improvement of quality of life, reduction of anxiety and depression (e).

Payment and legal basis

Rehabilitation services are services for participation, which can be paid for by a rehabilitation provider (e.g. German pension insurance, statutory health insurance, statutory accident insurance). In the field of oncological rehabilitation, the pension insurances are the service providers with the most frequent responsibility. According to German social legislation, disabled people or people at risk of disability receive rehabilitation services to promote their self-determination and equal participation in life in society, and to avoid or counteract disadvantages. The services are provided by the responsible rehabilitation provider in accordance with the Ninth Book of the German Social Code (SGB) and the benefit laws applicable to the respective rehabilitation provider (for example, SGB V in the case of SHI or SGB VI in the case of DRV).

Bio-psycho-social model

The bio-psycho-social understanding of illness is a prerequisite in medical and professionall rehabilitation for the initiation (including application/report) as well as for the (therapeutic) content of the rehabilitation and planning of the individual rehabilitation goals. The rehabilitation providers implement the recommendation of the WHO to apply the International Classification of Functioning, Disability and Health (ICF) in the field of health care.

ICF

The ICF complements the International Statistical Classification of Diseases and Related Health Problems (ICD) where the focus is not on the diseases (diagnosis and

findings) themselves, but includes associated impairments in, among other things, earning capacity, mobility, communication, self-care, home life or participation in social life.

11.4.1 Treatment of cancer-related Fatigue

11.17	Consensus-based recommendation	new 2022
EC	Endometrial cancer patients should be informed about tumor-associated fatigue and screened systematically and repeatedly during the different treatment phases. Screening according to NCCN is recommended.	
	Strong Consensus	

11.18	Consensus-based recommendation	new 2022
EC	If there is a value > 3 in the screening, there should be a diagnostic assessment for further clarification and specific advice on fatigue management and treatment if needed.	
	Strong Consensus	

11.19	Evidence-based recommendation	new 2022
GoR **B**	For moderate or severe fatigue, moderate strength and endurance training should be provided based on physical performance level.	
LoE **2**	[721] 2: Guideline adaptation S3 Guideline Palliative Care	
	Strong Consensus	

11.20	Evidence-based recommendation	new 2022
GoR **B**	Psychoeducation or cognitive behavioral therapy should be offered for moderate or severe fatigue	
LoE **2**	[721] 2: Guideline adaptation S3 Guideline Palliative Care	
	Strong Consensus	

11.21	Evidence-based recommendation	new 2022
GoR **0**	For moderate or severe fatigue, mindfulness-based stress reduction (MBSR) and yoga can be offered.	
LoE **1**	[881] 1: Guideline adaptation S3 Guideline Complementary Medicine	
	Strong Consensus	

11.22	Evidence-based recommendation	new 2022
GoR **B**	Yoga should be recommended to reduce fatigue in these patients.	
LoE **1**	[881] 1: Guideline adaptation S3 Guideline Complementary Medicine	
	Strong Consensus	

Fatigue is a common consequence of cancer and therapies, in the treatment phase 70-90% of all patients are affected, in one third the symptomatology persists after years (Extended S3 Guideline Palliative care for patients with a non-curable cancer long version 2.2 – September 2020, AWMF register number: 128/001OL https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/.

The NCCN defines tumor-associated fatigue as “a worrisome, persistent, subjective feeling of physical, emotional, and/or cognitive fatigue or exhaustion related to tumor disease or tumor treatment that is unrelated to current activities and interferes with usual functioning” [882].

To identify tumor-associated fatigue, NCCN [882] suggests a screening tool that is used to assess the subjective degree of fatigue experienced on a numerical scale ranging from 0 (no fatigue) to 10 (most severe fatigue). For patients older than 12 years, a score between 0 and 3 is considered as no or mild fatigue, between 4 and 6 as moderate fatigue and between 7 and 10 as severe fatigue.

There are ESMO guidelines [883] as well as NCCN guidelines on cancer-related fatigue and specific aspects of fatigue are also addressed in various German-language guidelines, e.g., in great detail in the S3 Guideline Palliative Medicine (https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/) and in the guideline Complementary Medicine in Oncological Patients

(https://www.leitlinienprogramm-onkologie.de/leitlinien/komplementaermedizin/. A separate guideline or a comprehensive separate chapter, e.g. in the Guideline Supportive Therapy in Oncological Patients, does not exist at present.

In the various guidelines, different treatment elements in the management of fatigue can be found:

- Information and education
- Systematic and repeated screening (with validated instruments)
- Diagnostic assessment (focused history, identification of other influenceable physical, psychological and social factors that can lead to fatigue; treatment/influence of these factors)
- Counseling and treatment services for the management of fatigue.

11.4.2 Physiotherapeutic treatment in the context of rehabilitation after endometrial carcinoma

The physiotherapeutic part of the aftercare focuses on the treatment of various side effects of cancer therapy (surgery, radiation or chemotherapy). This includes therapy of incontinence (ICD-10 codes see below), lymphedema (here: of the lower extremities: ICD-10 I89.0) [1] to interventions to alleviate fatigue syndrome (ICD-10 G93.3) [1].

Treatment of gynecologic tumors by surgery or radiation therapy may result in pelvic dysfunction. These are symptoms of urinary incontinence (urge, stress and mixed) (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 shortened or scarred vagina), circulatory changes or lack of elasticity of scar tissue.

Various physiotherapeutic passive (scar mobilization, stretching of vaginal tissue, positioning, complex physical decongestive therapy, etc.) and active techniques (instruction in low-pain everyday behavior, circulatory gymnastics, decongestive exercises, measures of exercise therapy and forms of training) can reduce these disorders.

11.4.3 Incontinence therapy

11.4.3.1 Urinary incontinence

11.23	Consensus-based recommendation	checked 2022
EC	Patients with stress urinary incontinence and/or fecal incontinence should be offered pelvic floor muscle training after endometrial cancer.	
	Strong Consensus	

Background

In the treatment of urge incontinence, various forms of therapy such as bladder training, pelvic floor muscle training and educational measures show good results, which are quite comparable to drug treatment [884], [885], [886]. Another option in the treatment of urge incontinence could be treatment with functional electrical stimulation [886], [887].

With regard to stress incontinence, pelvic floor training remains the treatment of choice [888], [889], [890]. Pelvic floor training is particularly effective for stress and mixed incontinence and especially for women under 60 years of age [891]. In addition, there is evidence that supervised training is more successful than when training is done independently [889]. If supportive forms of therapy are used in addition to pelvic floor training after appropriate diagnostics, such as device-supported biofeedback or electrostimulation, these can reinforce the pelvic floor training [892], [893].

There is strong evidence for anal sphincter or pelvic floor training in the treatment of fecal incontinence [894], [895]. Whether the additional use of biofeedback and electrical stimulation show better results than pelvic floor training alone is unclear [894], [895].

11.4.4 Lymphedema therapy

11.24	Consensus-based recommendation	checked 2022
EC	If lymphedema is manifest, patients should be offered therapy after endometrial cancer according to the "S2k Guideline Diagnostics and Therapy of Lymphedema (AWMF Reg. No. 058-001) May 2017".	
	Strong Consensus	

Background

Extensive removal of lymph nodes in pelvic or additionally para-aortic localization or radio(chemo)therapy alone or adjuvant with different target volumes may lead to lymphedema in the lower extremities. Data on prevalence vary widely. This is due to the different therapies and also times of inventory.

Long-term observations show an increase even 10 years after therapy [896]. The diagnosis of lymphedema is made by a precise clinical examination using the "skin fold test according to Stemmer" (lifting of tissue between thumb and index finger), which is always performed in a lateral comparison. With the aid of a tape measure, the circumference of the legs can be measured in a standardized manner over time. It makes sense to always measure at the same points on several parts of the lower and upper thighs and without pulling on the tape measure. The date and time of day should also be noted, since edema fluctuates throughout the day or depending on the season (summer/winter). (S2k Guideline "Diagnostics and therapy of lymphedema", May 2017, AWMF register number: 058-001).

Both legs should be measured already before surgery as initial findings and regularly thereafter. Oncological follow-up appointments, for example, offer favorable measurement times. Studies on the treatment of lymphedema of the lower extremities are very unsatisfactory. However, experience from breast cancer research in lymphedema of the upper extremities can be used and these data extrapolated. Combined physiotherapy (complex physical decongestive therapy) consisting of skin care, manual lymphatic drainage, exercise therapy and compression is the most appropriate treatment method here [897].

Twice weekly therapy frequency is recommended in the initial stage and once weekly therapy frequency is recommended in the chronic stage. The exercise program does not increase risk, but has a positive effect on mobility and quality of life [898], [899]. For the permanent volume reduction of lymphedema, compression (bandages or stockings) as well as laser therapy are particularly suitable [900], [901]. Laser therapy is hardly used in Germany. Compression with bandages seems to be more effective than pneumatic compression. Kinesio tape can be an alternative to conventional bandages, but is associated with increased costs [902]. There is currently no evidence for the effectiveness of manual lymphatic drainage as edema prevention.

12 Fragile patients/Geriatric assessment

12.1	Consensus-based recommendation	new 2022
EC	Treatment decisions for older patients shall be based on current standard recommendations and modified by general status, life expectancy, patient preference and an individual benefit-risk assessment.	
	Strong Consensus	

12.2	Evidence-based recommendation	new 2022
GoR **B**	Determination of general status in patients older than 75 years should be determined by geriatric assessment or by a screening/geriatric assessment algorithm, especially if surgery with general anesthesia or chemotherapy is planned to minimize complications as well as improve treatment adherence, chemotherapy tolerance and possibly survival.	
LoE **3**	[903], [904], [905], [906], [907], [908], [860]	
	Strong Consensus	

12.3	Evidence-based recommendation	new 2022
GoR **B**	The sole consideration of calendar age does not do justice to the complexity and multi-layered nature of the general status. Rather, geriatric assessment and management should include therapy-relevant geriatric domains (especially functionality-associated parameters such as activities of daily living, mobility, cognition, falls and morbidity-associated parameters such as multimedication, nutrition, fatigue and number of comorbidities) to adjust therapy selection accordingly and initiate supportive measures.	
LoE **3**	[903], [904], [860], [909]	
	Strong Consensus	

Although the evidence base for older patients with endometrial cancer is limited, there are an increasing number of study results, some of them interventional, of older patients with oncological diseases. These have meanwhile found their way into national and international evidence-based oncological guidelines [903], [904], [860], [909].

Identification of the fragile patient is achieved with the help of the comprehensive Geriatric Assessment (GA) or with an upstream validated screening tool. The GA is a multidimensional diagnostic process that attempts to capture relevant aspects of the elderly patient with validated tools that are relevant to the therapy of the elderly patient. The individual tests available including their test sizes can be found in the S1 Guideline "Geriatric Assessment Level 2" [909]. According to the SIOG (International Society of Geriatric Oncology) screening tools do not replace a comprehensive GA but are suitable in everyday life to identify elderly patients who benefit from a GA [904]. Screening tools that have been well studied in oncology patients include the G8, the VES-13 or the Groningen Frailty Indicator (GFI) [904].

Bourgin et al. published a review on the surgical approach to the elderly patient with endometrial cancer in 2016 [906]. The authors' conclusions were based on 16 surgical studies of older patients. The lower limit of age for patient inclusion varied from 63 to 80 years. The studies included between 115 and 1682 female patients. 2 studies were prospectively randomized, 2 retrospective studies were based on prospective databases, 7 studies were prospective cohort studies and 5 were retrospective cohort studies. 8 studies compared different surgical approaches, whereas the remaining 8 studies compared different age subgroups. Laparoscopic access was used in 8 studies, robotic access in 4 studies, open access in 2 studies, and vaginal access in 2 studies. The authors reached the following conclusions. The older patient with endometrial carcinoma suffers from a biologically more aggressive malignancy and is often undertreated. The more aggressive tumor type requires optimal surgical management based on the oncologic findings, which may include lymphadenectomy. The surgical approach should be laparoscopic and include a GA to determine fragility [906].

In 2018, Ahmed et al. published preliminary results of a prospective, multicenter cohort study of a total of 189 patients older than 70 years with a pre-operative suspected diagnosis of advanced endometrial cancer or ovarian cancer [908]. Patients received a short-form GA, which quantifies the extent of fragility with a score of 0-10. The primary endpoint of the study was an association between abnormal GA and postoperative complication rate. In the overall cohort of all patients, shortened GA was not associated with this (p=0.134). Due to a relatively large proportion of patients with benign disease (21.4%), two unplanned subgroup analyses were performed. In the cohort gynecologic malignancies of all stages, there was no statistically significant association between GA and complication rate (HR: 1.195; 95%-CI: 0.963 – 1.488; p= 0.089 per increasing point in GA). In the cohort of advanced stage III/IV gynecologic malignancies, a statistically significant association was identified (HR: 1.290; 95%-CI: 1.006 – 1.674; p=0.0456 per increasing point in GA) [908].

In 2017, Driver et al. published the results of a retrospective cohort study of 88 patients with endometrial cancer older than 60 years [907]. In this cohort, the presence of at least one marker of fragility (hypoalbuminemia, anemia, BMI ≤ 20kg/m2, unintentional weight loss, ECOG 2 and greater, osteopenia or osteoporosis and Charlson Comorbidity Score) was associated with a worse prognosis (recurrence, disease-specific survival, overall survival) [907].

In 2018, the American Society of Clinical Oncology (ASCO) published a guideline on the care of older patients who should receive chemotherapy [903]. In summary, patients 65 years of age and older should be referred to a GA to identify non-oncologic problems. At a minimum, a GA should include assessment of function,

secondary diseases, falls, depression, cognition and nutrition. Either the Cancer and Aging Research Group (CARG) tool or the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) should be used to assess the risk of experiencing adverse effects from the intended system therapy. The G8 Screening Test or Vulnerable Elders Survey-13 (VES-13) can be used to estimate the impact of frailty on mortality (2). Furthermore, a tool will be used to estimate life expectancy without considering oncologic prognosis. In summary, these measures bundled with the oncological situation should lead to an individualized indication of system therapy and furthermore non-oncological problems should be solved in an interdisciplinary way [903].

In 2020, Nadaraja et al. published a monocenter randomized study with 114 patients older than 70 years with gynecological, urological malignancies and non-small cell lung cancer [905]. In the standard arm, patients received system therapy as prescribed by the investigator. In the experimental trial arm, participants first received the G8 screening test and underwent geriatric assessment (GA) if abnormalities were detected, and then received system therapy. There was no difference with regard to the primary endpoint, protocol-compliant performance of indicated system therapy. Patients in the intervention arm showed a clinically but not statically significant lower rate of grade 3 and grade 4 adverse events (p=0.055). Performing GA led to intervention such as changing concomitant medication, initiating rehabilitation and nutritional counseling in 75% of patients. Four patients (8%) received system therapy at the dose-reduced dosage due to GA [905].

13 Supply structures

13.1 Preliminary remarks

Endometrial carcinoma is the most common genital carcinoma in women. The age of onset is unchanged at around 70 years. The incidence and mortality are slowly increasing. For endometrial carcinoma, there is no direct primary prevention and no secondary prevention. Risk reduction is possible only indirectly through behavioral variation with weight regulation. A number of women participating in the statutory cancer screening program for cervical carcinoma are randomly diagnosed with endometrial carcinoma.

In Germany, structures have been created to comprehensively regulate diagnostics, therapy and follow-up care, leading to better outcomes. These structures are continuously being developed: Goals to improve potential cancer prevention, further develop oncology care structures, ensure efficient oncology treatment and strengthen patient orientation have been included in the National Cancer Plan (http://www.bmg.bund.de/praevention/nationaler-krebsplan.html).

The need to evaluate the care situation in Germany was clearly recognized, as was the need for studies to survey long-term follow-up and the training situation.

The 10-year status quo of care data on patients with endometrial cancer treated in certified gynecologic cancer centers is now available (Kennzahlenauswertung 2020, https://www.onkozert.de/wordpress/wp-content/uploads/2020/04/qualitaetsindikatoren_gynaekologische-krebserkrankungen_2020-A1_200402.pdf?v=44353574). Based on the data now available, the strategies of the National Cancer Plan have been modified. However, there were no changes for endometrial cancer.

The data situation on the topic of care structures for women with endometrial carcinoma is still limited to a few studies. Clear evidence-based statements on the effects of care structures on patient-related outcome parameters in Germany are possible only to a limited extent.

13.2 Treatment in oncology centers

13.1	Consensus-based recommendation	checked 2022
EC	Patients with endometrial cancer should be treated by an interdisciplinary team. This team should include all necessary disciplines in a cross-sector network. This is most likely to be feasible in a certified center.	
	Strong Consensus	

13.2.1 Interdisciplinary and cross-sector care

The care of patients with suspected endometrial carcinoma or diagnosed endometrial carcinoma is an interdisciplinary and cross-sectoral task. In order to achieve an optimal treatment outcome for the patient, it is necessary that the various structures

and acting persons along the care chain work together in a coordinated, interdisciplinary and cooperative manner. [910], [911]. The basis for this care is the definition of centers established within the framework of the National Cancer Plan: “A network of qualified and jointly certified, interdisciplinary and trans-sectoral facilities (hospitals, medical practices, rehabilitation facilities), possibly spanning multiple locations, which, if professionally required, represent as far as possible the entire care chain for affected persons, forms a center” [910].

The work of the centers is based on the relevant organ cancer guidelines as well as the relevant cross-sectional guidelines (e.g., palliative care) of the German Guideline Program in Oncology.

Results of surveys in certified breast and colorectal cancer centers were able to show that the implementation of the center concept described has positive effects on the quality of care for patients in the certified networks from the point of view of the service providers [912], [913] and that patient satisfaction is also very high. [914], [915], [916]. In addition, evaluations of guideline-based quality indicators in certified centers show that the contents of the guidelines are well implemented and patients are treated in accordance with the guidelines [917].

In this system, the aim is to achieve high quality in prevention, diagnostics and therapy through to rehabilitation and palliation for the patient. To achieve this, processes and structures within the network must be optimized on an interdisciplinary and cross-sectoral basis. The 3-level center model with the formation of Organ Cancer Centers, Oncology Centers and Comprehensive Cancer Centers with cooperating partners (e.g. practices) at all levels of care is the basis for this high-quality care structure [910], [918].

Since 2008, Gynecologic Cancer Centers have been certified by the German Cancer Society (DKG) in cooperation with the German Society for Gynecology and Obstetrics (DGGG) and the Working Group for Gynecologic Oncology (AGO).

The 2020 key figure evaluation in the annual report of the Certified Gynecological Cancer Centers Audit Year 2019 – Key Figure Year 2018 (https://www.onkozert.de/wordpress/wp-content/uploads/2020/04/qualitaetsindikatoren_gynaekologische-krebserkrankungen_2020-A1_200402.pdf?v=44353574) shows 155 certified centers as of December 31, 2019. When the previous version was created, there were 100 certified centers (as of March 2014). This shows the continuous increase of certified centers since the beginning of certification in 2008.

The quality indicators of the present guideline are described in Chapter 14 .

Overall, between 43 to 50% of all gynecologic cancers are treated in certified centers [919]. In the meantime, due to the high treatment numbers, corresponding information on the implementation of the quality indicators of the individual guidelines is also available, so that a reflection of the individual data for the guideline commissions is possible. The gynecological tumors ovarian carcinoma, cervical carcinoma and endometrial carcinoma are all covered by S3 Guidelines from the German Guideline Program in Oncology. S2k Guidelines are available for vulvar carcinoma, vaginal carcinoma and other tumors (trophoblastic tumors and sarcomas). Thus, the diagnosis, therapy and follow-up of gynecological carcinomas are very well covered by recommendations and statements from guidelines.

Analogous to the breast cancer centers, the establishment of nationwide care is also aimed at, so that the care of patients with gynecological carcinomas takes place in a quality-assured, certified, interdisciplinary and cross-sectoral form. Especially due to the increasing number of new cases at the age of > 70 years with corresponding comorbidity, the interdisciplinary collaboration of proven and certified experts is even more important. Despite the overall good prognosis of endometrial carcinoma, it has now been shown that patients with endometrial carcinoma have a treatment advantage if they are treated by specialized gynecological oncologists [920], [921].

Since an invasive endometrial carcinoma is often already present at the time of diagnosis of endometrial hyperplasia with atypia in the curettage material or endometrial biopsy, treatment should already take place at a specialized center in the case of a primary diagnosis of endometrial hyperplasia with evidence of atypia [462]. Especially in more aggressive histological type, higher grading and advanced stage, treatment by specialized gynecologic oncologists results in a significant improvement of recurrence-free interval and overall survival [922].

Therefore, in certified centers, the qualitative and quantitative expertise of the treating physicians, for example via the subspecialisation Gynecologic Oncology [923], or the number of surgical and systemic therapies performed. [924]. Patients with endometrial carcinoma who are operated on at a center with a high number of cases have a lower mortality rate [924], [925]. Minimum case numbers are necessary to provide quality-assured care according to the current standard of care [924], [925]. Furthermore, a prompt start of therapy must be guaranteed in the treating gynecological cancer centers. A delay in therapy has been shown to have a negative impact on patient survival [926]. The goal must be that patients diagnosed with endometrial cancer have the opportunity to turn to centers that transparently present their quality and fulfill the corresponding criteria [910], [918], [927].

13.2.2 Center concept - Interdisciplinary tumor conferences

13.2	Consensus-based recommendation	checked 2022
EC	All patients with endometrial cancer shall be presented at an interdisciplinary tumor conference.	
	Strong Consensus	

Background

The interdisciplinary tumor conference is the central element for the necessary coordination of the different levels of care and patient-related decisions on diagnostics, therapy and follow-up, involving the various treatment partners. This is where decisions are made regarding the patient's diagnostic and therapeutic course of treatment. The determination of the interdisciplinary coordinated treatment concept for a patient with initial manifestation or new recurrence/metastases of endometrial carcinoma within the framework of this interdisciplinary tumor conference is considered a central prerequisite for achieving patient-related optimal oncological treatment results with the lowest possible morbidity at the same time. Therefore, the interdisciplinary tumor conference is a central point in the certification process. The interdisciplinary tumor conference for the treatment of patients with

endometrial carcinoma consists of at least one gynecological oncologist, pathologist, radiologist and radiation therapist present. Other disciplines are consulted as needed. These center structures must be funded in the health care system. Patient care should be focused on those units that offer the full spectrum of standard therapies, in order to provide comprehensive, quality-assured care for the patient here while making optimal use of limited resources. Resources should be used in a targeted manner, diagnostics and therapy should be in line with guidelines and quality should be verifiable through appropriate documentation [918], [927]. In December 2019, the G-BA (Joint Federal Committee) adopted nationwide quality requirements for the assumption of special tasks by hospitals in cutting-edge medicine. These tasks are to be financed via center surcharges, as they are services for other service providers or overarching tasks. Certified oncology centers have been a successful part of these deliberations and are thus eligible for surcharges.

13.2.3 Interdisciplinary supply chain

The first link in the care chain is the gynecologist in private practice, who identifies a patient with endometrial cancer either by an abnormal cytological or clinical finding in the course of the statutory cancer screening examinations or by the abnormal symptoms.

On April 3, 2013, the Act for the Further Development of Early Cancer Detection and for Quality Assurance through Clinical Cancer Registries (Krebsfrüherkennungs- und -Registergesetz (Cancer Early Detection and Register Act) – KFRG) was passed. As part of the law, among other objectives, two screening programs – namely for cervical carcinoma and colon carcinoma/rectal carcinoma – were established. As a result, people with statutory health insurance are entitled to participate in organized screening free of charge. After a gynecological examination and in the presence of a conspicuous cytological smear, a patient is given further histological clarification either on site or in a certified gynecological dysplasia consultation/unit, if appropriate expertise is available.

13.2.3.1 Consensus care algorithm of the Guideline Group

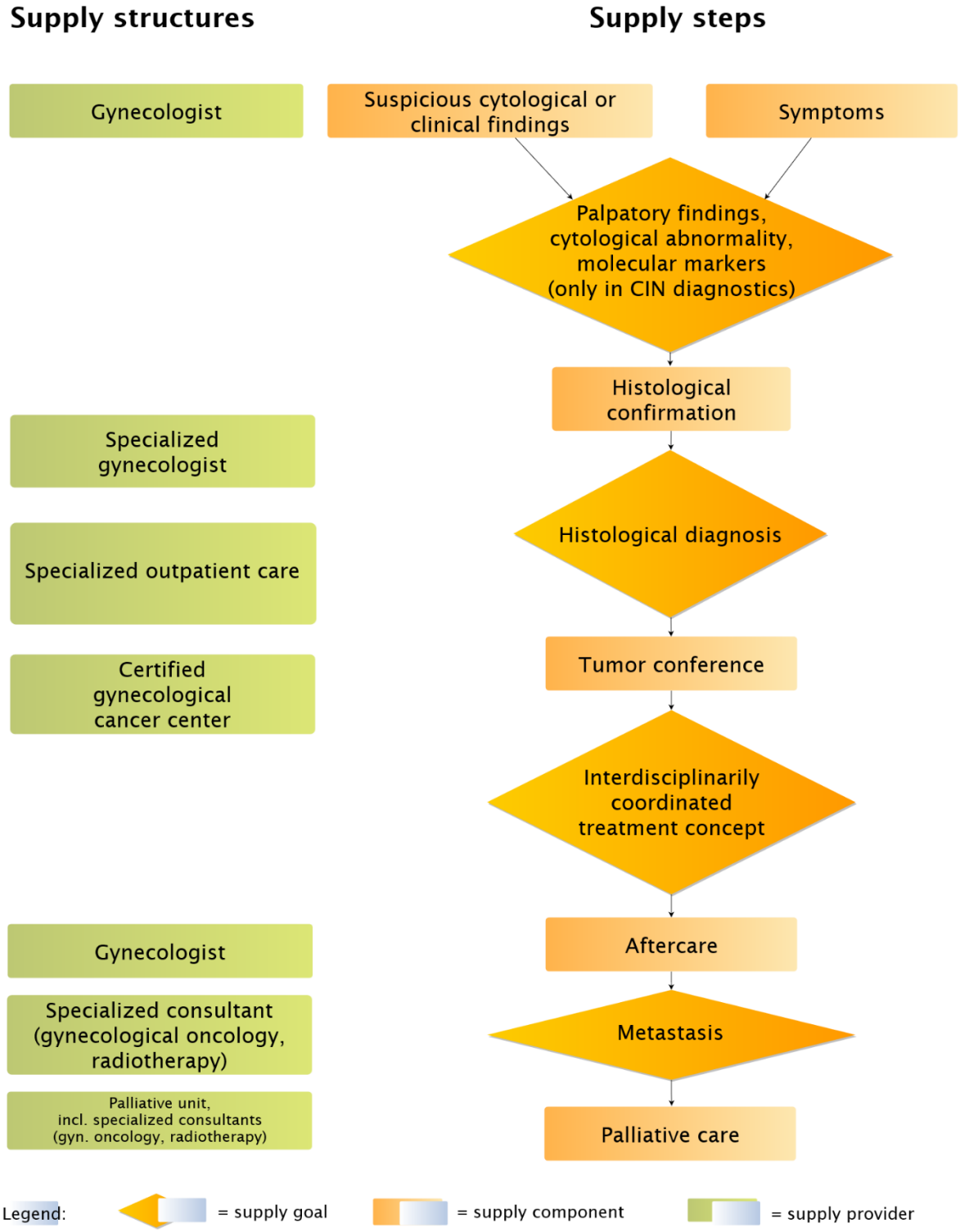


Figure 9: Care structures for the diagnosis and therapy of endometrial carcinoma

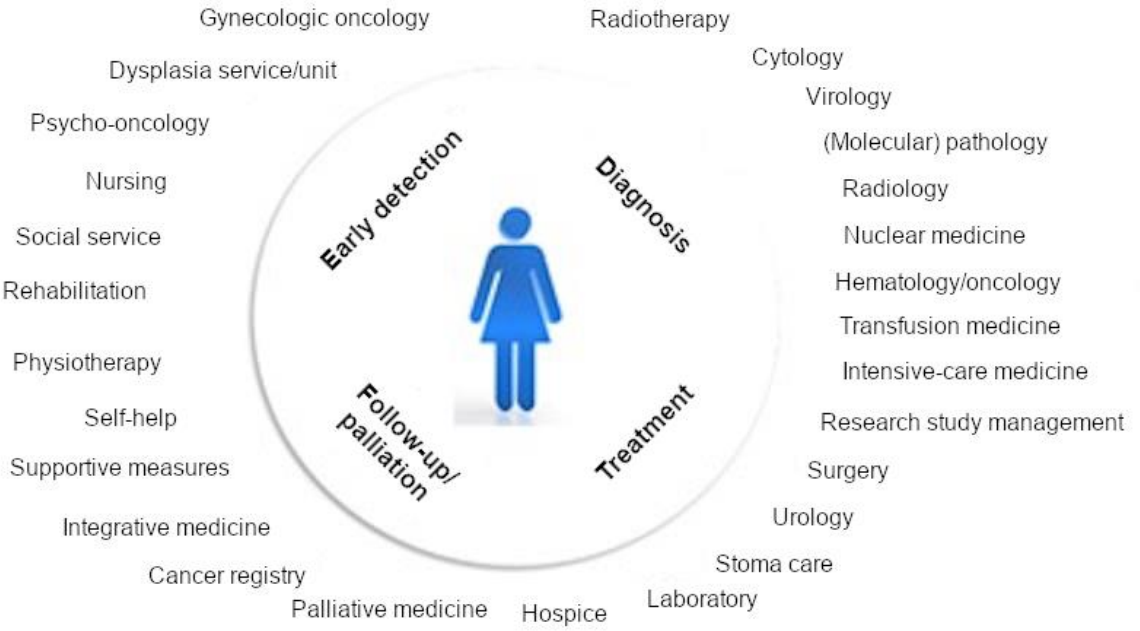


Figure 10: Treatment network in the certified Gynecological Cancer Center

Background

With histological confirmation of a suspected diagnosis and assessment of clinical tumor stage, a patient is referred to a unit that ensures the appropriate diagnostic and therapeutic options. For this purpose, the German Cancer Society (DKG), in cooperation with the German Society of Gynecology and Obstetrics (DGGG) and the Working Group for Gynecological Oncology (AGO), has established the certified Gynecological Cancer Centers [911], [910]. Certification ensures that interdisciplinary and intersectoral cooperation takes place, which determines the diagnostic and therapeutic algorithm for patients within the framework of the Interdisciplinary Tumor Conference. At present, only those units are certified and subsequently audited annually that present their treatment quality transparently and publicly.

If neoadjuvant or adjuvant drug therapy concepts are pursued, implementation is also possible within the certified network in the outpatient setting by specialized gynecologic oncologists (BNGO) or hematooncologists and internal oncologists (BNHO).

13.2.4 "Outpatient Specialized Medical Care"

Not all regions of Germany have a certified Gynecological Cancer Center. However, in order to ensure quality-assured care in such areas as well, so-called outpatient specialist care was created, in short "ASV" (from the German, "Ambulante Spezialfachärztliche Versorgung"). Here, too, specialized physicians from different disciplines work together in a team and jointly take over diagnostics and treatment. ASV is offered by hospitals, specialists in private practice and medical care centers.

13.2.5 Longitudinal documentation of patient history

The decisive factor in the entire care chain is that the information from the individual areas of care is collected and systematically documented in order to be able to make statements on process, structural and outcome quality that are relevant to care.

This approach is pursued by the Cancer Early Detection and Registry Act (KFRG), since a central data pooling is to take place here and thus data is collected both across sectors and across locations in order to then use it for the presentation of the quality of outcomes.

For this purpose, a basic data set is defined via the Data Efficient Uniform Tumor Documentation (DET) working group, initiated by the Federal Ministry of Health (BMG), with which the data are documented across sectors. This data set is revised on a regular basis. The basic data set also contains the data fields required for mapping the quality indicators relevant to planning, as well as quality assurance measures from the Joint Federal Committee (G-BA) or from the various sectors of the healthcare system's providers.

After the data has been entered by the providers, the necessary information is to be made available to the treating physicians and patients through central data documentation and evaluation by the clinical cancer registries of the federal states.

Due to the quality of the S3 Guidelines, it is possible to create corresponding quality indicators for the certification system and thus the verification for everyday care. Within the certification system of the gynecological cancer centers, corresponding quality indicators were taken from the Guidelines, which have been continuously reviewed over the past years. These results are fed back to the certification commission to see if any improvement or implementation has taken place in the context of day-to-day clinical care. In addition, however, recommendations for deletion or integration of new quality indicators into the certification system may be made by the Guideline Commission. The former, for example, in the case of standard value fulfillment over several years, at which point no further improvement in the quality of care can be achieved. The latter, if new current findings should be integrated into the daily patient care.

Thus, the system of certified gynecologic cancer centers, high-quality guidelines with their quality indicators and cancer registration in a quality cycle oncology functions in an exemplary manner. Through the progress of continuous development, this system supports the high-quality care of the patient with endometrial cancer.

These high-quality indicators also form the basis for IQTiG within the framework of the statutory quality assurance measures (see special Chapter 14).

13.2.6 Possibility for education and training

13.3	Consensus-based recommendation	checked 2022
EC	Physician education and training in the treatment of the patient with endometrial cancer should be provided at a Gynecologic Cancer Center/Oncology Center.	
	Strong Consensus	

The Guideline Group is not aware of any meta-analyses, randomized trials or observational studies on the specific training and continuing education situation for endometrial cancer in Germany. Training and continuing education generally take place as a specialist in the field or in specialized training. The overall comprehensive topic is the treatment of gynecological malignancies, for which treatment principles are often similar.

The training of physicians treating patients with endometrial carcinoma should focus on certified networks in order to ensure a high quality of training with regard to the implementation of the Guideline and the latest standards through high case numbers, interdisciplinarity and bundling of competencies [910], [918], [927]. The basic prerequisite is the guidelines laid down in the 2004 regulations for further training on the number of services that must be provided as part of specialist further training, specialist further training and/or facultative further training. The performance of major surgical interventions as part of the advanced training in gynecological oncology or the disease-specific chemotherapies as part of the additional training in drug-based tumor therapy can be provided only where a minimum number of patients with this clinical picture are treated on an interdisciplinary basis by physicians with corresponding further training or qualification requirements and proven oncological experience. The current high number of specialists and focal point holders in the various areas of care currently makes comprehensive care possible. However, the number of further training authorizations is stagnating or has declined slightly in recent years. It is becoming apparent that in the future the number of persons in specialized training will be smaller and thus the future care of patients with gynecological carcinomas will become more difficult [923], [927].

14 Quality indicators

Quality indicators are measured variables whose collection serves to assess the quality of the underlying structures, processes or results. Quality indicators are an important quality management tool. The aim of their use is the continuous improvement of care by presenting the results of care, critically reflecting on them and improving them if necessary. The present selection of quality indicators was created according to the methodology of the German Guideline Program in Oncology [928]. For the derivation process, a "Quality Indicators Working Group" (AG QI) was constituted. This created the final set of quality indicators based on the already existing quality indicators of the Guideline in Endometrial Cancer 2018, the new strong recommendations ("should") of the updated guideline Endometrial Cancer, the results of the existing quality indicators from the certified gynecological cancer centers of the German Cancer Society and the results of the search for existing national and international quality indicators. The exact procedure and composition of the WG QI are outlined in the Guideline Report.
After two online meetings of this working group, 5 new quality indicators (QIs) were defined and adopted, so that the final set consists of 9 QIs.

The numerator is always a subset of the denominator.
Quality indicators 2, 3, 4, 8, and 9 are to be documented with the oncology baseline data set of the cancer registries (as of 05/2022).

Table 16: Quality indicators

Quality Indicator	Reference recommendation	Evidence basis / Additional information
QI 1: No LNE for endometrial cancer c/pT1a, G1/2, cN0, LVSI neg. (modified 2022).		
Numerator Female patients of the denominator with systematic LNE **Denominator** All patients with initial diagnosis of endometrial cancer, c/p T1a, G1/G2, cN0, LVSI neg.	Recommendation 6.5 In low-risk type I endometrial carcinoma pT1a, G1/2, no bulky nodes, systematic lymphadenectomy shall not be performed.	EC A, LoE 1 Quality Objective: No systematic lymphadenectomy for endometrial cancer c/p T1a, G1/G2, cN0, LVSI neg.
QI 2: No adjuvant chemotherapy for type I endometrial cancer stage pT1a/b, G1 or G2, cN0/pNsn0 p53-wt (modified 2022).		
Numerator Patients of the denominator with adjuvant chemotherapy. **Denominator**	Recommendation 8.2 Patients with primary type I endometrial carcinoma stage pT1a/b G1 and G2 cN0/ pNsn0, p53-wt, shallnot	EC, strong consensus Quality Objective: No adjuvant chemotherapy for type I endometrial carcinoma pT1a/b

Quality Indicator	Reference recommendation	Evidence basis / Additional information
All patients with initial diagnosis of endometrioid or other type I endometrial cancer (ICD-0: 8380/3, 8570/3, 8263/3, 8382/3, 8480/3), pT1a/b G1 cN0/pNsn0 p53-wt or pT1a/b G2 cN0/pNsn0, p53-wt	receive adjuvant chemotherapy.	G1 cN0/pNsn0 p53-wt o. pT1a/b G2 cN0/pNsn0 p53-wt

QI 3: Social service counseling

Numerator Number of patients with counseling by social services **Denominator** All patients with initial diagnosis of endometrial cancer and treatment at the facility.	Recommendation 11.15 Medical-oncological rehabilitation serves the specific treatment of disease and therapy sequelae. All patients with endometrial carcinoma shall be informed and advised about the legal options for applying for and receiving rehabilitation services.	EC, consensus Quality objective: Consultations by social services as frequently as possible

QI 4: Presentation at the tumor conference (modified 2022)

Participating tumor conference: surgeon, radiologist, pathologist, radiation oncologist, gynecologic oncologist, medical oncologist (if system therapy is performed by medical I oncologist).

Numerator Patients of the denominator with presentation in the tumor conference **Denominator** All patients with endometrial cancer	Recommendation 13.2 All patients with endometrial cancer shallbe presented at an interdisciplinary tumor conference.	EC, strong consensus Quality objective: Presentation of patients at the tumor conference as often as possible

QI 5: Immunohistochemical determination of p53 and the MMR proteins (new 2022)

Numerator Patients of the denominator with immunohistochemical determination of p53 and the MMR proteins	Recommendation 4.39 In all histologically diagnosed primary EC, immunohistochemical determination of p53 as well	EC A, LoE 4 Quality objective: Determination of p53 and MMR proteins as frequently as possible.

Quality Indicator	Reference recommendation	Evidence basis / Additional information
Denominator All patients with histologically confirmed diagnosis of endometrial carcinoma (incl. M1).	as MMR proteins shall be performed.	

QI 6: POLE investigation (new 2022)

Numerator Female patients of the denominator with POLE examination **Denominator** All patients with initial diagnosis of endometrial cancer >pT1a and/or G3 and/or p53-abn and/or LVSI pos. and/or MSI/MMR pos. or initial diagnosis of type 2 endometrial cancer (serous, clear cell, carcinosarcoma) (ICD-0: 8441/3, 8441/2; 8310/3; 8950/3)	Recommendation 4.40 In G3 or in intermediate, high intermediate, and high-risk EC, mutational analysis of the exonuclease domain of POLE shall be performed.	EC A, LoE 4 Quality objective: POLE examination as often as possible

QI 7: Postoperative vaginal brachytherapy alone (new 2022)

Numerator Denominator patients with postoperative vaginal brachytherapy alone **Denominator** All patients with initial diagnosis of endometrial cancer stage pT1b, G1 or G2 pNX/0, p53-wt, L1CAM negative, without extensive LVSI with surgery	Recommendation 7.5 In stage pT1b, G1 or G2 pNX/0 and in stage pT1a (with myometrial involvement), G3 pNX/0, endometrioid endometrial carcinoma (type I), p53-wt, L1CAM negative, no extensive LVSI, postoperative vaginal brachytherapy alone shall be performed.	EC A, LoE 2 Quality objective: Vaginal brachytherapy alone as often as possible

Quality Indicator	Reference recommendation	Evidence basis / Additional information
QI 8: Percutaneous radiotherapy with simultaneous chemotherapy (PORTEC 3 regimen) (new 2022).		
Numerator Patients of the denominator with concurrent chemotherapy (PORTEC 3 regimen) **Denominator** All patients with initial diagnosis of endometrioid (morphology code: 8380/3) endometrial carcinoma pT1b or pT2, p53-abn, POLE-wt and percutaneous radiotherapy	Recommendation 7.12 Patients with endometrioid endometrial carcinoma (type1) stage pT1b and pT2 p53-abn, POLE-wt shall receive percutaneous radiotherapy in combination with chemotherapy (PORTEC 3 regimen).	EC A, LoE 3 Quality objective: Simultaneous chemotherapy as often as possible (PORTEC 3 regimen)
QI 9: Adjuvant chemotherapy with carboplatin and paclitaxel (new 2022)		
Numerator Patients of the denominator with chemotherapy with carboplatin and paclitaxel **Denominator** Patients with initial diagnosis of endometrial cancer and adjuvant chemotherapy	Recommendation 8.10 Adjuvant chemotherapy for endometrial cancer shall be given with carboplatin AUC 6 and paclitaxel 175 mg per square meter. After percutaneous radiotherapy, carboplatin AUC 5 should be dosed.	EC A, LoE 2 Quality objective: Adjuvant chemotherapy with carboplatin and paclitaxel as often as possible.

15 Research questions

The Guideline Group members first call attention to the consistent support of the recruiting study (ECLAT) on the therapeutic relevance of systematic lymphonodectomy, as an RCT-level reult is achievable here.

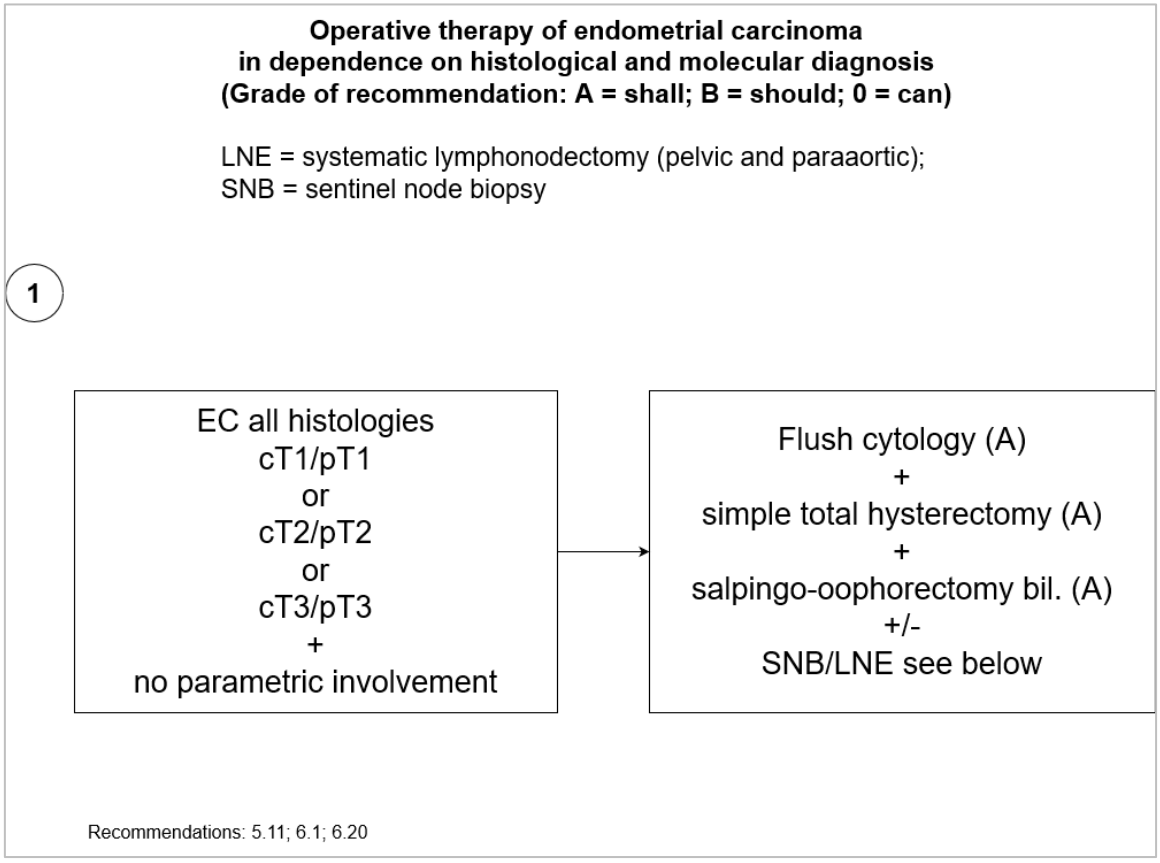
For more information, see: https://ago-ovar.de/profil/offene-studien/

In reviewing the systematically searched literature, the Guideline Group members found the following questions that should be answered by high-quality studies in the future:

- Evaluation of the prognostic and predictive relevance of the new molecular classification of endometrial cancer.
  Since RCTs on this topic are rather unlikely, prospective cohort studies, for example in the context of registries of certified gynecologic cancer centers, seem to be a reasonable option.
- The risk of progression of complex, non-atypical endometrial hyperplasia should be recorded more precisely (registries).
- The prognostic and predictive relevance (response, progression, recurrence) of molecular classification for fertility-preserving therapy of women with atypical endometrial hyperplasia and early endometrial cancer should be evaluated retrospectively (evaluation of existing collectives) and prospectively (registry).
- The prognostic, predictive and therapeutic relevance of sentinel node biopsy should ideally be evaluated by RCTs. However, these seem rather unrealistic. Therefore, high-quality prospective registry studies (see above) should be aimed for.
- Evaluation of the oncological safety of minimally invasive surgical methods (laparoscopy, robotic) at least by high-quality prospective registry studies.
- Evaluation of the role of surgical tumor reduction, palliative hysterectomy and prior neoadjuvant chemotherapy in advanced endometrial cancer (registry).
- Evaluation of the optimal sequence of adjuvant (chemo)radiotherapy and adjuvant chemotherapy.
- Evaluation of combination chemo- plus percutaneous radiotherapy versus chemo- plus vaginal brachytherapy.
- Evaluation of risk-adapted follow-up concepts.
- Evaluation of new drug therapy concepts (e.g. trastuzumab, immune checkpoint inhibitors) in RCTs.
- Evaluation of the detection rate of germline mutations of MMR genes as a consequence of the systematic implementation of molecular classification of endometrial carcinomas.
- Evaluation of the value of preventive hysterectomies ± adnexal extirpations in women with Lynch syndrome.
- Evaluation of palliative care (APV [outpatient palliative care] and SPV [specialized palliative care]).

16 Appendix

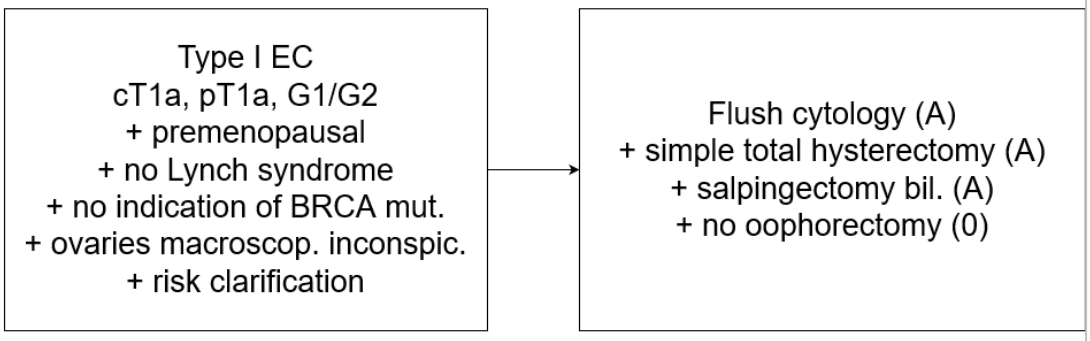
16.1 Action guiding algorithms



Operative therapy of endometrial carcinoma
in dependence on histological and molecular diagnosis
(Grade of recommendation: A = shall; B = should; 0 = can)

LNE = systematic lymphonodectomy (pelvic and paraaortic);
SNB = sentinel node biopsy

2

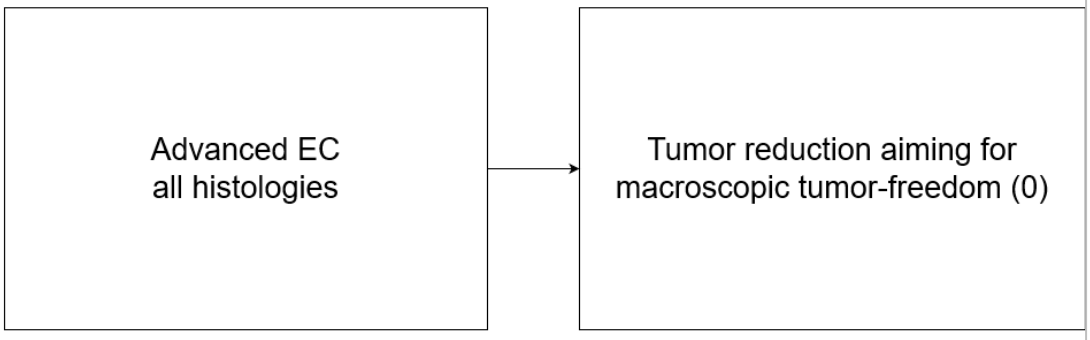


Recommendation: 5.12; Recommendations for proceeding if children are desired 5.13 - 5.22

Operative therapy of endometrial carcinoma
in dependence on histological and molecular diagnosis
(Grade of recommendation: A = shall; B = should; 0 = can)

LNE = systematic lymphonodectomy (pelvic and paraaortic);
SNB = sentinel node biopsy

3

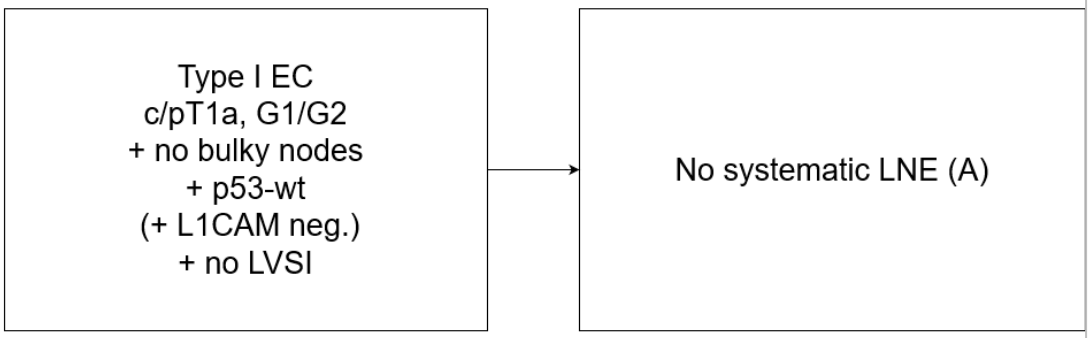


Recommendations: 6.20; 6.21

Operative therapy of endometrial carcinoma
in dependence on histological and molecular diagnosis
(Grade of recommendation: A = shall; B = should; 0 = can)

LNE = systematic lymphonodectomy (pelvic and paraaortic);
SNB = sentinel node biopsy

4

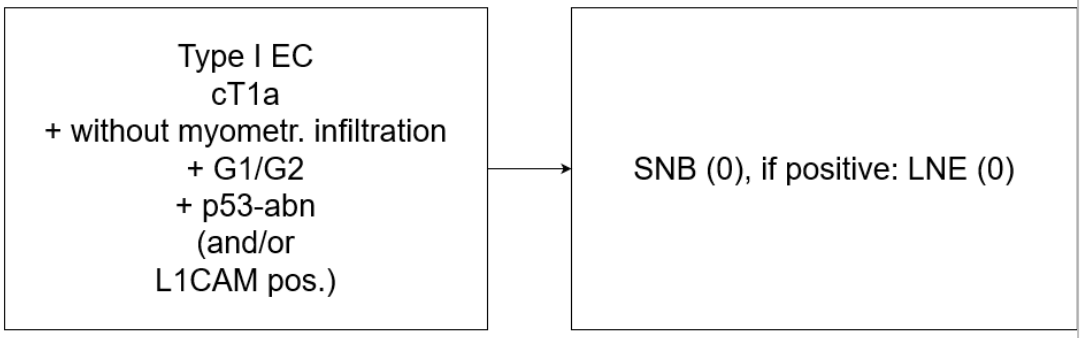


Recommendation 6.5

Operative therapy of endometrial carcinoma
in dependence on histological and molecular diagnosis
(Grade of recommendation: A = shall; B = should; 0 = can)

LNE = systematic lymphonodectomy (pelvic and paraaortic);
SNB = sentinel node biopsy

5

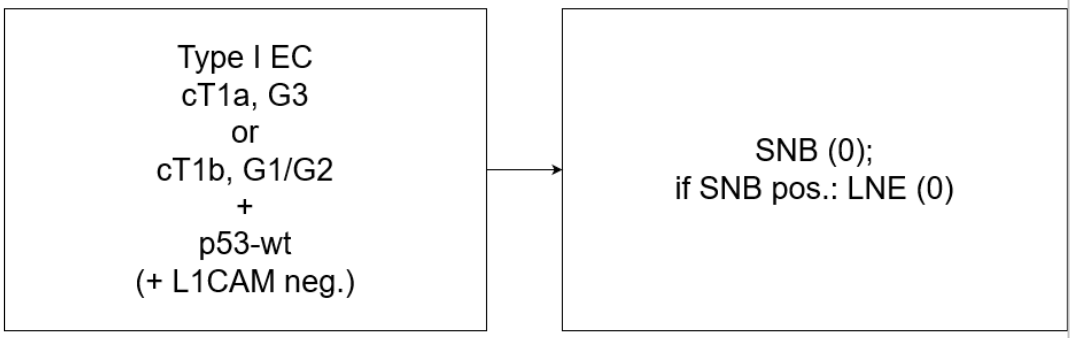


Recommendation 6.6

Operative therapy of endometrial carcinoma
in dependence on histological and molecular diagnosis
(Grade of recommendation: A = shall; B = should; 0 = can)

LNE = systematic lymphonodectomy (pelvic and paraaortic);
SNB = sentinel node biopsy

6

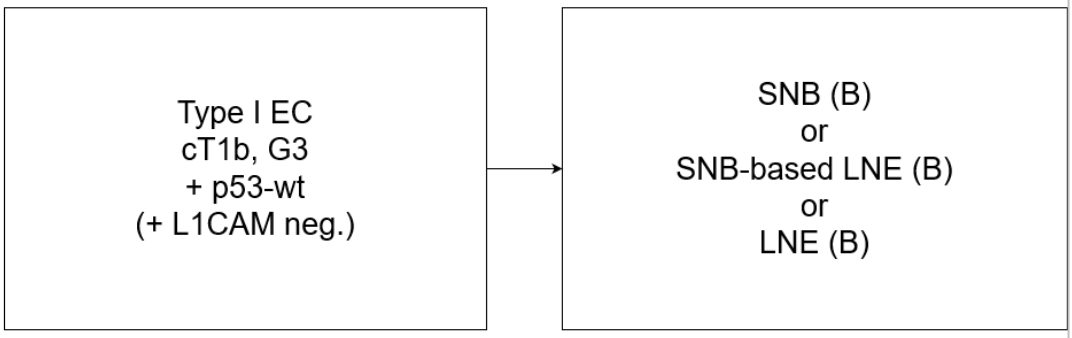


Recommendation 6.7

Operative therapy of endometrial carcinoma
in dependence on histological and molecular diagnosis
(Grade of recommendation: A = shall; B = should; 0 = can)

LNE = systematic lymphonodectomy (pelvic and paraaortic);
SNB = sentinel node biopsy

7

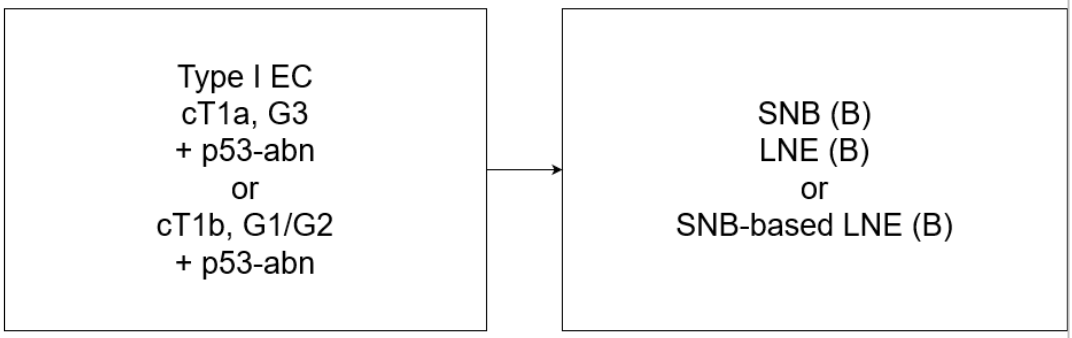


Recommendation 6.8

Operative therapy of endometrial carcinoma
in dependence on histological and molecular diagnosis
(Grade of recommendation: A = shall; B = should; 0 = can)

LNE = systematic lymphonodectomy (pelvic and paraaortic);
SNB = sentinel node biopsy

8

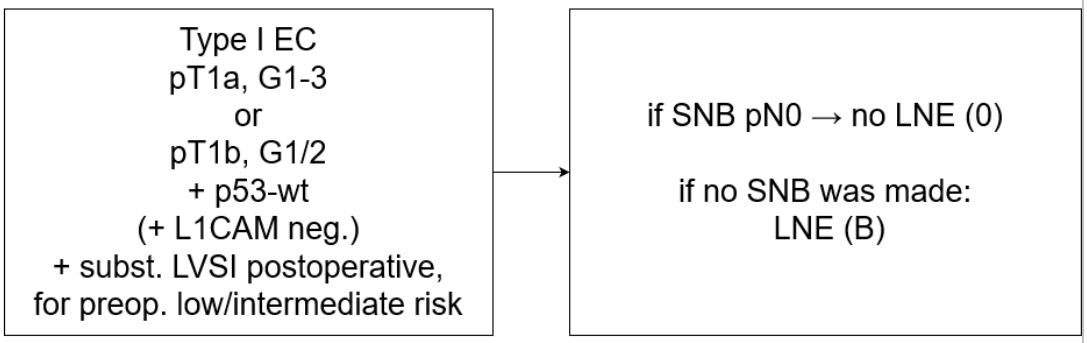


Recommendation 6.9

Operative therapy of endometrial carcinoma
in dependence on histological and molecular diagnosis
(Grade of recommendation: A = shall; B = should; 0 = can)

LNE = systematic lymphonodectomy (pelvic and paraaortic);
SNB = sentinel node biopsy

9



Recommendation 6.10

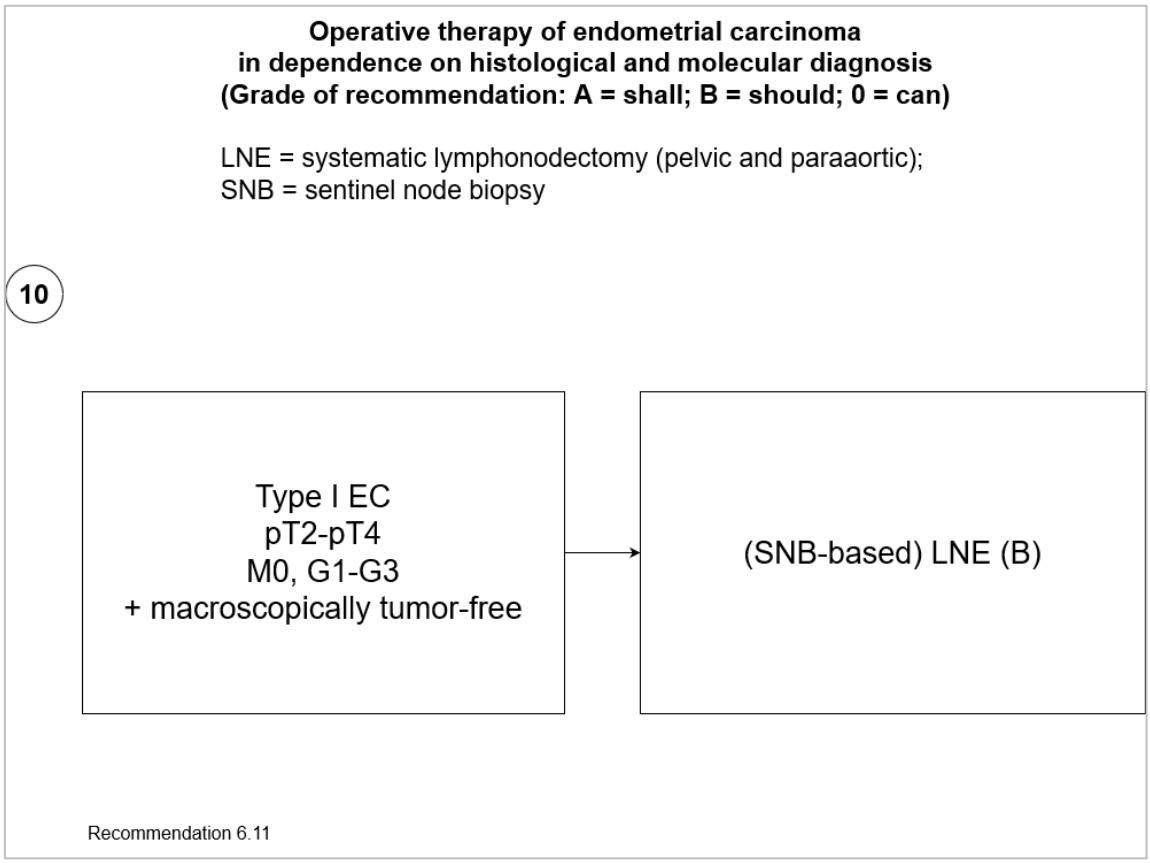
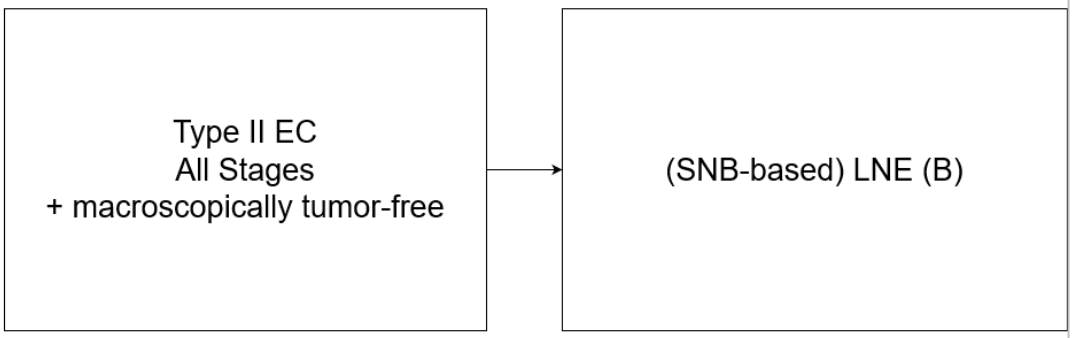


Figure 11: Action guiding algorithms 1-10

Operative therapy of endometrial carcinoma
in dependence on histological and molecular diagnosis
(Grade of recommendation: A = shall; B = should; 0 = can)

LNE = systematic lymphonodectomy (pelvic and paraaortic);
SNB = sentinel node biopsy

11

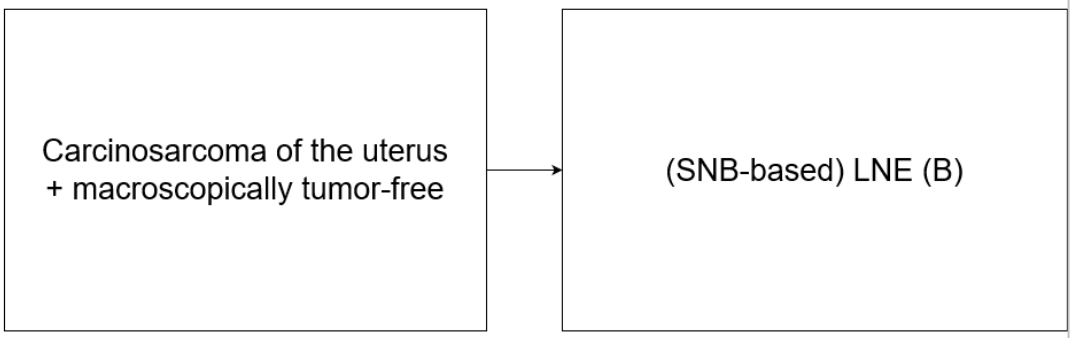


Recommendation 6.13

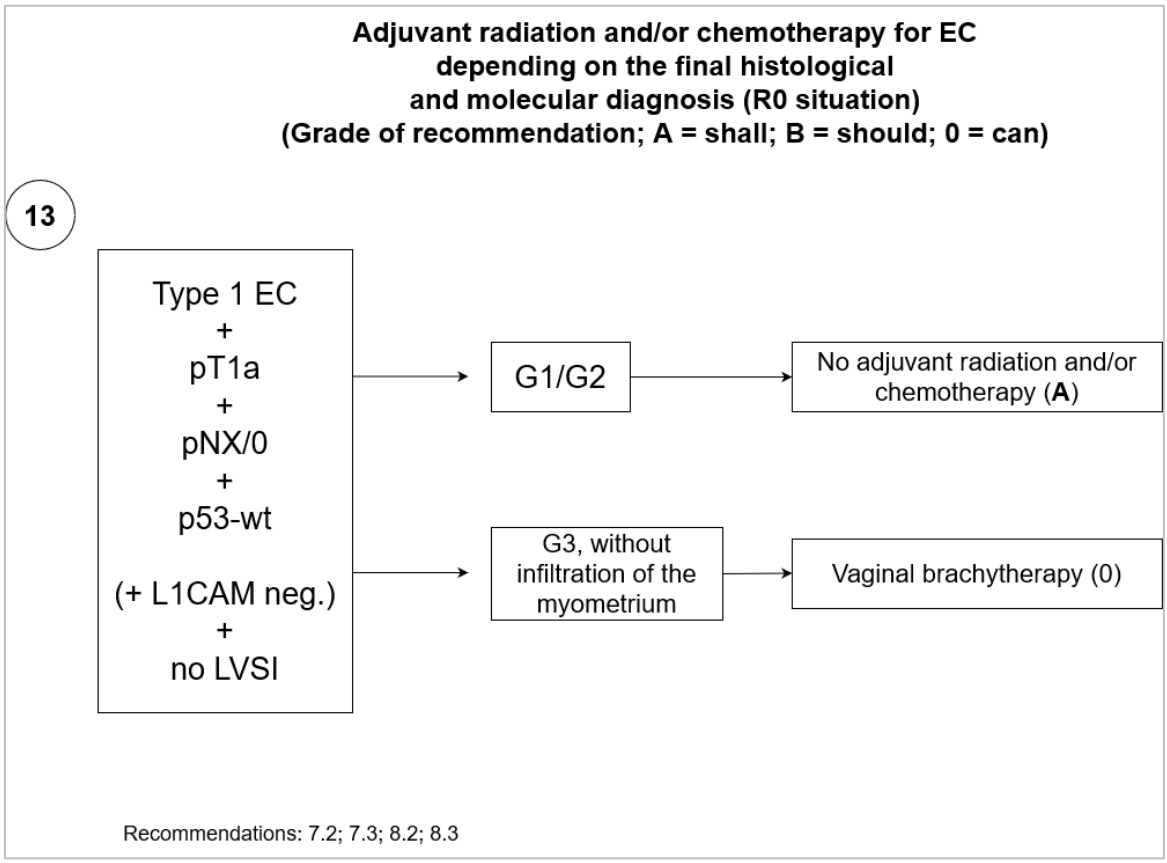
Operative therapy of endometrial carcinoma
in dependence on histological and molecular diagnosis
(Grade of recommendation: A = shall; B = should; 0 = can)

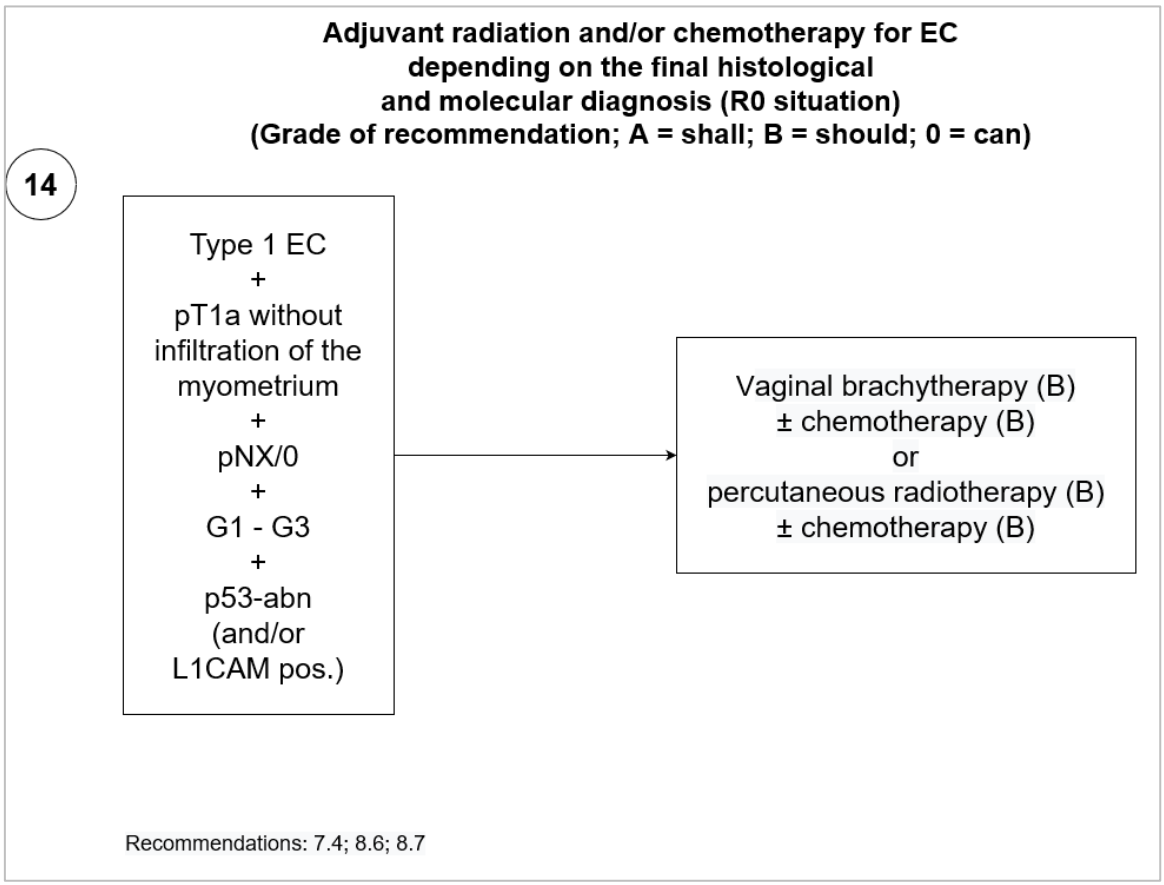
LNE = systematic lymphonodectomy (pelvic and paraaortic);
SNB = sentinel node biopsy

12



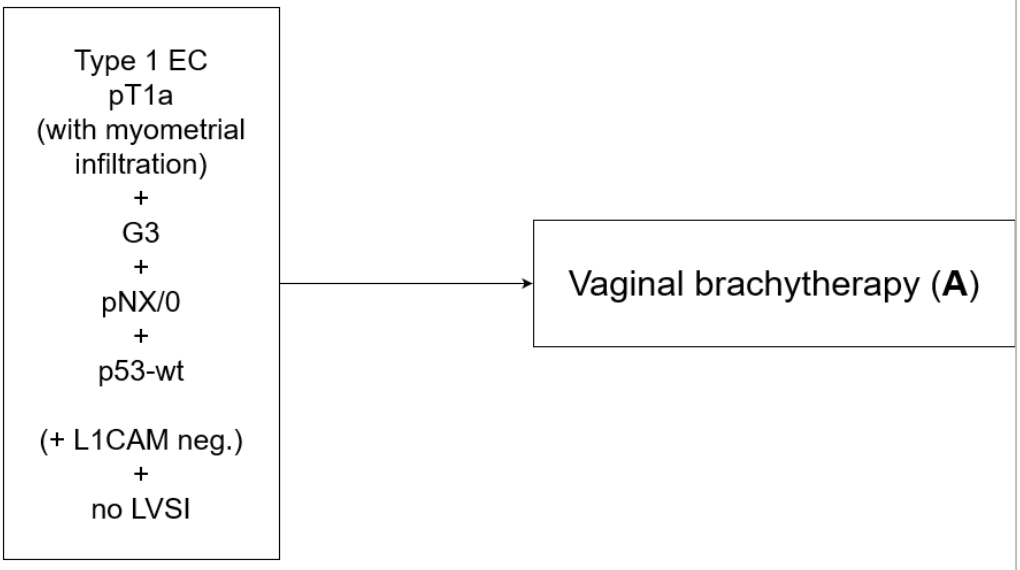
Recommendation 6.15


Adjuvant radiation and/or chemotherapy for EC
depending on the final histological
and molecular diagnosis (R0 situation)
(Grade of recommendation; A = shall; B = should; 0 = can)
13
Type 1 EC
+
pT1a
+
pNX/0
+
p53-wt
(+ L1CAM neg.)
+
no LVSI
G1/G2
No adjuvant radiation and/or chemotherapy (A)
G3, without infiltration of the myometrium
Vaginal brachytherapy (0)
Recommendations: 7.2; 7.3; 8.2; 8.3


Adjuvant radiation and/or chemotherapy for EC
depending on the final histological
and molecular diagnosis (R0 situation)
(Grade of recommendation; A = shall; B = should; 0 = can)
14
Type 1 EC
+
pT1a without infiltration of the myometrium
+
pNX/0
+
G1 - G3
+
p53-abn
(and/or
L1CAM pos.)
Vaginal brachytherapy (B)
± chemotherapy (B)
or
percutaneous radiotherapy (B)
± chemotherapy (B)
Recommendations: 7.4; 8.6; 8.7

Adjuvant radiation and/or chemotherapy for EC depending on the final histological and molecular diagnosis (R0 situation) (Grade of recommendation; A = shall; B = should; 0 = can)

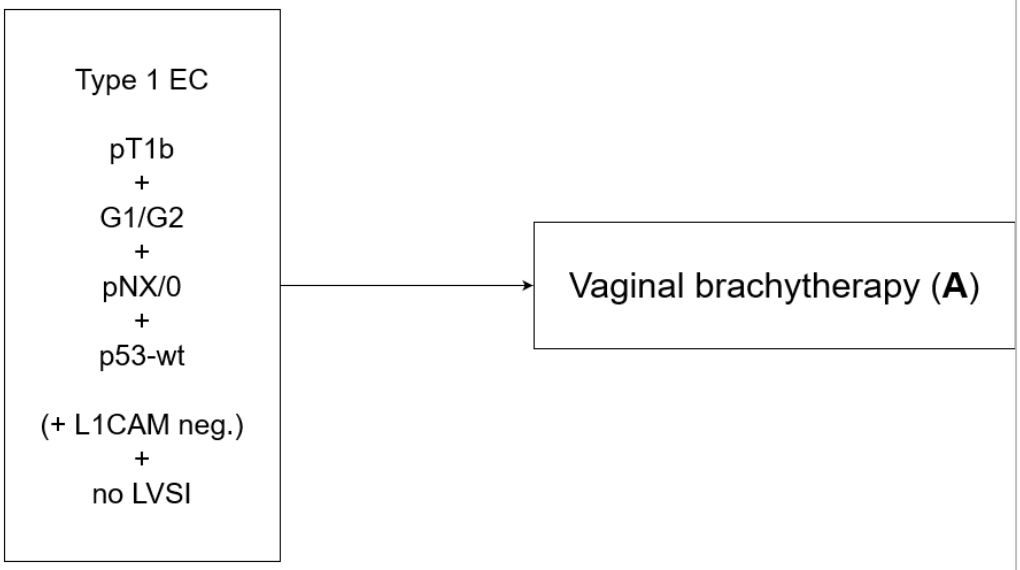
15



Recommendations: 7.5; 8.3

Adjuvant radiation and/or chemotherapy for EC depending on the final histological and molecular diagnosis (R0 situation) (Grade of recommendation; A = shall; B = should; 0 = can)

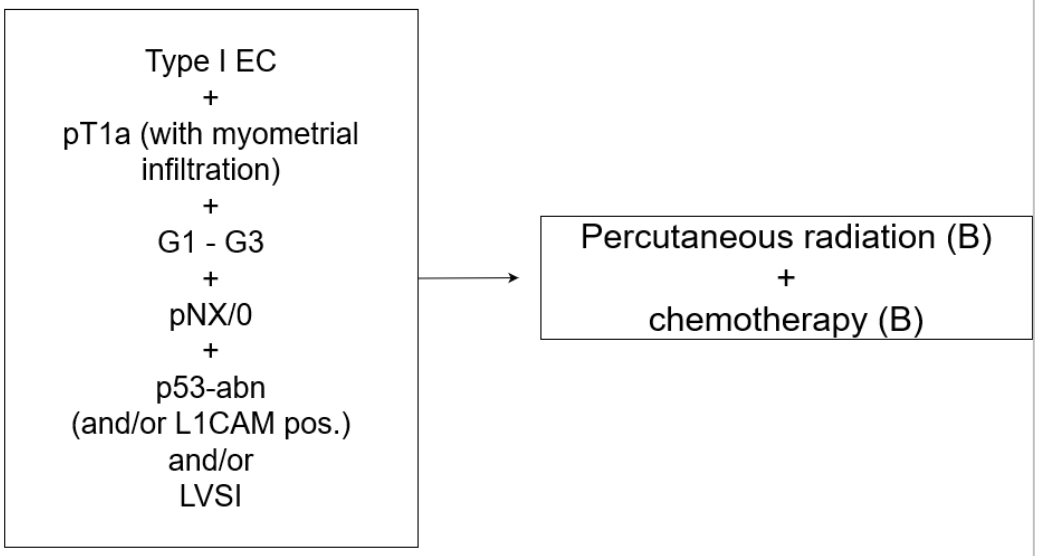
16



Recommendation 7.5

Adjuvant radiation and/or chemotherapy for EC depending on the final histological and molecular diagnosis (R0 situation) (Grade of recommendation; A = shall; B = should; 0 = can)

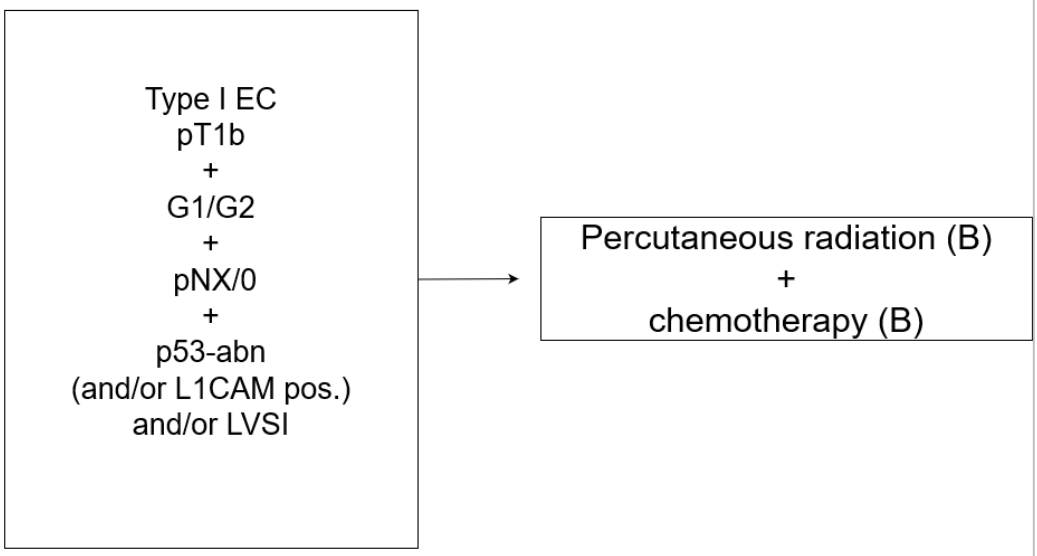
17



Recommendations: 7.6; 7.7; 8.6; 8.7

Adjuvant radiation and/or chemotherapy for EC depending on the final histological and molecular diagnosis (R0 situation) (Grade of recommendation; A = shall; B = should; 0 = can)

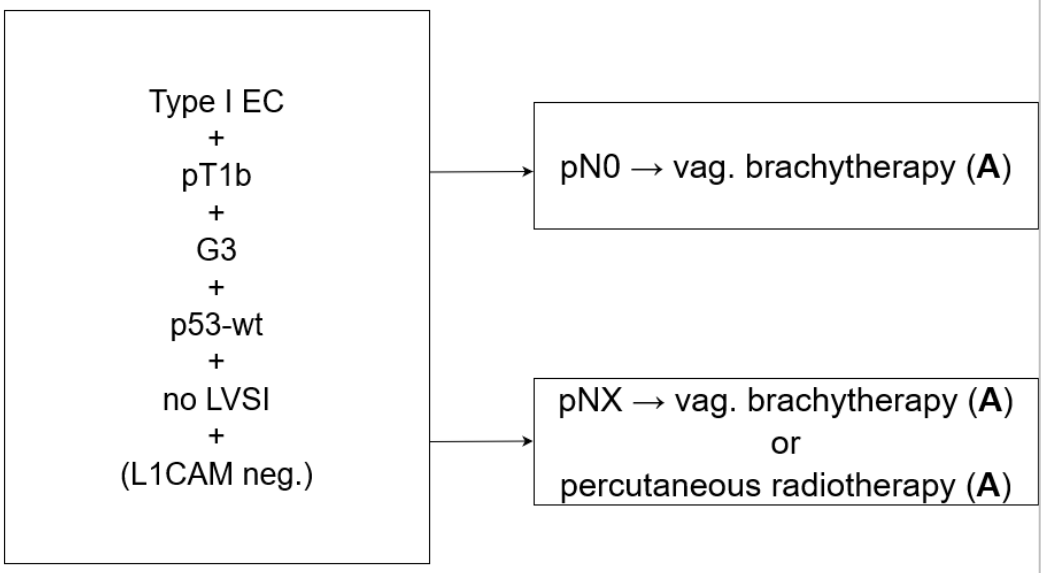
18



Recommendations: 7.6; 7.7; 8.6; 8.7

Adjuvant radiation and/or chemotherapy for EC depending on the final histological and molecular diagnosis (R0 situation) (Grade of recommendation; A = shall; B = should; 0 = can)

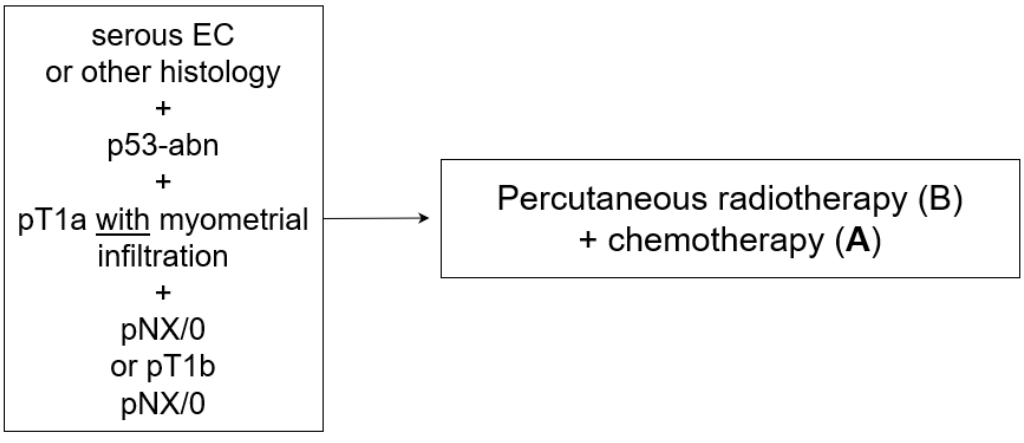
19



Recommendations: 7.8; 7.10

Adjuvant radiation and/or chemotherapy for EC depending on the final histological and molecular diagnosis (R0 situation) (Grade of recommendation; A = shall; B = should; 0 = can)

20



Recommendations: 7.6; 7.7; 7.12; 8.6; 8.7

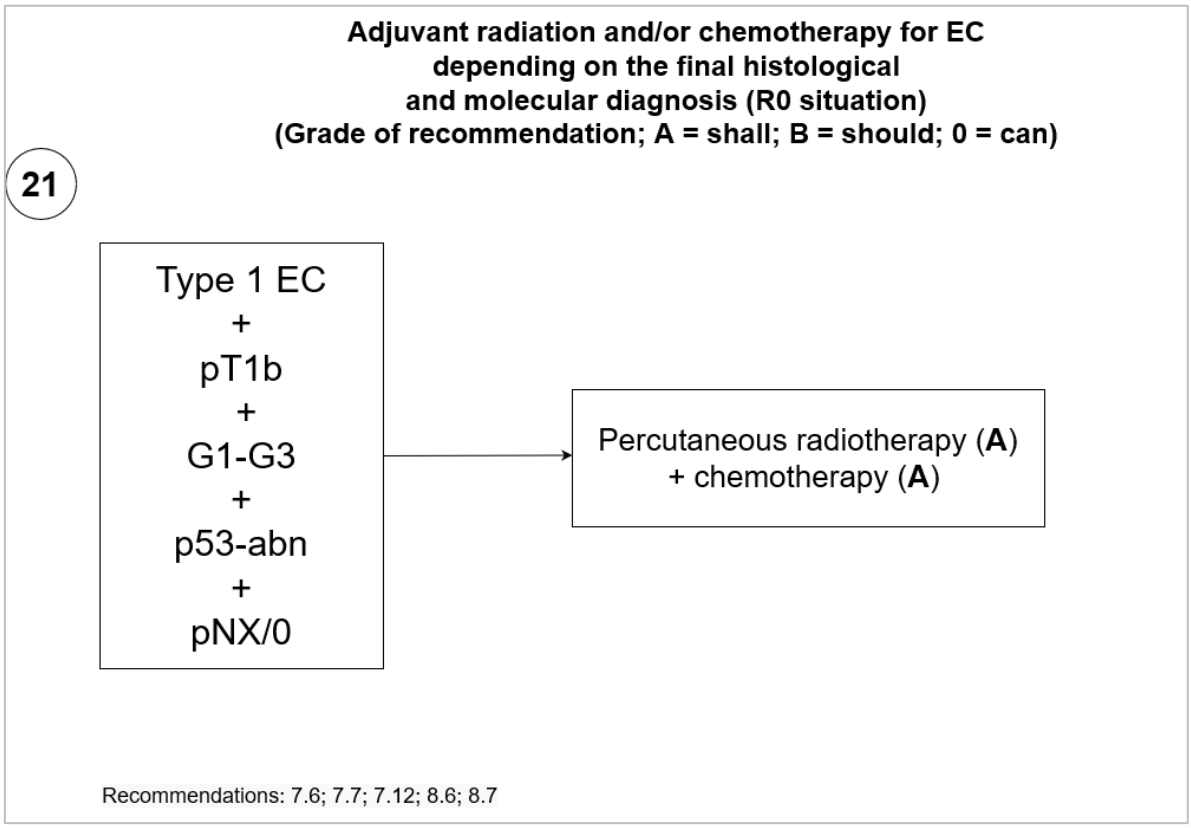
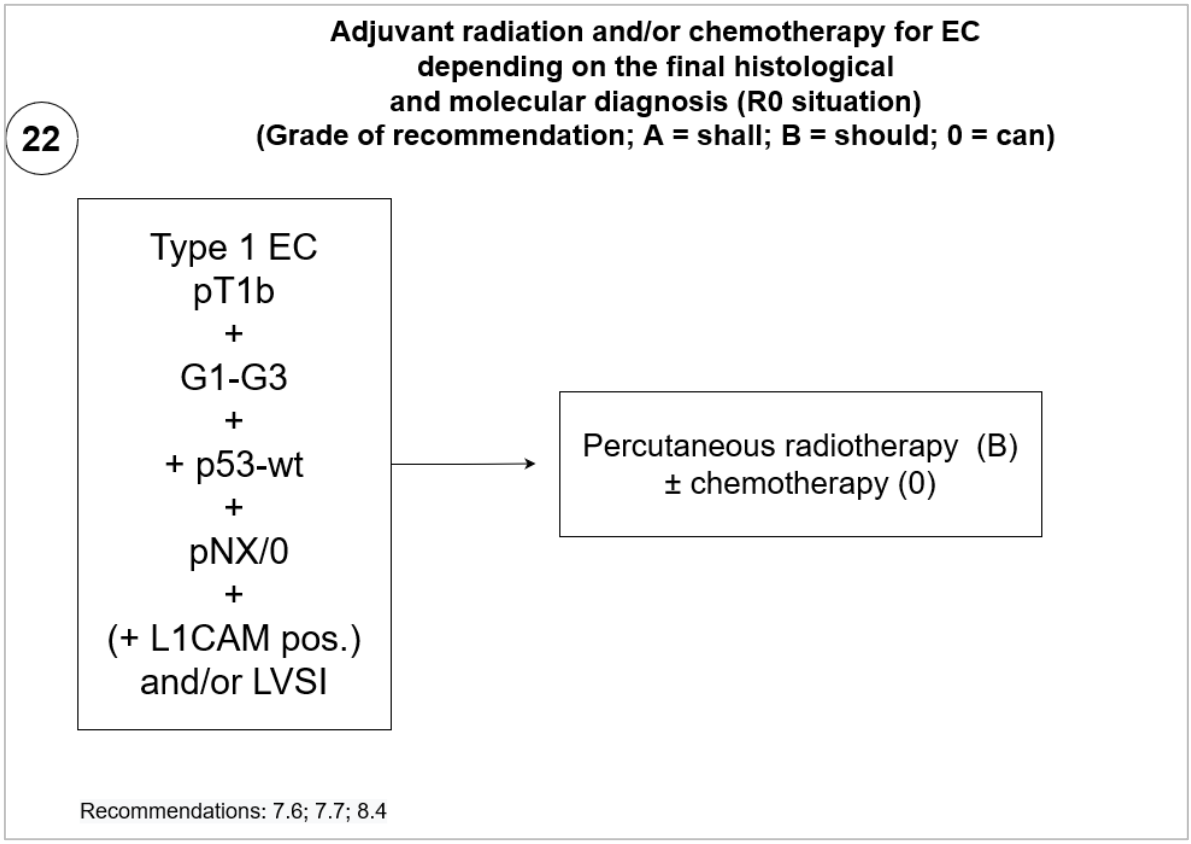
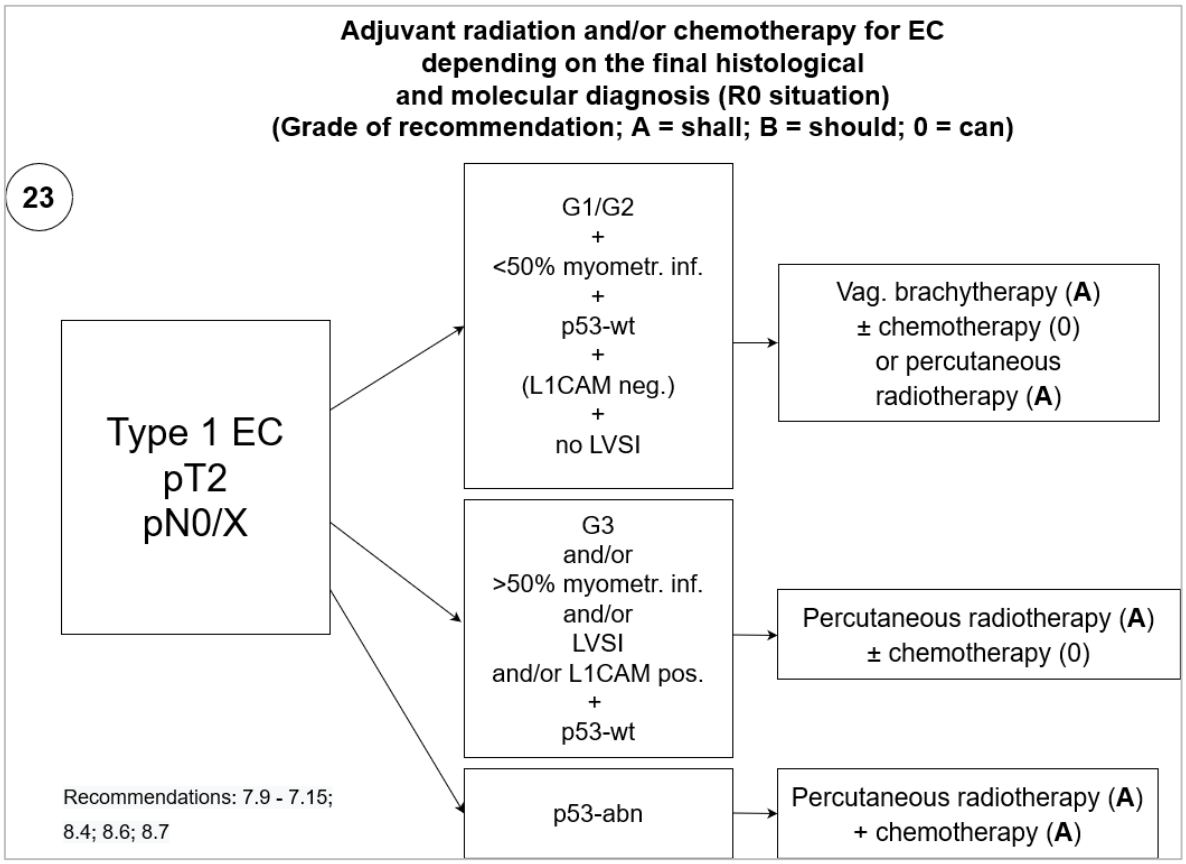
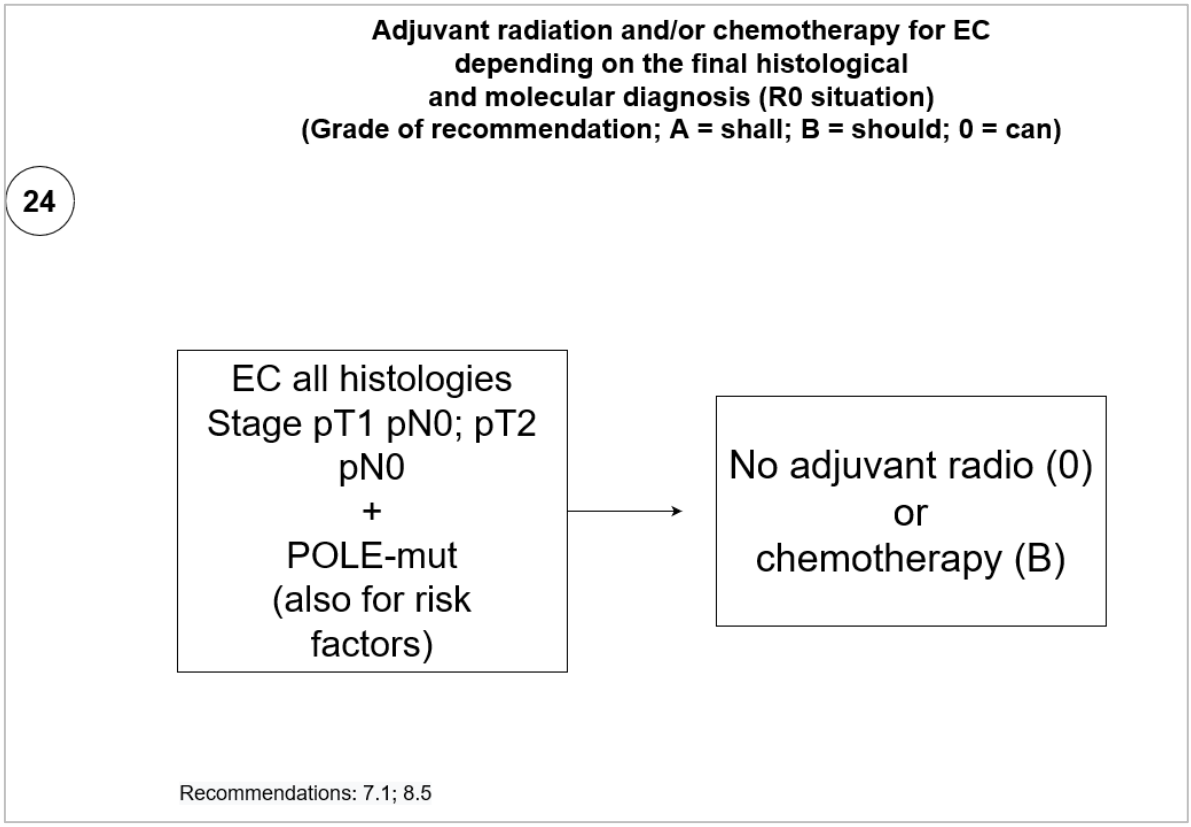


Figure 12: Action guiding algorithms 11-20

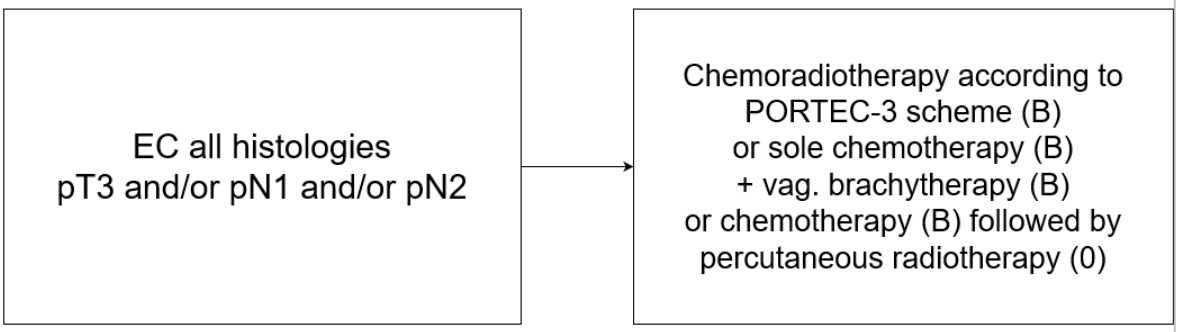



Adjuvant radiation and/or chemotherapy for EC
depending on the final histological
and molecular diagnosis (R0 situation)
(Grade of recommendation; A = shall; B = should; 0 = can)
23
Type 1 EC
pT2
pN0/X
G1/G2
+
<50% myometr. inf.
+
p53-wt
+
(L1CAM neg.)
+
no LVSI
Vag. brachytherapy (A)
± chemotherapy (0)
or percutaneous
radiotherapy (A)
G3
and/or
>50% myometr. inf.
and/or
LVSI
and/or L1CAM pos.
+
p53-wt
Percutaneous radiotherapy (A)
± chemotherapy (0)
p53-abn
Percutaneous radiotherapy (A)
+ chemotherapy (A)
Recommendations: 7.9 - 7.15;
8.4; 8.6; 8.7


Adjuvant radiation and/or chemotherapy for EC
depending on the final histological
and molecular diagnosis (R0 situation)
(Grade of recommendation; A = shall; B = should; 0 = can)
24
EC all histologies
Stage pT1 pN0; pT2
pN0
+
POLE-mut
(also for risk
factors)
No adjuvant radio (0)
or
chemotherapy (B)
Recommendations: 7.1; 8.5

Adjuvant radiation and/or chemotherapy for EC depending on the final histological and molecular diagnosis (R0 situation) (Grade of recommendation; A = shall; B = should; 0 = can)

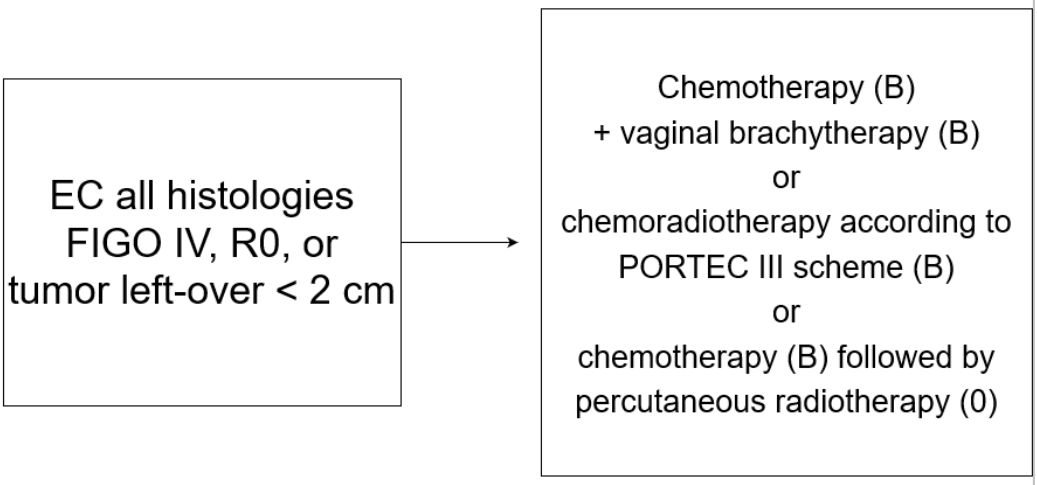
25



Recommendations: 7.16 - 7.19; 8.8

Adjuvant radiation and/or chemotherapy for EC depending on the final histological and molecular diagnosis (R0 situation) (Grade of recommendation; A = shall; B = should; 0 = can)

26



Recommendations: 7.16 - 7.19; 8.9

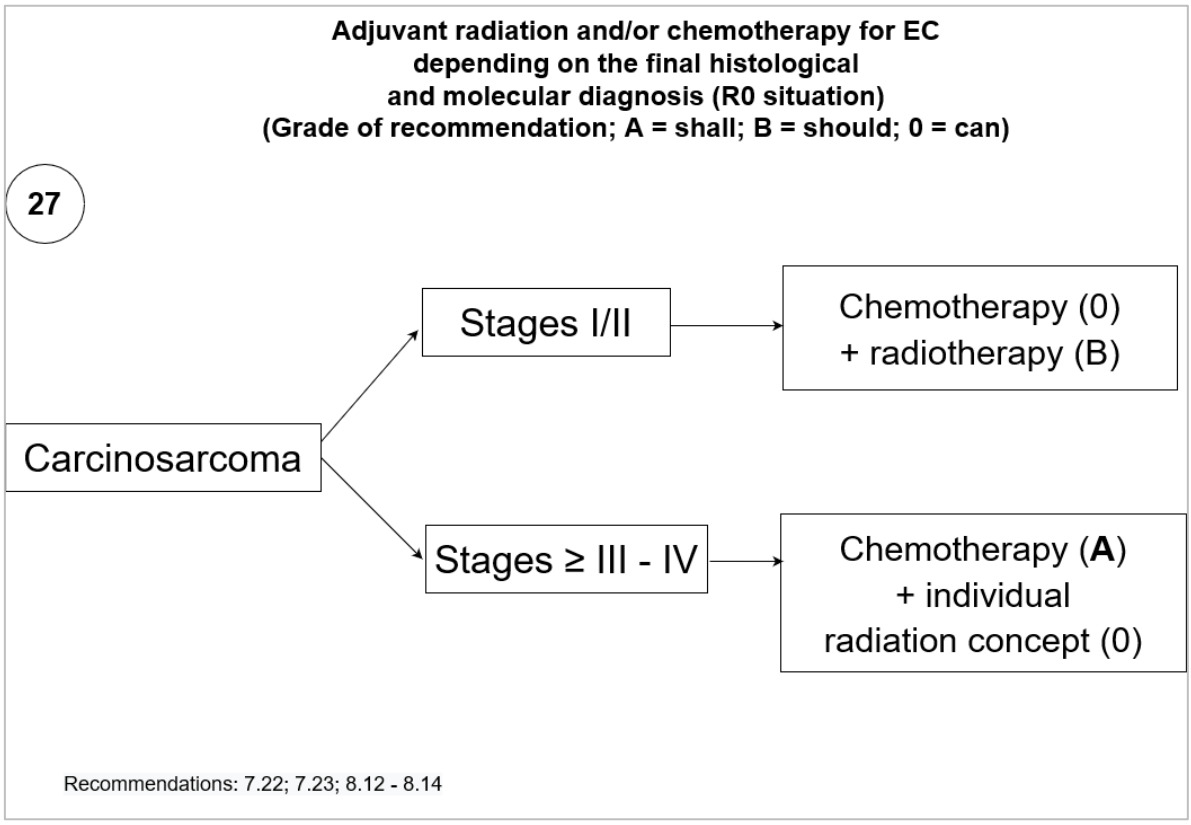


Figure 13: Algorithms guiding action 20-27

16.2 Lynch syndrome diagnostic criteria: extracolonic manifestations

16.2.1 Amsterdam II criteria

All criteria must apply:

- At least three family members with histologically confirmed colorectal carcinoma or carcinoma of the endometrium, small bowel, ureter or renal pelvis, one of whom is first-degree related to the other two; FAP must be excluded.
- At least two consecutive generations affected.
- Diagnosis before age 50 in at least one patient.

Source: [928], Institute of Human Genetics Bonn: https://www.humangenetics.uni-bonn.de/de/beratung/diagnostik/Molekulargenetische-Diagnostik/hereditaeres-nicht-polypoeses-kolonkarzinom-hnpcc-lynch-syndrom/klinische-kriterien-fuer-hnpcc; accessed 2017-08-24.

16.2.2 Revised Bethesda criteria

Tumors of patients should be evaluated for the presence of mismatch repair deficiency in the following cases:

- Patients with colorectal carcinoma before the age of 50.
- Patients with synchronous or metachronous colorectal carcinoma or other HNPCC-associated tumors*, regardless of age.
- Patients with colorectal carcinoma with MSI-H histology** before 60 years of age.
- Patient with colorectal cancer (regardless of age) who has a 1st-degree relative with colorectal cancer or HNPCC-associated tumor before age 50.
- Patient with colorectal cancer (regardless of age) who has at least two 1st or 2nd degree relatives diagnosed with colorectal cancer or HNPCC-associated tumor (regardless of age).

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

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

Source: [764], Bonn Institute of Human Genetics: https://www.humangenetics.uni-bonn.de/de/beratung/diagnostik/Molekulargenetische-Diagnostik/hereditaeres-nicht-polypoeses-kolonkarzinom-hnpcc-lynch-syndrom/klinische-kriterien-fuer-hnpcc; retrieved 2017-08-24.

16.3 Changes in Version 2

Table 17: Overview of changes in Version 2

Version 1.0	Version 2.0	Change
3.3	3.3	modified
A reduction in endometrial cancer risk was observed with continuous combined hormone replacement therapy with conjugated equine estrogens and medroxyprogesterone acetate as progestin with an average duration of use of 5.6 years.	Using progesterone or dydrogesterone as part of -combined hormone replacement therapy, an increase in the risk of developing endometrial cancer has been observed when used for more than 5 years.	
3.8	3.5	modified
Sequential-combined hormone replacement therapy with a duration of use <5 years and using a synthetic progestin for at least 12-14 days per month may be considered safe with respect to endometrial cancer risk.	No increase in endometrial cancer risk has been observed with the use of sequential combined hormone replacement therapy with a duration of use <5 years and using a synthetic progestin for at least 10 days per month.	
3.15	3.13	modified
A positive family history of endometrial cancer and/or colon cancer is associated with an increased risk of developing endometrial cancer.	Hereditary predisposition in the setting of Lynch syndrome or Cowden syndrome increases the risk of endometrial cancer.	
4.6	4.6	modified
In asymptomatic patients on tamoxifen therapy, transvaginal ultrasonography should not be performed for early detection of endometrial carcinoma.	In asymptomatic patients on tamoxifen therapy, transvaginal ultrasound examination for early detection of endometrial carcinoma should not be performed. This also applies to prolonged therapy over 10 years.	

Version 1.0	Version 2.0	Change
4.8	4.8	modified
In women with premenopausal abnormal uterine bleeding without risk factors (suspicious cytology, obesity, Lynch syndrome, diabetes, polyps, etc.), conservative therapy should be attempted first unless the bleeding is hemodynamically relevant. If conservative therapy fails, hysteroscopy/abrasio should be performed.	In women with premenopausal abnormal uterine bleeding, pathologic findings that do not pertain to this guideline (e.g., disturbed early pregnancy, cervical pathology, fibroids) should first be excluded clinically and sonographically. In women with endometrial findings without sonographic malignancy criteria and without risk factors (suspicious cytology, obesity, Lynch syndrome, diabetes, polyps), conservative therapy should be attempted initially unless the bleeding is hemodynamically relevant. If conservative therapy fails, hysteroscopy/abrasio should be performed.	
	4.21	new
	Histopathological diagnosis of endometrial carcinoma results from the combination of histomorphological and immunohistochemical parameters and, if necessary, supplementary molecular pathological findings.	
4.32	4.23	modified
Mixed carcinomas of the endometrium are defined according to the WHO classification as tumors with two or more histological subtypes, each of which is microscopically detectable in > 5 % within the total tumor extent. The respective percentage of each histological subtype should be stated in the histological report.	Mixed carcinomas of the endometrium have two or more histologic subtypes according to the WHO classification (2020), with one of these components being either serous or clear cell.	
	4.25	new

Version 1.0	Version 2.0	Change
	Endometrioid carcinomas are graded according to FIGO. According to WHO, a two-stage grading "low grade" (G1 or G2) and "high grade" (G3) should be preferred. Serous, clear cell, de- or undifferentiated endometrial carcinomas as well as carcinosarcomas are by definition high-grade carcinomas.	
	4.26	new
	Quantification of lymphatic vessel infiltration should be included in the histopathologic report. Focal lymphatic vessel infiltration is defined as involvement of <3 lymphatic vessels and extensive ("substantial") lymphatic vessel infiltration as involvement ≥ 3 lymphatic vessels.	
	4.27	new
	Because of a potential therapeutic consequence, HER2 status should be determined in serous endometrial carcinoma.	
4.29	4.33	modified
The report of findings from a (fractionated) abrasion or an endometrial biopsy should comment on the evidence and type of endometrial hyperplasia. If carcinoma is present, the histological tumor type should be indicated, taking into account the current WHO classification. If tumor tissue is detected in the cervical fraction of a fractionated abrasion, a specific statement should be made on the detection or	The report of findings from a (fractionated) abrasion or an endometrial biopsy should comment on the evidence and type of endometrial hyperplasia. If carcinoma is present, the histological tumor type should be indicated according to the current WHO classification. If tumor tissue is detected in the cervical fraction of a fractionated abrasion, a specific statement should be made on the detection or absence of endocervical stromal infiltration.	

Version 1.0	Version 2.0	Change
absence of endocervical stromal infiltration.		
4.31	4.34	modified
The report of findings of a hysterectomy specimen in endometrial carcinoma should include the following information: * histological type according to WHO * in case of mixed carcinoma, with indication of the respective percentage of the total tumor * grading * evidence/absence of lymphatic or blood vessel invasion (L- and V-status) * evidence/absence of perineural sheath infiltrates (Pn-status) * Staging (pTNM) * metric indication of depth of invasion in relation to myometrial thickness in mm * three-dimensional tumor size in cm * if vaginal infiltration is present, metric indication of minimum distance to vaginal resection margin * R classification (UICC).	The report of findings of a hysterectomy specimen in endometrial cancer should include the following information: histologic type according to WHO (for mixed tumors, components in %) * grading * staging (pT) * evidence/absence of lymphatic or blood vessel invasion (L and V status) * evidence/absence of perineural sheath infiltrates (Pn-status) * metric indication of depth of invasion in relation to myometrial thickness in cm/mm * three-dimensional tumor size in cm/mm * if vaginal infiltration is present, metric indication of minimal distance to vaginal resection margin * R classification (UICC).	
4.33	4.35	modified
The ovaries in endometrial carcinoma should be embedded completely, with acquisition of the hilus ovarii. The work-up of the tubes should follow the SEE-FIM protocol.	The refurbishment of the tubes should be based on the SEE-FIM-like protocol.	
	4.36	new
	Routine immunohistochemical analysis of MMR proteins should not be performed in the setting of endometrial hyperplasia.	

Version 1.0	Version 2.0	Change
	4.37	new
	MSI analysis in endometrial carcinoma should be primarily immunohistochemical. The primary use of two antibodies (MSH-6 and PMS-2) is possible, with addition of the respective partner antibody (MSH2 or MLH1) in case of negative results. Immunohistochemical analysis of MMR proteins should be supplemented by molecular pathological methods (MLH-1 promoter methylation, MSI-PCR) according to the indication. The sole use of molecular pathological methods should not be performed. Combined analysis by immunohistochemistry and molecular pathology should not be performed routinely.	
	4.38	new
	Every newly diagnosed endometrial carcinoma should be screened for MMR defect/MSI regardless of age and histological subtype. MMR/MSI analysis thus also serves to identify patients who should be offered human genetic counseling.	
	4.39	new
	In all histologically diagnosed primary endometrial carcinomas, immunohistochemical determination of p53 as well as MMR proteins should be performed.	
	4.40	new
	In G3 or high intermediate, high risk and intermediate risk endometrial cancer, mutational analysis of the exonuclease domain of POLE should be performed.	
	4.41	new

Version 1.0	Version 2.0	Change
	Molecular classification (P53 and MMR deficiency) should be performed preoperatively, i.e., on the abradate or endometrial biopsy.	
	4.42	new
	POLE mutation analysis can alternatively be performed postoperatively.	
	4.43	new
	In low risk endometrial cancer, IHC determination of L1CAM can be performed.	
	4.44	new
	Molecular typing of endometrial carcinoma should be performed on optimally fixed tissue, i.e. preferably on the abradate. Due to a high concordance rate between abradate and hysterectomy, a repeat determination on the surgical specimen should not be performed if no additional tumor component is detectable on the hysterectomy specimen.	
4.34	4.45	modified
As part of the pathological workup of an omentectomy specimen in endometrial carcinoma, at least one representative kerosene block should be examined in the case of macroscopic tumor infiltration. In the absence of macroscopic tumor infiltration, four to six kerosene blocks (embedding of multiple specimens in one block is possible) should be examined. Any additional	At least one kerosene block should be examined from omentectomy specimens with macroscopic tumor infiltration in endometrial carcinoma. In the case of macroscopically absent tumor infiltration, four to six kerosene blocks (embedding of several specimens in one block is possible) should be examined. Any additional abnormal findings (e.g., intraomental lymph nodes) should be described macroscopically and examined histologically.	

Version 1.0	Version 2.0	Change
abnormal findings (e.g., intraomental lymph nodes) should be described macroscopically and examined histologically.		
4.36	4.47	modified
Lymph nodes up to approximately 0.3 cm maximum extent should be embedded in toto, and larger lymph nodes should be bisected or lamellated along their long axis and also completely embedded.	Lymph nodes up to approximately 0.2 cm maximum extent should be embedded in toto, and larger lymph nodes should be bisected or lamellated along their short axis and also embedded completely.	
	4.49	new
	Isolated tumor cells in the sentinel LC (<0.2mm) (pN0 (i+) are per se not an indication for adjuvant radiotherapy and/or chemotherapy. This is only recommended in case of corresponding additional risks (e.g. p53 mutation, type II EC, LVSI).	
	4.50	new
	For micrometastases (>0.2 mm, <2mm) (pN1(mi)), adjuvant radiotherapy and/or chemotherapy should be given.	
4.39	4.51	modified
The sentinel lymph nodes harvested in studies of endometrial carcinoma are to be fully embedded and examined in staged sections. In addition, immunohistochemical examinations should be performed on sentinel lymph nodes that are	Sentinel lymph nodes in endometrial carcinoma should be lamellated parallel to their short axis and fully embedded and examined in staged sections. Sentinel lymph nodes that are negative in the hematoxylin-eosin stain should additionally be examined by immunohistochemistry (so-called ultrastaging).	

Version 1.0	Version 2.0	Change
negative in HE morphology (so-called ultrastaging).		
5.1	5.1	modified
Endometrial hyperplasia without atypia should not be treated by hysterectomy.	Simple endometrial hyperplasia without atypia should not be treated by hysterectomy.	
	5.2	new
	Hysterectomy may be considered for complex endometrial hyperplasia without atypia.	
	5.4	modified
	In the presence of atypical hyperplasia, the ovaries may be left in place when performing hysterectomy and bilateral salpingectomy in premenopausal women, provided there is no evidence of a hereditary predisposition to ovarian cancer (e.g., BRCA mutation or certain forms of Lynch syndrome).	
5.11	5.12	modified
In the presence of endometrioid EC G1, G2 pT1a, the ovaries may be left in place when performing hysterectomy and bilateral salpingectomy in premenopausal women, provided there is no evidence of hereditary predisposition to ovarian cancer (e.g., BRCA mutation, e.g., Lynch syndrome) and the patient is informed of the risk.	In the presence of endometrioid endometrial carcinoma G1, G2 pT1a, the ovaries may be left in place when performing hysterectomy and bilateral salpingectomy in premenopausal women, provided there is no evidence of hereditary predisposition to ovarian cancer (e.g., BRCA mutation, certain forms of Lynch syndrome) and the patient is informed of the risk.	
5.12	5.13	modified

Version 1.0	Version 2.0	Change
In women with incomplete family planning and endometrial cancer and a desire for fertility preservation, the uterus and adnexa may be left in place if the patient has been informed that the standard treatment almost always leading to cure is total hysterectomy and the patient temporarily forgoes curative treatment of a malignancy on her own responsibility, knowing the potentially fatal consequences (progression of the disease, metastasis), even if a pregnancy is carried to term.	In women with incomplete family planning and endometrioid cT1a without myometrial infiltration, G1, p53-wt and L1CAM-negative endometrial carcinoma and a desire for fertility preservation, the uterus and adnexa can be left in place if the patient has been informed, that the standard treatment almost always leading to cure is total hysterectomy and that the patient temporarily forgoes curative treatment of a malignancy on her own responsibility, knowing the potentially fatal consequences (progression of the disease, metastasis) even if a pregnancy is carried to term.	
5.13	5.14	modified
If uterus preservation is desired, the uterus and adnexa can be preserved in the presence of early endometrial carcinoma if the patient has been recommended a consultation with a reproductive physician to assess the chances of fulfilling a childbearing desire.	If uterus preservation is desired, the uterus and adnexa can be preserved in the presence of endometrioid cT1a, without myometrial infiltration G1, p53-wt, and L1CAM-negative endometrial carcinoma if the patient has been recommended a consultation with a reproductive physician to assess the chances of fulfilling a childbearing desire.	
5.14	5.15	modified
In cases of desire for uterine preservation and early endometrial cancer, the uterus and adnexa may be left in place if the patient agrees to close monitoring and has been informed of the need for hysterectomy after fulfillment or	If uterus preservation and endometrioid cT1a, without myometrial infiltration G1, p53-wt and L1CAM-negative endometrial carcinoma are desired, the uterus and adnexa can be left in place if the patient agrees to close monitoring and has been informed of the need for hysterectomy after fulfillment or abandonment of the desire to have children.	

Version 1.0	Version 2.0	Change
abandonment of the desire to have children.		
5.15	5.16	modified
In cases of early endometrial cancer and desire for fertility preservation, the uterus and adnexa may be left in place if a diagnosis of well-differentiated (G1) endometrioid EC expressing progesterone receptors has been made by hysteroscopy with targeted biopsy or with abrasion and evaluation by a pathologist experienced in gynecologic pathology.	In endometrioid cT1a without myometrial infiltration, G1 , p53-wt and L1CAM-negative endometrial carcinoma and desire for fertility preservation, the uterus and adnexa may be left in place if a diagnosis of well-differentiated (G1) endometrioid EC expressing progesterone receptors has been made by hysteroscopy with targeted biopsy or with abrasion and evaluation by a pathologist (m/f/d) experienced in gynecologic pathology.	
5.16	5.17	modified
In early endometrial cancer (pT1a, G1) and desire to preserve fertility, the uterus and adnexa can be left in place if laparoscopy with vaginal ultrasound or with MRI has ruled out adnexal involvement or myometrial infiltration as much as possible.	In endometrioid cT1a without myometrial infiltration, G1, p53-wt, and L1CAM-negative endometrial cancer and desire for fertility preservation, the uterus and adnexa may be left in place if laparoscopy with vaginal ultrasound or with MRI has ruled out adnexal involvement or myometrial infiltration as much as possible.	
5.17	5.18	modified
In early endometrial cancer and desire for fertility preservation, the uterus and adnexa can be left in place if sufficient drug treatment with medroxyprogesterone acetate or megestrol acetate or a levonorgestrel IUD is given.	In endometrioid cT1a without myometrial infiltration, G1, p53-wt, and L1CAM-negative endometrial cancer and desire for fertility preservation, the uterus and adnexa can be left in place if sufficient drug treatment is given with medroxyprogesterone acetate 200-250 mg/d/p.o.) or megestrol acetate (160-200 mg/d/p.o.)or a levonorgestrel IUD (52 mg).	
5.19	5.20	modified

Version 1.0	Version 2.0	Change
EC patients (pT1a without myometrial infiltration, G1) without a current desire to have children should receive maintenance therapy (levonorgestrel-IUD, oral contraceptives, cyclic progestins) and have an endometrial biopsy every 6 months.	Patients with endometrioid cT1a without myometrial infiltration, G1, p53-wt, and L1CAM-negative endometrial cancer without a current desire to have children should receive maintenance therapy (levonorgestrel-IUD, oral contraceptives, cyclic progestins) and have an endometrial biopsy every 6 months.	
5.21	5.22	modified
If uterus preservation is desired, uterus and adnexa can be left in the presence of endometrioid adenocarcinoma of the endometrium cT1A, G1 without evidence of myometrial infiltration, with expression of the progesterone receptor, if the following conditions are met: * information that the standard treatment almost always leading to cure is total hysterectomy, * consent with close follow-up, * education about the need for hysterectomy after fulfillment or abandonment of the desire to have children, * for confirmatory diagnosis hysteroscopy with targeted biopsy or abrasion, * Laparoscopy with vaginal ultrasound or with MRI to rule out adnexal involvement/myometrial infiltration, * Diagnosis made or confirmed by a pathologist experienced in gynecologic pathology, * Treatment with MPA or MGA or LNG-IUD, * After 6 months, repeat hysteroscopy with abrasio	If uterus preservation is desired, uterus and adnexa may be left in the presence of endometrioid endometrial cancer (cT1a, G1, p53-wt and L1CAM-negative) if the following conditions are met: * information that the standard treatment almost always leading to cure is total hysterectomy, * consent with close follow-up, * education about the need for hysterectomy after fulfillment or abandonment of the desire to have children, * for confirmatory diagnosis hysteroscopy with targeted biopsy or abrasion, * Laparoscopy with vaginal ultrasound or MRI to exclude adnexal involvement/myometrial infiltration, * Diagnosis made or confirmed by a pathologist (m/f/d) experienced in gynecologic pathology, * Treatment with MPA or MGA or LNG-IUD (52 mg), * After 6 months, repeat hysteroscopy with abrasio as well as imaging. If no response, hysterectomy, * if complete remission, strive for pregnancy (reproductive physician (m/f/d)), * if currently no desire to have children: maintenance therapy and endometrial biopsy every 6 months, after fulfillment or abandonment of the desire to have children: recommend total hysterectomy and bilateral adnexexstirpation.	

Version 1.0	Version 2.0	Change
as well as imaging. If no response, hysterectomy, * if complete remission, aim for pregnancy (reproductive physician), * if no current desire to have children: maintenance therapy and endometrial biopsy every 6 months, * after fulfillment or abandonment of desire to have children: recommend total hysterectomy and bilateral adnexal extirpation.		
6.1	6.1	modified
In endometrial carcinoma cT2 or pT2 (with histologic evidence of involvement of the cervical stroma) without clinical suspicion of parametrial infiltration, radical hysterectomy (parametrial resection) should not be performed.	In endometrial carcinoma cT2 or pT2 (with histologic evidence of involvement of the cervical stroma) without clinical suspicion of parametrial infiltration, radical hysterectomy (parametrial resection) should not be performed.	
	6.2	modified
	In patients with endometrial carcinoma (all stages and histologies), the LK that appear enlarged on laparoscopic or open inspection of the abdominal cavity and/or are palpatorily conspicuous ("bulky nodes") should be removed.	
	6.4	new
	When surgical LK staging is performed in patients with endometrial cancer, it should be performed as a systematic LNE or sentinel node biopsy rather than sampling.	
6.4	6.5	modified

Version 1.0	Version 2.0	Change
In type I endometrial carcinoma (ICD-0: 8380/3, 8570/3, 8263/3, 8382/3, 8480/3) pT1a, G1/2, systematic lymphadenectomy should not be performed for clinically unremarkable LK.	In low risk type I endometrial carcinoma pT1a, G1/2, no bulky nodes, systematic lymphadenectomy should not be performed.	
	6.6	new
	If pT1a (without myometrial infiltration), G1/G2, a p53 mutation (intermediate risk), or L1CAM overexpression (high-intermediate risk) is present in a type I endometrial carcinoma, a sentinel node biopsy can be performed, followed by systematic LNE if necessary.	
	6.7	new
	If type I endometrial carcinoma cT1a, G3, or cT1b, G1/2 and no p53 mutation (i.e., at least one intermediate risk endometrial carcinoma) is present preoperatively, sentinel node biopsy can be performed, followed by systematic LNE if necessary. Primary systematic LNE should be omitted.	
	6.8	new
	In endometrial cancer type I, cT1b, G3 (high-intermediate risk group), surgical LK staging - sentinel LNE or (sentinel-assisted) systematic LNE) should be performed.	
	6.9	new
	If type I endometrial carcinoma cT1a, G3, or cT1b, G1/2 and a p53 mutation (high risk) are present preoperatively, surgical LK staging (sentinel LNE and/or (sentinel-assisted) systematic LNE) should be performed.	

Version 1.0	Version 2.0	Change
6.5	6.10	modified
For endometrial carcinoma type I, pT1a, G3, pT1b, G1/2, systematic lymphadenectomy can be performed.	If extensive lymphatic vessel invasion (at least high-intermediate risk group) is present in endometrial carcinoma type I stage I, pT1a G1-G3, pT1b G1/G2, a systematic LNE should be performed, even if no other risk factors are present. If a negative sentinel is present, LNE can be omitted.	
6.7	6.11	modified
B For endometrial carcinoma type I, pT2 to pT4, M0, G1-3, systematic lymphadenectomy should be performed if macroscopic tumor clearance can be achieved.	In endometrial carcinoma type I, pT2 to pT4, M0, G1-3, (sentinel-assisted) systematic lymphadenectomy should be performed if macroscopic tumor clearance can be achieved.	
	6.12	new
	If bulky nodes are present in patients with endometrial cancer (all stages, all histologies), sentinel node biopsy is no longer informative.	
6.9	6.13	modified
In type II endometrial carcinoma, systematic lymphadenectomy should be performed when macroscopic tumor freedom can be achieved.	In endometrial carcinoma type II, (sentinel-assisted) systematic lymphadenectomy should be performed if tumor freedom can be achieved macroscopically.	
6.10	6.15	modified
If lymphatic vessel invasion is present in endometrial cancer, even in the absence of other risk factors, LNE may be performed.	For carcinosarcomas of the uterus, (sentinel-assisted) systematic LNE should be performed.	

Version 1.0	Version 2.0	Change
6.12	6.16	modified
Sentinel lymph node biopsy alone for endometrial cancer should be performed only in controlled trials.	The combination of systematic LNE and sentinel biopsy (that is, sentinel-assisted LNE) may improve the detection of positive lymph nodes.	
	6.17	new
	If sentinel node biopsy is performed, it should be performed according to the following algorithm: 1. laparoscopy and visualization of the situs (adhesiolysis if necessary) 2. intracervical injection of ICG 3. post-injection of ICG, if necessary 4. If despite post-injection of ICG only unilateral visualization of a sentinel is possible, a systematic pelvic LNE should be performed on the ICG-negative side (except in pT1a/G1-2) 5. Work-up of the sentinel LK by ultrastaging (see background text for details).	
6.14	6.19	modified
Robotic-assisted laparoscopic procedures can be used in the same manner as conventional laparoscopy for EC surgery.	Robotic-assisted laparoscopic procedures can be used in the same manner as conventional laparoscopy for endometrial cancer surgery. They may offer advantages in morbidly obese patients.	
	6.21	new
	For advanced primary unresectable endometrial cancer, neoadjuvant platinum-containing chemotherapy followed by cytoreductive surgery may be considered.	
	7.1	new
	In all stage I and II endometrial carcinomas with POLE mutation, adjuvant radiotherapy and/or chemotherapy can be omitted in R0 situation, even if risk factors are present.	

Version 1.0	Version 2.0	Change
7.1	7.2	modified
In stage pT1a, pNX/0, G1 or G2, endometrioid EC (type I), after hysterectomy with or without lymph node dissection, neither brachytherapy nor percutaneous irradiation should be performed.	In stage pT1a, pNX/0, G1 or G2, endometrioid endometrial carcinoma (type I), p53-wt and L1CAM negative, no extensive LVSI after hysterectomy with or without lymph node dissection, neither brachytherapy nor percutaneous irradiation should be performed.	
7.2	7.4	modified
In stage pT1a, pNX/0 without involvement of the myometrium, G3, endometrioid EC (type I), vaginal brachytherapy may be performed to reduce the risk of vaginal recurrence.	In stage pT1a, pNX/0 without involvement of the myometrium, G1-3, p53-abn or L1CAM positive (each POLE wild type), endometrioid endometrial carcinoma (type I), adjuvant vaginal brachytherapy or percutaneous radiotherapy can be performed, if necessary in combination with chemotherapy.	
7.3	7.5	modified
In stage pT1b, G1 or G2 pNX/0 and in stage pT1a (with myometrial involvement), G3 pNX/0, endometrioid EC (type I), vaginal brachytherapy alone should be performed postoperatively to reduce the risk of vaginal recurrence.	In stage pT1b, G1 or G2 pNX/0 and in stage pT1a (with myometrial involvement), G3 pNX/0, endometrioid endometrial carcinoma (type I), p53-wt, L1 CAM negative, no extensive LVSI, vaginal brachytherapy alone should be performed postoperatively.	
	7.6	new
	In stage pT1b, G1-3 pNX/0 and in stage pT1a (with myometrial involvement), G1-3 pNX/0, endometrioid endometrial carcinoma (type I), p53- abn and/or L1CAM positive and/or extensive LVSI, percutaneous irradiation should be performed postoperatively.	

Version 1.0	Version 2.0	Change
	7.7	new
	Radiation should be given in combination with chemotherapy in this situation (7.6.). See chapter System therapy.	
	7.8	new
	Patients with endometrioid endometrial carcinoma (type I) stage pT1b pN0 G3 (without LVSI and p53-wt and L1CAM negative) should undergo vaginal brachytherapy.	
	7.9	new
	Patients with stage pT2 pNX with additional risk factors (G3 or > 50% myometrial infiltration or LVSI) should receive percutaneous radiotherapy.	
7.4	7.10	modified
Patients with stage pT1b pNX G3 or stage pT2 pNX, endometrioid EC (type I), should receive vaginal brachytherapy; alternatively, percutaneous radiotherapy may be performed.	For patients with stage pT1b pNX G3 (without LVSI, p53-wt, L1CAM negative), endometrioid endometrial cancer (type I), vaginal brachytherapy or percutaneous radiotherapy should be performed	
7.4	7.11	modified
Patients with stage pT1b pNX G3 or stage pT2 pNX, endometrioid EC (type I), should receive vaginal brachytherapy; alternatively, percutaneous radiotherapy may be performed.	For patients with stage pT2 pNx, G1/G2, (less than 50% myometrial infiltration, without LVSI, p53-wt, L1CAM negative), endometrioid EC (type I), vaginal brachytherapy or percutaneous radiotherapy should be performed.	
	7.12	new

Version 1.0	Version 2.0	Change
	Patients with endometrioid endometrial carcinoma (type1) stage pT1b and pT2 p53-abn, POLE-wt should receive percutaneous radiotherapy in combination with chemotherapy (PORTEC 3 regimen).	
	7.13	new
	For patients with stage pT2 pNX G3 or > 50% myometrial infiltration or LVSI, radiation may be given in combination with chemotherapy.	
	7.14	new
	In patients with endometrioid endometrial carcinoma (type I) stage pT2 pN0 (without other risk factors such as G3, > 50% myometrial infiltration or LVSI and p53-wt AND L1CAM negative), endometrioid EC (type I), vaginal brachytherapy should be performed.	
	7.15	new
	Patients with endometrioid endometrial carcinoma (type I) pT2 pN0 with risk factors (> 50% myometrial infiltration or LVSI or L1CAM positive) should undergo percutaneous pelvic radiotherapy.	
	7.16	modified
For patients with positive LK, involvement of the uterine serosa, adnexa, vagina, bladder, or rectum (i.e., stages III to IVA overall) with endometrioid EC (type I), postoperative external pelvic irradiation may be performed in addition to chemotherapy to improve local control.	Patients with endometrioid endometrial carcinoma (type I) and positive LK, involvement of the uterine serosa, adnexa, vagina, bladder, or rectum (stages III-IVA) should receive adjuvant percutaneous radiotherapy followed by simultaneous chemotherapy or, alternatively, chemotherapy alone in combination with vaginal brachytherapy.	

Version 1.0	Version 2.0	Change
7.17 Patients with endometrioid EC (type I) and positive LK, involvement of the uterine serosa, adnexa, vagina, bladder, or rectum (stages III-IVA) may alternatively receive adjuvant chemotherapy followed by percutaneous radiotherapy.	new	
	7.18	new
	If simultaneous radiochemotherapy followed by chemotherapy is chosen, the regimen used in the PORTEC-3 trial should be applied.	
	7.19	new
	When chemotherapy is combined with vaginal brachytherapy alone, brachytherapy may be given after or between chemotherapy administrations.	
7.8	7.20	modified
In the presence of specific risk factors for vaginal recurrence (stage II or stage IIIB-vaginal, each with close or positive incision margins), additional vaginal brachytherapy may be performed as a boost after postoperative external pelvic irradiation after hysterectomy due to endometrioid EC.	In the presence of specific risk factors for vaginal recurrence (stage II or stage IIIB-vaginal or LSVI or close vaginal resection margin, additional vaginal brachytherapy may be performed as a boost after postoperative pelvic irradiation after hysterectomy due to endometrioid endometrial carcinoma.	
7.9	7.21	modified
The indication for postoperative vaginal brachytherapy or external pelvic irradiation for type II	Patients with serous endometrial carcinoma and patients with p53-mutated endometrial carcinoma of all stages should receive vaginal	

Version 1.0	Version 2.0	Change
carcinoma (serous or clear cell) should be based on the recommendations for type I carcinoma (endometrioid) of grade G3 of the same stage.	brachytherapy (stage I) or adjuvant percutaneous radiotherapy (stage II and above).	
7.10	7.22	modified
To improve local control, postoperative radiotherapy should be given for carcinosarcoma in the presence of stage FIGO I or II.	To improve local control, postoperative radiotherapy should be given in addition to chemotherapy for carcinosarcoma when stage FIGO I or II is present.	
	7.23	new
	In the case of carcinosarcoma, an individualized radiation concept can be carried out if higher stages are present.	
8.2	8.2	modified
Patients with endometrioid or other type I endometrial carcinoma (ICD-0: 8380/3, 8570/3, 8263/3, 8382/3, 8480/3) at stage pT1a/b G1 and G2 cN0/pN0 should not receive adjuvant chemotherapy.	Patients with primary type I endometrial carcinoma stage pT1a/b G1 and G2 cN0/ pNsn0, p53-wt, should not receive adjuvant chemotherapy.	
8.3	8.3	modified
For patients with endometrioid or other type I endometrial carcinoma at stage pT1a G3 cN0 or pN0, there are insufficient data on the benefit of adjuvant chemotherapy.	For patients with endometrioid or other type I endometrial carcinoma at stage pT1a G3 cN0 or pN0, p53-wt, there are insufficient data on the benefit of adjuvant chemotherapy.	
8.4	8.4	modified
Adjuvant chemotherapy can be given to patients with	For patients with type I endometrial carcinoma G3 pT1b, without POLE	

Version 1.0	Version 2.0	Change
type II endometrial carcinoma and to patients with type I endometrial carcinoma G3 pT1b and stage pT2 (both pN0).	mutation or stage pT2 (each pN0), adjuvant chemotherapy with 3 or 6 cycles (see Statement 8.13) may be considered as an adjunct to vaginal brachytherapy (see Radiation Therapy recommendation) or percutaneous radiotherapy alone without chemotherapy.	
	8.5	new
	Patients with type I endometrial carcinoma G3 pT1b or stage pT2 (both pN0) with POLE mutation should not receive adjuvant chemotherapy.	
	8.6	new
	In patients with serous endometrial carcinoma in FIGO stage I - III, adjuvant therapy should be performed according to the PORTEC III regimen (= radiochemotherapy followed by chemotherapy). For stage III serous endometrial carcinoma, adjuvant chemotherapy alone may be given as an alternative (carboplatin AUC 6 / paclitaxel 175 mg/m2).	
	8.7	new
	Patients with type 1 endometrial carcinoma and abnormal p53 status on immunohistochemistry (type I endometrial carcinoma stage 1a or higher, with infiltration into the myometrium, or clear cell endometrial carcinoma) should be treated as patients with serous endometrial carcinoma.	
8.5	8.8	new
Patients with stage pT3 and/or pN1 endometrial cancer should receive adjuvant chemotherapy.	Patients with stage pT3 and/or pN1 endometrial cancer should receive adjuvant chemotherapy or adjuvant therapy according to the PORTEC-3 regimen.	

Version 1.0	Version 2.0	Change
8.6	8.9	new
Patients with stage pT4a or M1 endometrial cancer who have undergone macroscopic tumor-free surgery or have a maximum postoperative residual tumor less than 2 cm should receive chemotherapy.	Patients with stage pT4a or M1 endometrial cancer who have undergone macroscopic tumor-free surgery or have a maximum postoperative residual tumor less than 2 cm should receive adjuvant chemotherapy, possibly in combination with radiotherapy.	
8.7	8.10	modified
Adjuvant chemotherapy for endometrial cancer should be performed with carboplatin and paclitaxel.	Adjuvant chemotherapy for endometrial cancer should be given with carboplatin AUC 6 and paclitaxel 175 mg per square meter. After percutaneous radiotherapy, carboplatin AUC 5 should be dosed.	
8.11		
If chemotherapy alone is contraindicated to paclitaxel or carboplatin, adriamycin and cisplatin may also be used.	modified	
8.8	8.12	modified
Patients with carcinosarcoma FIGO stage I or II may receive adjuvant chemotherapy with cisplatin/ifosfamide at a dose of ifosfamide 1.6 g/m2 i. v. day 1-4 and cisplatin 20 mg/m2 i. v. day 1-4 or carboplatin/paclitaxel at a dose of paclitaxel 175 mg/m2 day 1 and carboplatin AUC 5.	Patients with carcinosarcoma FIGO stage I or II may receive adjuvant chemotherapy with carboplatin/paclitaxel (at a dosage of paclitaxel 175 mg/m² day 1 carboplatin AUC 6 day 1) or cisplatin/ifosfamide (at a dosage of ifosfamide 1.6 g/m² day 1-4 and cisplatin 20 mg/m² day 1-4).	
8.10	8.14	modified
Given the high toxicity of ifosfamide-containing combinations, the combination of carboplatin and paclitaxel may also be	Given the high toxicity of ifosfamide-containing combinations, the combination of carboplatin and paclitaxel can also be used as adjuvant chemotherapy in patients with stage	

Version 1.0	Version 2.0	Change
used as adjuvant chemotherapy in patients with carcinosarcoma.	FIGO III or IV carcinosarcoma at a dosage of paclitaxel 175 mg/m2 day 1 and carboplatin AUC 6 or cisplatin/ifosfamide at a dosage of ifosfamide 1.6 g/m2 i. v. day 1-4 and cisplatin 20 mg/m2i. v. day 1-4.	
9.14	9.14	modified
Endocrine therapy with MPA (200 mg/d) or MGA (160 mg/d) can be given to women with recurrence after EC.	Endocrine therapy with MPA (200-250 mg/d) or MGA (160 mg/d) or tamoxifen (20 mg/d or 40 mg/d) or a combination of tamoxifen and MPA/MGA can be given to women with recurrence after endometrial cancer.	
9.15	9.15	modified
In women with recurrence after EC, endocrine therapy with MPA results in higher response rates when progesterone receptor expression or estrogen receptor expression or good-to-moderate tumor differentiation (G1/G2) is detectable.	In women with recurrence after endometrial cancer, endocrine therapy with MPA or tamoxifen results in higher response rates when progesterone receptor expression or estrogen receptor expression or good-to-moderate tumor differentiation (G1/G2) is detectable.	
9.16	9.16	modified
Systemic chemotherapy may be given to women with EC recurrence that cannot be treated locally or distant metastasis.	Chemotherapy may be given to women with EC recurrence that cannot be treated locally or distant metastasis.	
9.17	9.17	modified
The superiority of a particular chemotherapy regimen in women with recurrence after EC has not been established. Platinum salts, anthracyclines, and taxanes are considered the most effective agents for	The superiority of a particular chemotherapy regimen in women with recurrence after endometrial carcinoma has not been established. The carboplatin/paclitaxel and doxorubicin/cisplatin/paclitaxel combinations have been shown to be equieffective agents for	

Version 1.0	Version 2.0	Change
chemotherapeutic therapy of advanced or recurrent EC. The combination of carboplatin with paclitaxel has been established as a relatively well-tolerated and safe therapy.	chemotherapeutic therapy of advanced or recurrent endometrial carcinoma. Because of better tolerability, carboplatin (AUC 6) should be used with paclitaxel (175 mg/m2).	
	9.18	new
	Patients with locally advanced or recurrent serous endometrial carcinoma with her2/neu overexpression may receive systemic chemotherapy with carboplatin (AUC 5) and paclitaxel (175 mg/m2) combined with trastuzumab (8 mg/kg as initial dose, followed by 6 mg/kg as maintenance therapy).	
	9.19	new
	Patients with recurrent or primary advanced endometrial cancer with microsatellite-stable/mismatch-repair functional tumor tissue and progression after at least one line of chemotherapy should receive combined immune and multikinase inhibitor therapy with pembrolizumab (200 mg i.v. d1, q21 or 400 mg i.v. d1, q42) and lenvatinib (20 mg p.o. 1 x daily). The high toxicity should be noted.	
	9.20	new
	In patients with recurrent or primary advanced endometrial cancer with microsatellite unstable/mismatch-repair deficient tumor tissue (MSI-H or MMRd), immunotherapy with dostarlimab (4 cycles 500mg i.v. d1, q3w followed by 1000mg i.v. d1, q6w) or with pembrolizumab (200 mg i.v. d1, q21 or 400 mg i.v. d1, q42).	
10.3	10.3	modified

Version 1.0	Version 2.0	Change
If a hereditary form of endometrial cancer is suspected, the patient should present to a certified gynecologic cancer center.	If a hereditary form of endometrial cancer is suspected, the patient should present to a certified gynecologic cancer center or a center for hereditary tumor diseases.	
10.4	10.4	modified
Already ill persons, carriers and persons at risk for monogenic hereditary diseases with increased risk for endometrial carcinoma and other malignancies should be informed about the possibility and benefit of psychosocial counseling and care.	People who already have the disease, carriers of the disease and people who have not yet been tested (persons at risk) from families with a hereditary tumor syndrome should be made aware of the possibility and benefit of psychosocial counseling and care.	
10.6	10.6	modified
A (molecular) pathological examination with regard to Lynch syndrome in tumor tissue should be performed in case of endometrial carcinoma diagnosed before the age of 60.	If a suspicious finding is raised during routine testing for MMR deficiency (immunohistochemical testing of MMR genes or microsatellite analysis), education and, if necessary, counseling under the Genetic Diagnostics Act should be offered regarding diagnostic genetic testing for Lynch syndrome.	
10.7	10.7	modified
In patients from families in which the Amsterdam criteria are fulfilled and whose tumor tissue does not show Lynch syndrome-typical abnormalities, Lynch syndrome cannot be excluded. Therefore, genetic counseling should be performed for assessment and, if necessary, further diagnosis.	In patients from families in which the Amsterdam criteria are fulfilled and whose tumor tissue does not show Lynch syndrome-typical abnormalities, Lynch syndrome cannot be excluded. Therefore, for assessment and, if necessary, further diagnostics, education and, if necessary, genetic counseling for diagnostic genetic testing should be offered in a center for familial tumor diseases with appropriate expertise.	

Version 1.0	Version 2.0	Change
10.8	10.8	modified
If Lynch syndrome is suspected based on an abnormal molecular pathology finding, the affected individual should be offered a germline mutation search in the likely affected MMR gene(s).	If there is evidence of MMR deficiency and suspicion of Lynch syndrome based on abnormal immunohistochemistry or molecular pathology (failure of MMR proteins) or high microsatellite instability (MSI-H), the affected individual should be offered education and, if appropriate, genetic counseling for germline mutation analysis in the likely affected MMR gene(s).	
10.13	10.10	modified
Once the causative mutation is known to run in the family, the patient should be advised to inform family members who may be affected of the increased risk.	Once the causative mutation is known in the family, the patient should be advised to inform family members of the increased risk and the options for genetic counseling and (predictive) genetic testing.	
11.9	11.8	modified
The communication of information and education of the patient should take place early and according to the basic principles of patient-centered communication, which enables participatory decision-making.	The communication of information and education of the patient should take place at an early stage and according to the basic principles of patient-centered communication, which enables participatory decision-making. This should include the following aspects: * expression of empathy and active listening, * direct and empathetic addressing of difficult issues, * avoidance of medical terminology, explanation of technical terms when appropriate, * strategies to improve understanding (repetition, summary of important information, use of graphics, etc.), * encouragement to ask questions, * permission and encouragement to express feelings, * offering further help.	
	11.9	new

Version 1.0	Version 2.0	Change
	To improve patient education, physicians should complete quality-assured training on communication with patients.	
11.12	11.12	modified
All patients should be offered palliative care after diagnosis of a non-curable cancer, regardless of whether tumor-specific therapy is used.	All patients should be offered palliative care (APV or SPV) after diagnosis of noncurable endometrial cancer, regardless of whether tumor-specific therapy is used.	
	11.13	new
	For patients with noncurable endometrial cancer, the complexity of the palliative situation should be repeatedly assessed; this includes: the patient and family needs, the patient's functional status, and the disease phase.	
11.12.2		deleted
Specialized palliative care should be integrated into oncology decision-making processes, e.g., through participation in interdisciplinary tumor conferences.		
11.12.3	11.14	modified
Patients with a non-curable cancer and a high complexity of their situation should receive specialized palliative care.	Patients with noncurable endometrial cancer and high complexity of their situation should receive specialized palliative care. S3 Guideline Palliative Care.<https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/>	
	11.17	new
	Endometrial cancer patients should be informed about tumor-associated fatigue and screened systematically and	

Version 1.0	Version 2.0	Change
	repeatedly during the different treatment phases. Screening according to NCCN is recommended.	
	11.18	new
	If there is a value > 3 in the screening, a diagnostic assessment should be performed for further clarification and specific counseling on fatiguemanagement and treatment if needed.	
	11.19	new
	For moderate or severe fatigue, moderate strength and endurance training should be provided based on physical performance level	
	11.20	new
	Psychoeducation or cognitive behavioral therapy should be offered for moderate or severe fatigue	
	11.21	new
	For moderate or severe fatigue, mindfulness-based stress reduction (MBSR) and yoga may be offered.	
	11.22	new
	Yoga should be recommended to reduce fatigue in these patients.	
	12.1	new
	Treatment decisions for older patients should be based on current standard recommendations and modified by general status, life expectancy, patient preference, and an individual benefit-risk assessment.	

Version 1.0	Version 2.0	Change
	12.2	new
	Determination of general status in patients older than 75 years should be determined by geriatric assessment or by a screening/geriatric assessment algorithm especially if surgery with general anesthesia or chemotherapy is planned to minimize complications as well as improve treatment adherence, chemotherapy tolerance, and possibly survival.	
	12.3	new
	The sole consideration of calendrical age does not do justice to the complexity and multi-layered nature of the general status. Rather, geriatric assessment and management should include therapy-relevant geriatric domains (especially functionality-associated parameters such as activities of daily living, mobility, cognition, falls, and morbidity-associated parameters such as multimedication, nutrition, fatigue, and number of comorbidities) to adjust therapy selection accordingly and initiate supportive measures.	

17 Table of Figures

18 Table of Tables

19 Literature References

1. ICD-10-GM 2018 Systematisches Verzeichnis : Internationale statistische Klassifikation der Krankheiten und verwandter Gesundheitsprobleme, 2017;

2. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), AWMF-Regelwerk „Leitlinien“, 2017;

3. Atkins D. Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et.al. Grading quality of evidence and strength of recommendations. BMJ, 2004; 328: p. 1490. https://www.ncbi.nlm.nih.gov/pubmed/15205295

4. Robert, Koch-Institut, Gesellschaft der epidemiologischen Krebsregister in Deutschland e, V.. *Krebs in Deutschland 2015/2016.* 2019.

5. Tempfer, CB, Hilal, Z, Kern, P, et al. *Menopausal Hormone Therapy and Risk of Endometrial Cancer: A Systematic Review.*. Cancers (Basel), 2020. **12 (8):** https://pubmed.ncbi.nlm.nih.gov/32781573/

6. Lacey, J. V., Jr., Brinton, L. A., Lubin, J. H., 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:** p. 1724-31. https://www.ncbi.nlm.nih.gov/pubmed/16030108

7. Allen, N. E., Tsilidis, K. K., Key, T. J., 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:** p. 1394-403. https://www.ncbi.nlm.nih.gov/pubmed/20961969

8. Marjoribanks, J., Farquhar, C., Roberts, H., et al. *Long-term hormone therapy for perimenopausal and postmenopausal women.* Cochrane Database Syst Rev, 2017. **1 (1):** p. Cd004143.

9. Beral, V., Bull, D., Reeves, G.. *Endometrial cancer and hormone-replacement therapy in the Million Women Study.* Lancet, 2005. **365:** p. 1543-51. https://www.ncbi.nlm.nih.gov/pubmed/15866308

10. Nelson, H. D., Humphrey, L. L., Nygren, P., et al. *Postmenopausal hormone replacement therapy: scientific review.* JAMA, 2002. **288:** p. 872-81. https://www.ncbi.nlm.nih.gov/pubmed/12186605

11. Grady, D., Gebretsadik, T., Kerlikowske, K., et al. *Hormone replacement therapy and endometrial cancer risk: a meta-analysis (Structured abstract).* Obstetrics and Gynecology, 1995. **85:** p. 304-313. https://www.ncbi.nlm.nih.gov/pubmed/7824251

12. Razavi, P., Pike, M. C., Horn-Ross, P. L., et al. *Long-term postmenopausal hormone therapy and endometrial cancer.* Cancer Epidemiol Biomarkers Prev, 2010. **19:** p. 475-83. https://www.ncbi.nlm.nih.gov/pubmed/20086105

13. Beral V, Bull D, Reeves G. Endometrial cancer and hormone-replacement therapy in the Million Women Study. Lancet, 2005; 365: p. 1543-51. https://www.ncbi.nlm.nih.gov/pubmed/15866308

14. Lacey JV, Jr. Brinton LA, Lubin JH, Sherman ME, Schatzkin, A, Schairer C. Endometrial carcinoma risks among menopausal estrogen plus progestin and unopposed estrogen users in a cohort of postmenopausal women. Cancer Epidemiol Biomarkers Prev, 2005; 14: p. 1724-31. https://www.ncbi.nlm.nih.gov/pubmed/16030108

15. Nelson HD. Humphrey LL, Nygren P, Teutsch SM, Allan JD, Postmenopausal hormone replacement therapy: scientific review. JAMA, 2002; 288: p. 872-81. https://www.ncbi.nlm.nih.gov/pubmed/12186605

16. Grady D. Gebretsadik T, Kerlikowske K, Ernster V, Petitti D, Hormone replacement therapy and endometrial cancer risk: a meta-analysis (Structured abstract). Obstetrics and Gynecology, 1995; 85: p. 304-313. https://www.ncbi.nlm.nih.gov/pubmed/7824251

17. Allen NE, Tsilidis KK, Key TJ, Dossus L, Kaaks R, Lund, 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: p. 1394-403. https://www.ncbi.nlm.nih.gov/pubmed/20961969

18. Chlebowski, R. T., Anderson, G. L., Sarto, G. E., et al. *Continuous Combined Estrogen Plus Progestin and Endometrial Cancer: The Women's Health Initiative Randomized Trial.* J Natl Cancer Inst, 2015. **108:** https://www.ncbi.nlm.nih.gov/pubmed/26668177

19. Mørch, LS, Kjaer, SK, Keiding, N, et al. *The influence of hormone therapies on type I and II endometrial cancer: A nationwide cohort study..* Int J Cancer, 2016. **138 (6):** p. 1506-15. https://pubmed.ncbi.nlm.nih.gov/26421912/

20. Fournier, A., Dossus, L., Mesrine, S., et al. *Risks of endometrial cancer associated with different hormone replacement therapies in the E3N cohort, 1992-2008.* Am J Epidemiol, 2014. **180:** p. 508-17. https://www.ncbi.nlm.nih.gov/pubmed/25008104

21. Doherty, J. A., Cushing-Haugen, K. L., Saltzman, B. S., et al. *Long-term use of postmenopausal estrogen and progestin hormone therapies and the risk of endometrial cancer.* Am J Obstet Gynecol, 2007. **197:** p. 139 e1-7. https://www.ncbi.nlm.nih.gov/pubmed/17689625

22. Sjögren, L. L., Mørch, L. S., Løkkegaard, E.. *Hormone replacement therapy and the risk of endometrial cancer: A systematic review.* Maturitas, 2016. **91:** p. 25-35.

23. Chlebowski RT, Anderson GL, Sarto GE, Haque R, Runowicz CD, Aragaki AK. et.al. Continuous Combined Estrogen Plus Progestin and Endometrial Cancer: The Women's Health Initiative Randomized Trial. J Natl Cancer Inst, 2015; 108. https://www.ncbi.nlm.nih.gov/pubmed/26668177

24. Phipps AI, Doherty JA. Voigt LF, Hill DA, Beresford SA, Rossing MA, et.al. Long-term use of continuous-combined estrogen-progestin hormone therapy and risk of endometrial cancer. Cancer Causes Control, 2011; 22: p. 1639-46. https://link.springer.com/article/10.1007%2Fs10552-011-9840-6

25. Razavi P, Pike MC, Horn-Ross P L, Templeman, C, Bernstein, L, Ursin G. Long-term postmenopausal hormone therapy and endometrial cancer. Cancer Epidemiol Biomarkers Prev, 2010; 19: p. 475-83. https://www.ncbi.nlm.nih.gov/pubmed/20086105

26. Fournier A, Dossus L, Mesrine S, Vilier A, Boutron-Ruault MC, Clavel-Chapelon F. et.al. Risks of endometrial cancer associated with different hormone replacement therapies in the E3N cohort, 1992-2008. Am J Epidemiol, 2014; 180: p. 508-17. https://www.ncbi.nlm.nih.gov/pubmed/25008104

27. Judd H L, Mebane-Sims I, Legault C et al et.al. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. JAMA, 1996; 275: p. 370-5. https://www.ncbi.nlm.nih.gov/pubmed/8569016

28. Crosbie EJ, Zwahlen M, Kitchener HC, Egger M, Renehan AG. Body mass index, hormone replacement therapy, and endometrial cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev, 2010; 19: p. 3119-30. https://www.ncbi.nlm.nih.gov/pubmed/21030602

29. Emons, G, Mustea, A, Tempfer, C. *Tamoxifen and Endometrial Cancer: A Janus-Headed Drug..* Cancers (Basel), 2020. **12 (9):** https://pubmed.ncbi.nlm.nih.gov/32906618/

30. Nelson, H. D., Smith, M. E., Griffin, J. C., 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:** p. 604-14. https://www.ncbi.nlm.nih.gov/pubmed/23588749

31. Braithwaite, R. S., Chlebowski, R. T., Lau, J., et al. *Meta-analysis of vascular and neoplastic events associated with tamoxifen.* J Gen Intern Med, 2003. **18:** p. 937-47. https://www.ncbi.nlm.nih.gov/pubmed/14687281

32. Al-Mubarak, M., Tibau, A., Templeton, A. J., et al. *Extended adjuvant tamoxifen for early breast cancer: a meta-analysis.* PLoS One, 2014. **9:** p. e88238. https://www.ncbi.nlm.nih.gov/pubmed/24586311

33. DeMichele, A., Troxel, A. B., Berlin, J. A., et al. *Impact of raloxifene or tamoxifen use on endometrial cancer risk: a population-based case-control study.* J Clin Oncol, 2008. **26:** p. 4151-9. https://www.ncbi.nlm.nih.gov/pubmed/18757329

34. Braithwaite RS, Chlebowski RT, Lau J, George, S, Hess R, Col NF. Meta-analysis of vascular and neoplastic events associated with tamoxifen. J Gen Intern Med, 2003; 18: p. 937-47. https://www.ncbi.nlm.nih.gov/pubmed/14687281

35. Nelson HD, Smith ME, Griffin JC, Fu R, Use of medications to reduce risk for primary breast cancer: a systematic review for the USPreventive Services Task Force. Ann Intern Med, 2013; 158: p. 604-14. https://www.ncbi.nlm.nih.gov/pubmed/23588749

36. C. l, a, r, k, e, et.al. WITHDRAWN: Tamoxifen for early breast cancer. Cochrane Database Syst Rev, 2008; p. Cd000486. https://www.ncbi.nlm.nih.gov/pubmed/18843611

37. Al-Mubarak M, Tibau A, Templeton A J, Cescon DW, Ocana A, Seruga B. et.al. Extended adjuvant tamoxifen for early breast cancer: a meta-analysis. PLoS One, 2014; 9: p. e88238. https://www.ncbi.nlm.nih.gov/pubmed/24586311

38. Emons G, Mustea A, Tempfer C. Tamoxifen and Endometrial Cancer: A Janus-Headed Drug. Cancers (Basel), 2020; 12(9). https://pubmed.ncbi.nlm.nih.gov/32906618/

39. DeMichele A, Troxel A B, Berlin JA, Weber A L, Bunin GR, Turzo E. et.al. Impact of raloxifene or tamoxifen use on endometrial cancer risk: a population-based case-control study. J Clin Oncol, 2008; 26: p. 4151-9. https://www.ncbi.nlm.nih.gov/pubmed/18757329

40. Ignatov, A, Ortmann, O. *Endocrine Risk Factors of Endometrial Cancer: Polycystic Ovary Syndrome, Oral Contraceptives, Infertility, Tamoxifen..* Cancers (Basel), 2020. **12 (7):** https://pubmed.ncbi.nlm.nih.gov/32630728/

41. 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:** p. 1061-1070. https://www.ncbi.nlm.nih.gov/pubmed/26254030

42. Gierisch, J. M., Coeytaux, R. R., Urrutia, R. P., et al. *Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review.* Cancer Epidemiol Biomarkers Prev, 2013. **22:** p. 1931-43. https://www.ncbi.nlm.nih.gov/pubmed/24014598

43. Schlesselman J. Risk of endometrial cancer in relation to use of combined oral contraceptives. A practitioner's guide to meta-analysis. Hum Reprod, 1997; 12: p. 1851-63. https://www.ncbi.nlm.nih.gov/pubmed/9363696

44. Gorenoi V, Schonermark MP, Hagen A. Benefits and risks of hormonal contraception for women. GMS Health Technol Assess, 2007; 3: p. Doc06. https://www.ncbi.nlm.nih.gov/pubmed/21289940

45. Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ. Moorman, P G, Lowery WJ, et.al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic

review. Cancer Epidemiol Biomarkers Prev, 2013; 22: p. 1931-43. https://www.ncbi.nlm.nih.gov/pubmed/24014598

46. Dossus L, Allen N, Kaaks R, Bakken K, Lund E, Tjonneland A. et.al. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. Int J Cancer, 2009; 127: p. 442-51. https://www.ncbi.nlm.nih.gov/pubmed/19924816

47. 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: p. 1061-1070. https://www.ncbi.nlm.nih.gov/pubmed/26254030

48. Parazzini, F., Pelucchi, C., Talamini, R., et al. *Use of fertility drugs and risk of endometrial cancer in an Italian case-control study.* Eur J Cancer Prev, 2010. **19:** p. 428-30. https://www.ncbi.nlm.nih.gov/pubmed/20634699

49. Siristatidis, C., Sergentanis, T. N., Kanavidis, P., 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:** p. 105-123. https://www.ncbi.nlm.nih.gov/pubmed/23255514

50. Skalkidou, A., Sergentanis, T. N., Gialamas, S. P., et al. *Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility.* Cochrane Database Syst Rev, 2017. **3 (3):** p. Cd010931.

51. Parazzini F, Pelucchi C. Talamini R, Montella M, La Vecchia C, Use of fertility drugs and risk of endometrial cancer in an Italian case-control study. Eur J Cancer Prev, 2010; 19: p. 428-30. https://www.ncbi.nlm.nih.gov/pubmed/20634699

52. Siristatidis C, Sergentanis TN, Kanavidis P, Trivella M, Sotiraki M, Mavromatis I. 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: p. 105-123. https://www.ncbi.nlm.nih.gov/pubmed/23255514

53. Ettinger, B., Kenemans, P., Johnson, S. R., et al. *Endometrial effects of tibolone in elderly, osteoporotic women.* Obstet Gynecol, 2008. **112:** p. 653-9. https://www.ncbi.nlm.nih.gov/pubmed/18757665

54. Ettinger B, Kenemans P, Johnson SR, Mol-Arts M, Van Os S, Seifert W. et.al. Endometrial effects of tibolone in elderly, osteoporotic women. Obstet Gynecol, 2008; 112: p. 653-9. https://www.ncbi.nlm.nih.gov/pubmed/18757665

55. Formoso G, Perrone E, Maltoni S, Balduzzi S, D'Amico R, Bassi C. et.al. Short and long term effects of tibolone in postmenopausal women. Cochrane Database Syst Rev, 2012; 2: p. Cd008536.

56. Dossus, L., Allen, N., Kaaks, R., et al. *Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition.* Int J Cancer, 2009. **127:** p. 442-51. https://www.ncbi.nlm.nih.gov/pubmed/19924816

57. Setiawan, V. W., Pike, M. C., Karageorgi, S., 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:** p. 269-78. https://www.ncbi.nlm.nih.gov/pubmed/22831825

58. Karageorgi, S., Hankinson, S. E., Kraft, P., 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, 2009. **126:** p. 208-16. https://www.ncbi.nlm.nih.gov/pubmed/19551854

59. Friberg, E., Orsini, N., Mantzoros, C. S., et al. *Diabetes mellitus and risk of endometrial cancer: a meta-analysis.* Diabetologia, 2007. **50:** p. 1365-74. https://www.ncbi.nlm.nih.gov/pubmed/17476474

60. Barone, B. B., Yeh, H. C., Snyder, C. F., et al. *Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis.* Jama, 2008. **300:** p. 2754-64. https://www.ncbi.nlm.nih.gov/pubmed/19088353

61. Huang, Y., Cai, X., Qiu, M., et al. *Prediabetes and the risk of cancer: a meta-analysis.* Diabetologia, 2014. **57:** p. 2261-9. https://www.ncbi.nlm.nih.gov/pubmed/25208757

62. Zhang, Z. H., Su, P. Y., Hao, J. 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:** p. 294-303. https://www.ncbi.nlm.nih.gov/pubmed/23287960

63. Liao, C., Zhang, D., Mungo, 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:** p. 163-171. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4404750/

64. Luo, J., Beresford, S., Chen, C., et al. *Association between diabetes, diabetes treatment and risk of developing endometrial cancer.* Br J Cancer, 2014. **111:** p. 1432-9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4183842/

65. Gnagnarella, P., Gandini, S., La Vecchia, C., et al. *Glycemic index, glycemic load, and cancer risk: a meta-analysis.* Am J Clin Nutr, 2008. **87:** p. 1793-801. https://www.ncbi.nlm.nih.gov/pubmed/18541570

66. Mulholland, H. G., Murray, L. J., Cardwell, C. R., et al. *Dietary glycaemic index, glycaemic load and endometrial and ovarian cancer risk: a systematic review and meta-analysis.* Br J Cancer, 2008. **99:** p. 434-41. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2527795/

67. Choi, Y., Giovannucci, E., Lee, J. E.. *Glycaemic index and glycaemic load in relation to risk of diabetes-related cancers: a meta-analysis.* Br J Nutr, 2012. **108:** p. 1934-47. https://www.ncbi.nlm.nih.gov/pubmed/23167978

68. Nagle, C. M., Olsen, C. M., Ibiebele, T. I., 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, 2012. **52:** p. 705-15. https://www.ncbi.nlm.nih.gov/pubmed/22648201

69. Fearnley, E. J., Marquart, L., Spurdle, A. B., 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:** p. 2303-8. https://www.ncbi.nlm.nih.gov/pubmed/20953904

70. Gottschau, M., Kjaer, S. K., Jensen, A., et al. *Risk of cancer among women with polycystic ovary syndrome: a Danish cohort study.* Gynecol Oncol, 2014. **136:** p. 99-103. https://www.ncbi.nlm.nih.gov/pubmed/25451694

71. Chittenden, B. G., Fullerton, G., Maheshwari, A., et al. *Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review.* Reprod Biomed Online, 2009. **19:** p. 398-405. https://www.ncbi.nlm.nih.gov/pubmed/19778486

72. Haoula, Z., Salman, M., Atiomo, W.. *Evaluating the association between endometrial cancer and polycystic ovary syndrome.* Hum Reprod, 2012. **27:** p. 1327-31. https://www.ncbi.nlm.nih.gov/pubmed/22367984

73. Barry, J. A., Azizia, M. M., Hardiman, P. J.. *Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis.* Hum Reprod Update, 2014. **20:** p. 748-58. https://www.ncbi.nlm.nih.gov/pubmed/24688118

74. Crosbie, E. J., Zwahlen, M., Kitchener, H. C., et al. *Body mass index, hormone replacement therapy, and endometrial cancer risk: a meta-analysis.* Cancer Epidemiol Biomarkers Prev, 2010. **19:** p. 3119-30. https://www.ncbi.nlm.nih.gov/pubmed/21030602

75. Ward, K. K., Roncancio, A. M., Shah, N. R., 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:** p. 579 e1-5. https://www.ncbi.nlm.nih.gov/pubmed/23938608

76. Renehan, A. G., Tyson, M., Egger, M., et al. *Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies.* Lancet, 2008. **371:** p. 569-78. https://www.ncbi.nlm.nih.gov/pubmed/18280327

77. Dobbins, M., Decorby, K., Choi, B. C.. *The Association between Obesity and Cancer Risk: A Meta-Analysis of Observational Studies from 1985 to 2011.* ISRN Prev Med, 2013. **2013:** p. 680536. https://www.ncbi.nlm.nih.gov/pubmed/24977095

78. Bergstrom, A., Pisani, P., Tenet, V., et al. *Overweight as an avoidable cause of cancer in Europe.* Int J Cancer, 2001. **91:** p. 421-30. https://www.ncbi.nlm.nih.gov/pubmed/11169969

79. Reeves, K. W., Carter, G. C., Rodabough, R. J., et al. *Obesity in relation to endometrial cancer risk and disease characteristics in the Women's Health Initiative.* Gynecol Oncol, 2011. **121:** p. 376-82. https://www.ncbi.nlm.nih.gov/pubmed/21324514

80. Dörk, T, Hillemanns, P, Tempfer, C, et al. *Genetic Susceptibility to Endometrial Cancer: Risk Factors and Clinical Management..* Cancers (Basel), 2020. **12 (9):** https://pubmed.ncbi.nlm.nih.gov/32854222/

81. Ma, X, Zhao, LG, Sun, JW, et al. *Association between breastfeeding and risk of endometrial cancer: a meta-analysis of epidemiological studies..* Eur J Cancer Prev, 2018. **27 (2):** p. 144-151. https://pubmed.ncbi.nlm.nih.gov/26258808/

82. Setiawan VW, Pike MC, Karageorgi S, Deming S L. Anderson K, Bernstein, L, 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: p. 269-78. https://www.ncbi.nlm.nih.gov/pubmed/22831825

83. Karageorgi S, Hankinson S E, Kraft P, De Vivo I. Reproductive factors and postmenopausal hormone use in relation to endometrial cancer risk in the Nurses' Health Study cohort 1976-2004. Int J Cancer, 2009; 126: p. 208-16. https://www.ncbi.nlm.nih.gov/pubmed/19551854

84. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia, 2007; 50: p. 1365-74. https://www.ncbi.nlm.nih.gov/pubmed/17476474

85. Barone BB, Yeh HC, Snyder, C F, Peairs KS, Stein KB, Derr RL. et.al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. Jama, 2008; 300: p. 2754-64. https://www.ncbi.nlm.nih.gov/pubmed/19088353

86. Huang Y. Cai X, Qiu M, Chen P, Tang H, Hu Y, et.al. Prediabetes and the risk of cancer: a meta-analysis. Diabetologia, 2014; 57: p. 2261-9. https://www.ncbi.nlm.nih.gov/pubmed/25208757

87. Zhang ZH. Su PY, Hao JH, Sun, Y H, 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: p. 294-303. https://www.ncbi.nlm.nih.gov/pubmed/23287960

88. Liao C, Zhang D, Mungo C, Andrew Tompkins D, Zeidan AM. 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: p. 163-171. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4404750/

89. Luo J, Beresford S, Chen C, Chlebowski R, Garcia L. Kuller L, et.al. Association between diabetes, diabetes treatment and risk of developing endometrial cancer. Br J Cancer, 2014; 111: p. 1432-9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4183842/

90. Gnagnarella P. Gandini S, La Vecchia C, Maisonneuve P, Glycemic index, glycemic load, and cancer risk: a meta-analysis. Am J Clin Nutr, 2008; 87: p. 1793-801. https://www.ncbi.nlm.nih.gov/pubmed/18541570

91. Mulholland HG, Murray LJ, Cardwell CR, Cantwell MM. Dietary glycaemic index, glycaemic load and endometrial and ovarian cancer risk: a systematic review and meta-analysis. Br J Cancer, 2008; 99: p. 434-41. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2527795/

92. Choi Y, Giovannucci E. Lee JE, Glycaemic index and glycaemic load in relation to risk of diabetes-related cancers: a meta-analysis. Br J Nutr, 2012; 108: p. 1934-47. https://www.ncbi.nlm.nih.gov/pubmed/23167978

93. Nagle CM. Olsen CM, Ibiebele TI, Spurdle AB, Webb PM, 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, 2012; 52: p. 705-15. https://www.ncbi.nlm.nih.gov/pubmed/22648201

94. Bjorge T, Stocks T, Lukanova A, Tretli S, Selmer R, Manjer J. et.al. Metabolic syndrome and endometrial carcinoma. Am J Epidemiol, 2010; 171: p. 892-902. https://www.ncbi.nlm.nih.gov/pubmed/20219764

95. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care, 2012; 35: p. 2402-11. https://www.ncbi.nlm.nih.gov/pubmed/23093685

96. Baptiste CG, Battista MC, Trottier A, Baillargeon JP. Insulin and hyperandrogenism in women with polycystic ovary syndrome. J Steroid Biochem Mol Biol, 2009; 122: p. 42-52. https://www.ncbi.nlm.nih.gov/pubmed/20036327

97. Palomba S, de Wilde MA, Falbo, A, Koster MP, La Sala GB, Fauser, B C. Pregnancy complications in women with polycystic ovary syndrome. Hum Reprod Update, 2015; 21: p. 575-92. https://www.ncbi.nlm.nih.gov/pubmed/26117684

98. Fearnley EJ, Marquart L, Spurdle AB, Weinstein P, Webb P M. 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: p. 2303-8. https://www.ncbi.nlm.nih.gov/pubmed/20953904

99. Gottschau M, Kjaer SK, Jensen A, Munk C, Mellemkjaer L. Risk of cancer among women with polycystic ovary syndrome: a Danish cohort study. Gynecol Oncol, 2014; 136: p. 99-103. https://www.ncbi.nlm.nih.gov/pubmed/25451694

100. Chittenden BG, Fullerton, G, Maheshwari A, Bhattacharya S. Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review. Reprod Biomed Online, 2009; 19: p. 398-405. https://www.ncbi.nlm.nih.gov/pubmed/19778486

101. Haoula Z, Salman M, Atiomo W. Evaluating the association between endometrial cancer and polycystic ovary syndrome. Hum Reprod, 2012; 27: p. 1327-31. https://www.ncbi.nlm.nih.gov/pubmed/22367984

102. Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update, 2014; 20: p. 748-58. https://www.ncbi.nlm.nih.gov/pubmed/24688118

103. Ward KK, Roncancio AM, Shah NR, Davis, M A, Saenz CC, McHale, M T. 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: p. 579 e1-5. https://www.ncbi.nlm.nih.gov/pubmed/23938608

104. Renehan AG, Tyson M. Egger M, Heller RF, Zwahlen M, Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet, 2008; 371: p. 569-78. https://www.ncbi.nlm.nih.gov/pubmed/18280327

105. Dobbins M, Decorby K, Choi BC. The Association between Obesity and Cancer Risk: A Meta-Analysis of Observational Studies from 1985 to 2011. ISRN Prev Med, 2013; 2013: p. 680536. https://www.ncbi.nlm.nih.gov/pubmed/24977095

106. Bergstrom A, Pisani P, Tenet V, Wolk A, Adami HO. Overweight as an avoidable cause of cancer in Europe. Int J Cancer, 2001; 91: p. 421-30. https://www.ncbi.nlm.nih.gov/pubmed/11169969

107. Reeves KW, Carter GC, Rodabough RJ, Lane D, McNeeley SG, Stefanick ML. et.al. Obesity in relation to endometrial cancer risk and disease characteristics in the Women's Health Initiative. Gynecol Oncol, 2011; 121: p. 376-82. https://www.ncbi.nlm.nih.gov/pubmed/21324514

108. Cote ML, Alhajj T, Ruterbusch JJ. Bernstein, L, Brinton, L A, Blot WJ, et.al. Risk factors for endometrial cancer in black and white women: a pooled analysis from the Epidemiology of Endometrial Cancer Consortium (E2C2). Cancer Causes Control, 2014; 26: p. 287-96. https://www.ncbi.nlm.nih.gov/pubmed/25534916

109. Win AK, Reece JC, Ryan S. Family history and risk of endometrial cancer: a systematic review and meta-analysis. Obstet Gynecol, 2015; 125: p. 89-98. https://www.ncbi.nlm.nih.gov/pubmed/25560109

110. Liu J, Jiang W, Mao K, An Y. Su F, Kim BY, et.al. Elevated risks of subsequent endometrial cancer development among breast cancer survivors with different hormone receptor status: a SEER analysis. Breast Cancer Res Treat, 2015; 150: p. 439-45. https://www.ncbi.nlm.nih.gov/pubmed/25764167

111. Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough, M L. Association between dietary fiber and endometrial cancer: a dose-response meta-analysis. Am J Clin Nutr, 2007; 86: p. 1730-7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2214669/

112. Myung SK. Ju W, Choi HJ, Kim SC, Soy intake and risk of endocrine-related gynaecological cancer: a meta-analysis. BJOG, 2009; 116: p. 1697-705. https://www.ncbi.nlm.nih.gov/pubmed/19775307

113. Ollberding NJ, Lim U, Wilkens LR, Setiawan VW, Shvetsov YB, Henderson, B E. et.al. Legume, soy, tofu, and isoflavone intake and endometrial cancer risk in postmenopausal women in the multiethnic cohort study. J Natl Cancer Inst, 2011; 104: p. 67-76. https://www.ncbi.nlm.nih.gov/pubmed/22158125

114. Bandera EV, Gifkins DM, Moore DF, McCullough, M L, Kushi, L H. Antioxidant vitamins and the risk of endometrial cancer: a dose-response meta-analysis. Cancer Causes Control, 2009; 20: p. 699-711. https://www.ncbi.nlm.nih.gov/pubmed/19083131

115. Inoue-Choi M, Robien K, Mariani A, Cerhan JR, Anderson K E. Sugar-sweetened beverage intake and the risk of type I and type II endometrial cancer among postmenopausal women. Cancer Epidemiol Biomarkers Prev, 2013; 22: p. 2384-94. https://www.ncbi.nlm.nih.gov/pubmed/24273064

116. Yu X, Bao Z, Zou J. Dong J, Coffee consumption and risk of cancers: a meta-analysis of cohort studies. BMC Cancer, 2011; 11: p. 96. https://www.ncbi.nlm.nih.gov/pubmed/21406107

117. Je Y, Hankinson SE, Tworoger SS, De Vivo I, Giovannucci, E. A prospective cohort study of coffee consumption and risk of endometrial cancer over a 26-year follow-up. Cancer Epidemiol Biomarkers Prev, 2011; 20: p. 2487-95. https://www.ncbi.nlm.nih.gov/pubmed/22109346

118. Bravi F, Scotti L, Bosetti C. Gallus S, Negri E, La Vecchia C, et.al. Coffee drinking and endometrial cancer risk: a metaanalysis of observational studies. Am J Obstet Gynecol, 2009; 200: p. 130-5. https://www.ncbi.nlm.nih.gov/pubmed/19110217

119. Uccella S, Mariani A, Wang A H, Vierkant RA, Cliby WA, Robien K. et.al. Intake of coffee, caffeine and other methylxanthines and risk of Type I vs Type II endometrial cancer. Br J Cancer, 2013; 109: p. 1908-13. https://www.ncbi.nlm.nih.gov/pubmed/24022184

120. Tang NP, Li H, Qiu YL, Zhou GM, Ma J. Tea consumption and risk of endometrial cancer: a metaanalysis. Am J Obstet Gynecol, 2009; 201: p. 605.e1-8. https://www.ncbi.nlm.nih.gov/pubmed/19766982

121. Ma. X, Zhao, LG, Sun, JW, Yang, Y, Zheng, JL, Gao, J, et.al. Association between breastfeeding and risk of endometrial cancer: a meta-analysis of epidemiological studies. 2018; 27 (2)(2): p. 144-151. https://pubmed.ncbi.nlm.nih.gov/26258808/

122. McCullough ML, Bandera EV, Moore DF, Kushi, L H. Vitamin D and calcium intake in relation to risk of endometrial cancer: a systematic review of the literature. Prev Med, 2007; 46: p. 298-302. https://www.ncbi.nlm.nih.gov/pubmed/18155758

123. Neill AS, Nagle CM. Protani, M M, Obermair A, Spurdle AB, Webb PM, Aspirin, nonsteroidal anti-inflammatory drugs, paracetamol and risk of endometrial cancer: a case-control study, systematic review and meta-analysis. Int J Cancer, 2012; 132: p. 1146-55. https://www.ncbi.nlm.nih.gov/pubmed/22777678

124. Zhou B, Yang L, Sun Q, Cong R, Gu H, Tang N. et.al. Cigarette smoking and the risk of endometrial cancer: a meta-analysis. Am J Med, 2008; 121: p. 501-508.e3. https://www.ncbi.nlm.nih.gov/pubmed/18501231

125. Viswanathan AN, Hankinson SE, Schernhammer, E S. Night shift work and the risk of endometrial cancer. Cancer Res, 2007; 67: p. 10618-22. https://www.ncbi.nlm.nih.gov/pubmed/17975006

126. Raglan, Olivia, Kalliala, Ilkka, Markozannes, Georgios, Cividini, Sofia, Gunter, Marc J. Nautiyal, Jaya, et.al. Risk factors for endometrial cancer: An umbrella review of the literature. International journal of cancer, 2019; 145(7): p. 1719-1730. https://doi.org/10.1002/ijc.31961http://europepmc.org/abstract/MED/30387875,

127. Kohler, LN, Garcia, DO, Harris, RB, et al. *Adherence to Diet and Physical Activity Cancer Prevention Guidelines and Cancer Outcomes: A Systematic Review.*. Cancer Epidemiol Biomarkers Prev, 2016. **25 (7):** p. 1018-28. https://pubmed.ncbi.nlm.nih.gov/27340121/

128. Zhang, X, Rhoades, J, Caan, BJ, et al. *Intentional weight loss, weight cycling, and endometrial cancer risk: a systematic review and meta-analysis.*. Int J Gynecol Cancer, 2019. **29 (9):** p. 1361-1371. https://pubmed.ncbi.nlm.nih.gov/31451560/

129. Keum, N., Ju, W., Lee, D. H., et al. *Leisure-time physical activity and endometrial cancer risk: dose-response meta-analysis of epidemiological studies.* Int J Cancer, 2014. **135:** p. 682-94. https://www.ncbi.nlm.nih.gov/pubmed/24375149

130. Gierach, G. L., Chang, S. C., Brinton, L. A., et al. *Physical activity, sedentary behavior, and endometrial cancer risk in the NIH-AARP Diet and Health Study.* Int J Cancer, 2009. **124:** p. 2139-47. https://www.ncbi.nlm.nih.gov/pubmed/19123463

131. Moore, S. C., Gierach, G. L., Schatzkin, A., et al. *Physical activity, sedentary behaviours, and the prevention of endometrial cancer.* Br J Cancer, 2010. **103:** p. 933-8. https://www.ncbi.nlm.nih.gov/pubmed/20877336

132. Voskuil, D. W., Monninkhof, E. M., Elias, S. G., et al. *Physical activity and endometrial cancer risk, a systematic review of current evidence.* Cancer Epidemiol Biomarkers Prev, 2007. **16:** p. 639-48. https://www.ncbi.nlm.nih.gov/pubmed/17416752

133. Schmid, D., Leitzmann, M. F.. *Television viewing and time spent sedentary in relation to cancer risk: a meta-analysis.* J Natl Cancer Inst, 2014. **106:** https://www.ncbi.nlm.nih.gov/pubmed/24935969

134. Soini, T., Hurskainen, R., Grenman, S., et al. *Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland.* Obstet Gynecol, 2014. **124:** p. 292-9. https://www.ncbi.nlm.nih.gov/pubmed/25004338

135. Felix, A. S., Gaudet, M. M., La Vecchia, C., et al. *Intrauterine devices and endometrial cancer risk: a pooled analysis of the Epidemiology of Endometrial Cancer Consortium.* Int J Cancer, 2014. **136:** p. E410-22. https://www.ncbi.nlm.nih.gov/pubmed/25242594

136. Keum N, Ju W, Lee DH, Ding EL, Hsieh CC, Goodman JE. et.al. Leisure-time physical activity and endometrial cancer risk: dose-response meta-analysis of epidemiological studies. Int J Cancer, 2014; 135: p. 682-94. https://www.ncbi.nlm.nih.gov/pubmed/24375149

137. Gierach GL, Chang SC, Brinton, L A. Lacey JV, Jr. Hollenbeck, A R, Schatzkin, A, et.al. Physical activity, sedentary behavior, and endometrial cancer risk in the NIH-AARP Diet and Health Study. Int J Cancer, 2009; 124: p. 2139-47. https://www.ncbi.nlm.nih.gov/pubmed/19123463

138. Moore SC, Gierach GL, Schatzkin A, Matthews, C E. Physical activity, sedentary behaviours, and the prevention of endometrial cancer. Br J Cancer, 2010; 103: p. 933-8. https://www.ncbi.nlm.nih.gov/pubmed/20877336

139. Voskuil DW, Monninkhof EM, Elias SG, Vlems FA, van Leeuwen FE. Physical activity and endometrial cancer risk, a systematic review of current evidence. Cancer Epidemiol Biomarkers Prev, 2007; 16: p. 639-48. https://www.ncbi.nlm.nih.gov/pubmed/17416752

140. Schmid D, Leitzmann MF. Television viewing and time spent sedentary in relation to cancer risk: a meta-analysis. J Natl Cancer Inst, 2014; 106. https://www.ncbi.nlm.nih.gov/pubmed/24935969

141. Soini T, Hurskainen R, Grenman S, Maenpaa J, Paavonen J, Pukkala E. Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. Obstet Gynecol, 2014; 124: p. 292-9. https://www.ncbi.nlm.nih.gov/pubmed/25004338

142. Felix AS, Gaudet MM, La Vecchia C, Nagle C M, Shu XO, Weiderpass E. et.al. Intrauterine devices and endometrial cancer risk: a pooled analysis of the Epidemiology of Endometrial Cancer Consortium. Int J Cancer, 2014; 136: p. E410-22. https://www.ncbi.nlm.nih.gov/pubmed/25242594

143. Ward KK, Roncancio AM, Shah NR, Davis, M A, Saenz CC, McHale, M T. et.al. Bariatric surgery decreases the risk of uterine malignancy. Gynecol Oncol, 2014; 133: p. 63-6. https://www.ncbi.nlm.nih.gov/pubmed/24680593

144. Neff R, Havrilesky LJ, Chino, J, O'Malley DM, Cohn DE. Bariatric surgery as a means to decrease mortality in women with type I endometrial cancer - An intriguing option in a population at risk for

dying of complications of metabolic syndrome. Gynecol Oncol, 2015; 138: p. 597-602. https://www.ncbi.nlm.nih.gov/pubmed/26232518

145. Ishihara. BP, Farah, D, Fonseca, MCM, Nazario, A, The risk of developing breast, ovarian, and endometrial cancer in obese women submitted to bariatric surgery: a meta-analysis. 2020; 16 (10)(10): p. 1596-1602. https://pubmed.ncbi.nlm.nih.gov/32690459/

146. Raatz H. Glinz, Dominik, Systematische Reviews und Bewertung der Qualität der Evidenz im Rahmen der S3-Leitlinie EndometriumkarzinomCEB, 2015; p. 1-45. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Endometriumkarzinom/Evidenzbericht_Screening_CEB_Basel.pdf

147. Woolas R, Talaat A. Anderson M, Brinkmann D, Gardner F, Gentry-Maharaj A, et.al. Significant endometrial pathology detected during a transvaginal ultrasound screening trial for ovarian cancer. Gynecologic Oncology, 2011; 120, Supplement 1: p. S39.

148. Jacobs I, Gentry-Maharaj A. Burnell M, Manchanda R, Singh N, Sharma A, et.al. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. Lancet Oncol, 2010; 12: p. 38-48. https://www.ncbi.nlm.nih.gov/pubmed/21147030

149. Jacobs I, Gentry-Maharaj A. Burnell M, Manchanda R, Singh N, Sharma A, et.al. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. Lancet Oncol, 2010; 12: p. 38-48. https://www.ncbi.nlm.nih.gov/pubmed/21147030

150. Breijer MC, Peeters JA, Opmeer BC, Clark TJ, Verheijen RH, Mol BW. et.al. Capacity of endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal women: a systematic review and meta-analysis. Ultrasound Obstet Gynecol, 2012; 40: p. 621-9. https://www.ncbi.nlm.nih.gov/pubmed/23001905

151. Alcázar. JL, Bonilla, L, Marucco, J, Padilla, AI, Chacón, E, Manzour, N, et.al. Risk of endometrial cancer and endometrial hyperplasia with atypia in asymptomatic postmenopausal women with endometrial thickness ≥ 11 mm: A systematic review and meta-analysis. 2018; 46 (9)(9): p. 565-570. https://pubmed.ncbi.nlm.nih.gov/30113073/

152. Smith-Bindman. R, Weiss, E, Feldstein, V, How thick is too thick? When endometrial thickness should prompt biopsy in postmenopausal women without vaginal bleeding. 2004; 24 (5)(5): p. 558-65. https://pubmed.ncbi.nlm.nih.gov/15386607/

153. Epstein. E, Fischerova, D, Valentin, L, Testa, AC, Franchi, D, Sladkevicius, P, et.al. Ultrasound characteristics of endometrial cancer as defined by International Endometrial Tumor Analysis (IETA) consensus nomenclature: prospective multicenter study. 2018; 51 (6)(6): p. 818-828. https://pubmed.ncbi.nlm.nih.gov/28944985/

154. Manchanda, R., Saridogan, E., Abdelraheim, A., et al. *Annual outpatient hysteroscopy and endometrial sampling (OHES) in HNPCC/Lynch syndrome (LS).* Arch Gynecol Obstet, 2012. **286:** p. 1555-62. https://www.ncbi.nlm.nih.gov/pubmed/22865035

155. Helder-Woolderink, J. M., De Bock, G. H., Sijmons, R. H., et al. *The additional value of endometrial sampling in the early detection of endometrial cancer in women with Lynch syndrome.* Gynecol Oncol, 2013. **131:** p. 304-8. https://www.ncbi.nlm.nih.gov/pubmed/23769810

156. Raatz, H., Glinz, Dominik. *Systematische Reviews und Bewertung der Qualität der Evidenz im Rahmen der S3-Leitlinie Endometriumkarzinom.* 2015. p. 1-45. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Endometriumkarzinom/Evidenzbericht_Screening_CEB_Basel.pdf

157. Vasen HF, Blanco I, Aktan-Collan K, Gopie JP, Alonso A, Aretz S. et.al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut, 2013; 62: p. 812-23. https://www.ncbi.nlm.nih.gov/pubmed/23408351

158. Fleming, CA, Heneghan, HM, O'Brien, D, et al. *Meta-analysis of the cumulative risk of endometrial malignancy and systematic review of endometrial surveillance in extended tamoxifen therapy.*. Br J Surg, 2018. **105 (9):** p. 1098-1106. https://pubmed.ncbi.nlm.nih.gov/29974455/

159. Saccardi, C., Gizzo, S., Patrelli, T. S., et al. *Endometrial surveillance in tamoxifen users: role, timing and accuracy of hysteroscopic investigation: observational longitudinal cohort study.* Endocr Relat Cancer, 2013. **20:** p. 455-62. https://www.ncbi.nlm.nih.gov/pubmed/23629476

160. Gao, W. L., Zhang, L. P., Feng, L. M.. *Comparative study of transvaginal ultrasonographic and diagnostic hysteroscopic findings in postmenopausal breast cancer patients treated with tamoxifen.* Chin Med J (Engl), 2011. **124:** p. 2335-9. https://www.ncbi.nlm.nih.gov/pubmed/21933565

161. Bertelli, G., Valenzano, M., Costantini, S., et al. *Limited value of sonohysterography for endometrial screening in asymptomatic, postmenopausal patients treated with tamoxifen.* Gynecol Oncol, 2000. **78:** p. 275-7. https://www.ncbi.nlm.nih.gov/pubmed/10985880

162. Gerber, B., Krause, A., Muller, H., 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:** p. 3464-70. https://www.ncbi.nlm.nih.gov/pubmed/11032586

163. Fung, M. F., Reid, A., Faught, W., et al. *Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen.* Gynecol Oncol, 2003. **91:** p. 154-9. https://www.ncbi.nlm.nih.gov/pubmed/14529676

164. Gao WL, Zhang, L P, Feng, L M. Comparative study of transvaginal ultrasonographic and diagnostic hysteroscopic findings in postmenopausal breast cancer patients treated with tamoxifen. Chin Med J (Engl), 2011; 124: p. 2335-9. https://www.ncbi.nlm.nih.gov/pubmed/21933565

165. Bertelli G, Valenzano M, Costantini S, Rissone R, Angiolini C, Signorini A. et.al. Limited value of sonohysterography for endometrial screening in asymptomatic, postmenopausal patients treated with tamoxifen. Gynecol Oncol, 2000; 78: p. 275-7. https://www.ncbi.nlm.nih.gov/pubmed/10985880

166. Gerber B, Krause A, Muller H, Reimer T, Kulz T, Makovitzky J. 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: p. 3464-70. https://www.ncbi.nlm.nih.gov/pubmed/11032586

167. Fung MF, Reid A, Faught W, Le T, Chenier C, Verma S. et.al. Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen. Gynecol Oncol, 2003; 91: p. 154-9. https://www.ncbi.nlm.nih.gov/pubmed/14529676

168. Saccardi C, Gizzo S. Patrelli TS, Ancona E, Anis O, Di Gangi S, et.al. Endometrial surveillance in tamoxifen users: role, timing and accuracy of hysteroscopic investigation: observational longitudinal cohort study. Endocr Relat Cancer, 2013; 20: p. 455-62. https://www.ncbi.nlm.nih.gov/pubmed/23629476

169. Van den Bosch T, Van Schoubroeck D. Ameye L, De Brabanter J, Van Huffel S, Timmerman D, Ultrasound assessment of endometrial thickness and endometrial polyps in women on hormonal replacement therapy. Am J Obstet Gynecol, 2003; 188: p. 1249-53. https://www.ncbi.nlm.nih.gov/pubmed/12748493

170. Pennant, M. E., Mehta, R., Moody, P., et al. *Premenopausal abnormal uterine bleeding and risk of endometrial cancer.* BJOG, 2016. **124:** p. 404-411. https://www.ncbi.nlm.nih.gov/pubmed/27766759

171. Huang, G. S., Gebb, J. S., Einstein, M. H., et al. *Accuracy of preoperative endometrial sampling for the detection of high-grade endometrial tumors.* Am J Obstet Gynecol, 2007. **196:** p. 243 e1-5. https://www.ncbi.nlm.nih.gov/pubmed/17346538

172. Leitao, M. M., Jr., Kehoe, S., Barakat, R. R., et al. *Accuracy of preoperative endometrial sampling diagnosis of FIGO grade 1 endometrial adenocarcinoma.* Gynecol Oncol, 2008. **111:** p. 244-8. https://www.ncbi.nlm.nih.gov/pubmed/18752842

173. Clark, T. J., Mann, C. H., Shah, N., et al. *Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review (Structured abstract).* BJOG. An International Journal of Obstetrics and Gynaecology, 2002. **109:** p. 313-321. https://www.ncbi.nlm.nih.gov/pubmed/11950187

174. Al-Azemi, M., Labib, N. S., Motawy, M. M., et al. *Prevalence of endometrial proliferation in Pipelle biopsies in tamoxifen-treated postmenopausal women with breast cancer in Kuwait.* Med Princ Pract, 2003. **13:** p. 30-4. https://www.ncbi.nlm.nih.gov/pubmed/14657616

175. Pennant ME. Mehta R, Moody P, Hackett G, Prentice A, Sharp SJ, et.al. Premenopausal abnormal uterine bleeding and risk of endometrial cancer. BJOG, 2016; 124: p. 404-411. https://www.ncbi.nlm.nih.gov/pubmed/27766759

176. Van Den Bosch. T, Verbakel, JY, Valentin, L, Wynants, L, De Cock, B, Pascual, MA, et.al. Typical ultrasound features of various endometrial pathologies described using International Endometrial Tumor Analysis (IETA) terminology in women with abnormal uterine bleeding. 2021; 57 (1)(1): p. 164-172. https://pubmed.ncbi.nlm.nih.gov/32484286/

177. Leone. FP, Timmerman, D, Bourne, T, Valentin, L, Epstein, E, Goldstein, SR, et.al. Terms, definitions and measurements to describe the sonographic features of the endometrium and intrauterine lesions: a consensus opinion from the International Endometrial Tumor Analysis (IETA) group. 2010; 35 (1)(1): p. 103-12. https://pubmed.ncbi.nlm.nih.gov/20014360/

178. Munro. MG, Critchley, HO, Broder, MS, Fraser, IS, FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. 2011; 113 (1)(1): p. 3-13. https://pubmed.ncbi.nlm.nih.gov/21345435/

179. Wise MR, Gill P, Lensen S, Thompson JM. Farquhar CM, Body mass index trumps age in decision for endometrial biopsy: cohort study of symptomatic premenopausal women. Am J Obstet Gynecol, 2016; 215: p. 598 e1-598 e8. https://www.ncbi.nlm.nih.gov/pubmed/27287687

180. Ge. L, Liu, G, Hu, K, Huang, K, Zhang, M, Zhou, J, et.al. A New Risk Index Combining d-Dimer, Fibrinogen, HE4, and CA199 Differentiates Suspecting Endometrial Cancer From Patients With Abnormal Vaginal Bleeding or Discharge. 19: p. 1533033819901117. https://pubmed.ncbi.nlm.nih.gov/32167027/

181. Li. J, Wang, X, Qu, W, Wang, J, Jiang, SW, Comparison of serum human epididymis protein 4 and CA125 on endometrial cancer detection: A meta-analysis. 2019; 488: p. 215-220. https://pubmed.ncbi.nlm.nih.gov/30414437/

182. Matsuo K, Opper NR, Ciccone MA, Garcia J, Tierney K E, Baba T. et.al. Time interval between endometrial biopsy and surgical staging for type I endometrial cancer: association between tumor characteristics and survival outcome. Obstet Gynecol, 2015; 125: p. 424-33. https://www.ncbi.nlm.nih.gov/pubmed/25569000

183. Clark TJ. Voit D, Gupta, J K, Hyde C, Song F, Khan, K S, Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. JAMA, 2002; 288: p. 1610-21. https://www.ncbi.nlm.nih.gov/pubmed/12350192

184. Svirsky R. Smorgick N, Rozowski U, Sagiv R, Feingold M, Halperin R, et.al. Can we rely on blind endometrial biopsy for detection of focal intrauterine pathology? Am J Obstet Gynecol, 2008; 199: p. 115 e1-3. https://www.ncbi.nlm.nih.gov/pubmed/18456238

185. Leitao MM, Jr. Kehoe S, Barakat RR, Alektiar K, Gattoc LP, Rabbitt C. et.al. Accuracy of preoperative endometrial sampling diagnosis of FIGO grade 1 endometrial adenocarcinoma. Gynecol Oncol, 2008; 111: p. 244-8. https://www.ncbi.nlm.nih.gov/pubmed/18752842

186. Huang GS, Gebb JS, Einstein MH, Shahabi, S, Novetsky AP, Goldberg GL. Accuracy of preoperative endometrial sampling for the detection of high-grade endometrial tumors. Am J Obstet Gynecol, 2007; 196: p. 243 e1-5. https://www.ncbi.nlm.nih.gov/pubmed/17346538

187. Deckardt R, Lueken R P, Gallinat A, Möller CP, Busche D, Nugent W. et.al. Comparison of Transvaginal Ultrasound, Hysteroscopy, and Dilatation and Curettage in the Diagnosis of Abnormal Vaginal Bleeding and Intrauterine Pathology in Perimenopausal and Postmenopausal Women. The Journal of the American Association of Gynecologic Laparoscopists, 2002; 9(3): p. 277-282.

188. Dueholm M, Hjorth IM, Secher P, Jorgensen A, Ortoft G. Structured Hysteroscopic Evaluation of Endometrium in Women With Postmenopausal Bleeding. J Minim Invasive Gynecol, 2015; 22: p. 1215-24. https://www.ncbi.nlm.nih.gov/pubmed/26140830

189. Guido RS, Kanbour-Shakir A. Rulin MC, Christopherson WA, Pipelle endometrial sampling. Sensitivity in the detection of endometrial cancer. J Reprod Med, 1995; 40: p. 553-5. https://www.ncbi.nlm.nih.gov/pubmed/7473450

190. Tanriverdi HA, Barut, A, Gun BD, Kaya E. Is Pipelle biopsy really adequate for diagnosing endometrial disease? Med Sci Monit, 2004; 10: p. CR271-4. https://www.ncbi.nlm.nih.gov/pubmed/15173672

191. Del Priore G, Williams R, Harbatkin CB, Wan LS, Mittal K, Yang G C. Endometrial brush biopsy for the diagnosis of endometrial cancer. J Reprod Med, 2001; 46: p. 439-43. https://www.ncbi.nlm.nih.gov/pubmed/11396369

192. Fakhar S, Saeed G, Khan AH, Alam AY. Validity of Pipelle endometrial sampling in patients with abnormal uterine bleeding. Ann Saudi Med, 2008; 28: p. 188-91. https://www.ncbi.nlm.nih.gov/pubmed/18500186

193. Abdelazim IA, Abdelrazak KM, Elbiaa, A A, Al-Kadi, M, Yehia, A H. Accuracy of endometrial sampling compared to conventional dilatation and curettage in women with abnormal uterine bleeding. Arch Gynecol Obstet, 2014; 291: p. 1121-6. https://www.ncbi.nlm.nih.gov/pubmed/25367600

194. Sanam M. Majid M M, Comparison the Diagnostic Value of Dilatation and Curettage Versus Endometrial Biopsy by Pipelle--a Clinical Trial. Asian Pac J Cancer Prev, 2015; 16: p. 4971-5. https://www.ncbi.nlm.nih.gov/pubmed/26163624

195. Wu HH, Harshbarger KE, Berner HW, Elsheikh TM. Endometrial brush biopsy (Tao brush). Histologic diagnosis of 200 cases with complementary cytology: an accurate sampling technique for the detection of endometrial abnormalities. Am J Clin Pathol, 2000; 114: p. 412-8. https://www.ncbi.nlm.nih.gov/pubmed/10989642

196. Wu HH, Casto BD, Elsheikh TM. Endometrial brush biopsy. An accurate outpatient method of detecting endometrial malignancy. J Reprod Med, 2003; 48: p. 41-5. https://www.ncbi.nlm.nih.gov/pubmed/12611094

197. Williams AR. Brechin S, Porter AJ, Warner P, Critchley HO, Factors affecting adequacy of Pipelle and Tao Brush endometrial sampling. BJOG, 2008; 115: p. 1028-36. https://www.ncbi.nlm.nih.gov/pubmed/18651884

198. Critchley HO, Warner P, Lee AJ, Brechin S, Guise, J, Graham B. Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status. Health Technol Assess, 2004; 8: p. iii-iv, 1-139. https://www.ncbi.nlm.nih.gov/pubmed/15361316

199. Al-Azemi M, Labib NS, Motawy M M, Temmim L, Moussa M A, Omu, A E. Prevalence of endometrial proliferation in Pipelle biopsies in tamoxifen-treated postmenopausal women with breast cancer in Kuwait. Med Princ Pract, 2003; 13: p. 30-4. https://www.ncbi.nlm.nih.gov/pubmed/14657616

200. Narice. BF, Delaney, B, Dickson, JM, Endometrial sampling in low-risk patients with abnormal uterine bleeding: a systematic review and meta-synthesis. 2018; 19 (1)(1): p. 135. https://pubmed.ncbi.nlm.nih.gov/30060741/

201. Verdoodt. F, Jiang, X, Williams, M, Schnatz, PF, Arbyn, M, High-risk HPV testing in the management of atypical glandular cells: A systematic review and meta-analysis. 2016; 138 (2)(2): p. 303-10. https://pubmed.ncbi.nlm.nih.gov/25583258/

202. Timmermans, A., Opmeer, B. C., Khan, K. S., et al. *Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis.* Obstet Gynecol, 2010. **116:** p. 160-7. https://www.ncbi.nlm.nih.gov/pubmed/20567183

203. Clarke. MA, Long, BJ, Del Mar Morillo, A, Arbyn, M, Bakkum-Gamez, JN, Wentzensen, N, Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. 2018; 178 (9)(9): p. 1210-1222. https://pubmed.ncbi.nlm.nih.gov/30083701/

204. Timmermans A, Opmeer BC, Khan KS, Bachmann LM, Epstein E, Clark TJ. et.al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. Obstet Gynecol, 2010; 116: p. 160-7. https://www.ncbi.nlm.nih.gov/pubmed/20567183

205. Bittencourt. CA, Dos Santos Simões, R, Bernardo, WM, Fuchs, LFP, Soares Júnior, JM, Pastore, AR, et.al. Accuracy of saline contrast sonohysterography in detection of endometrial polyps and submucosal leiomyomas in women of reproductive age with abnormal uterine bleeding: systematic review and meta-analysis. 2017; 50 (1)(1): p. 32-39. https://pubmed.ncbi.nlm.nih.gov/27862503/

206. Nieuwenhuis. LL, Hermans, FJ, Bij de Vaate, AJM, Leeflang, MM, Brölmann, HA, Hehenkamp, WJ, et.al. Three-dimensional saline infusion sonography compared to two-dimensional saline infusion sonography for the diagnosis of focal intracavitary lesions. 2017; 5: p. CD011126. https://pubmed.ncbi.nlm.nih.gov/28472862/

207. Vroom. AJ, Timmermans, A, Bongers, MY, van den Heuvel, ER, Geomini, PMAJ, van Hanegem, N, Diagnostic accuracy of saline contrast sonohysterography in detecting endometrial polyps in women with postmenopausal bleeding: systematic review and meta-analysis. 2019; 54 (1)(1): p. 28-34. https://pubmed.ncbi.nlm.nih.gov/30693579/

208. Endometriumcarcinoom, Endometriumcarcinoom, 2011. https://www.oncoline.nl/endometriumcarcinoom

209. Lalwani N. Dubinsky T, Javitt MC, Gaffney DK, Glanc P, Elshaikh MA, et.al. ACR Appropriateness Criteria(®) pretreatment evaluation and follow-up of endometrial cancer. Ultrasound Q, 2014; 30: p. 21-8. https://www.ncbi.nlm.nih.gov/pubmed/24901775

210. Amkreutz LC, Mertens HJ, Nurseta T, Engelen MJ, Bergmans M, Nolting E. et.al. The value of imaging of the lungs in the diagnostic workup of patients with endometrial cancer. Gynecol Oncol, 2013; 131: p. 147-50. https://www.ncbi.nlm.nih.gov/pubmed/23838035

211. Savelli, L., Ceccarini, M., Ludovisi, M., et al. *Preoperative local staging of endometrial cancer: transvaginal sonography vs. magnetic resonance imaging.* Ultrasound Obstet Gynecol, 2008. **31:** p. 560-6. https://www.ncbi.nlm.nih.gov/pubmed/18398926

212. Savelli L, Ceccarini M, Ludovisi M, Fruscella E. De Iaco PA, Salizzoni E, et.al. Preoperative local staging of endometrial cancer: transvaginal sonography vs. magnetic resonance imaging. Ultrasound Obstet Gynecol, 2008; 31: p. 560-6. https://www.ncbi.nlm.nih.gov/pubmed/18398926

213. Alc<PLACEHOLDER_3/>zar. JL, Pérez, L, Güell, O, Haro, N, Manzour, N, Chacon, E, et.al. Diagnostic Performance of Transvaginal Ultrasound for Detecting Cervical Invasion In Women With Endometrial Carcinoma: A Systematic Review and Meta-analysis. 2019; 38 (1)(1): p. 179-189. https://pubmed.ncbi.nlm.nih.gov/29732585/

214. *Endometriumcarcinoom.* 2011. https://www.oncoline.nl/endometriumcarcinoom

215. Lalwani, N., Dubinsky, T., Javitt, M. C., et al. *ACR Appropriateness Criteria(®) pretreatment evaluation and follow-up of endometrial cancer.* Ultrasound Q, 2014. **30:** p. 21-8. https://www.ncbi.nlm.nih.gov/pubmed/24901775

216. Selman, T. J., Mann, C. H., Zamora, J., et al. *A systematic review of tests for lymph node status in primary endometrial cancer.* BMC Womens Health, 2008. **8:** p. 8. https://www.ncbi.nlm.nih.gov/pubmed/18457596

217. *18F-FDG PET or PET/CT for detection of metastatic lymph nodes in patients with endometrial cancer: a systematic review and meta-analysis.* 2012. https://www.ncbi.nlm.nih.gov/pubmed/22305013

218. Kakhki, V. R., Shahriari, S., Treglia, G., 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.* Int J Gynecol Cancer, 2013. **23:** p. 1536-43. https://www.ncbi.nlm.nih.gov/pubmed/24172090

219. Antonsen, S. L., Jensen, L. N., Loft, A., et al. *MRI, PET/CT and ultrasound in the preoperative staging of endometrial cancer - a multicenter prospective comparative study.* Gynecol Oncol, 2012. **128:** p. 300-8.

220. Nougaret. S, Horta, M, Sala, E, Lakhman, Y, Thomassin-Naggara, I, Kido, A, et.al. Endometrial Cancer MRI staging: Updated Guidelines of the European Society of Urogenital Radiology. 2019; 29 (2)(2): p. 792-805. https://pubmed.ncbi.nlm.nih.gov/29995239/

221. Haldorsen IS, Gruner R, Husby JA, Magnussen IJ, Werner HM, Salvesen OO. et.al. Dynamic contrast-enhanced MRI in endometrial carcinoma identifies patients at increased risk of recurrence. Eur Radiol, 2013; 23: p. 2916-25. https://www.ncbi.nlm.nih.gov/pubmed/23732687

222. Luomaranta A, Leminen A, Loukovaara M. Magnetic Resonance Imaging in the Assessment of High-Risk Features of Endometrial Carcinoma: A Meta-Analysis. Int J Gynecol Cancer, 2014. https://www.ncbi.nlm.nih.gov/pubmed/25010040

223. Radiologic staging in patients with endometrial cancer: a meta-analysis. 1999. https://www.ncbi.nlm.nih.gov/pubmed/10478237

224. Andreano A, Rechichi G, Rebora P, Sironi S. Valsecchi MG, Galimberti S, MR diffusion imaging for preoperative staging of myometrial invasion in patients with endometrial cancer: a systematic review and meta-analysis. Eur Radiol, 2014; 24: p. 1327-38. https://www.ncbi.nlm.nih.gov/pubmed/24668009

225. Das SK, Niu XK, Wang JL, Zeng, L C, Wang WX, Bhetuwal A. et.al. Usefulness of DWI in preoperative assessment of deep myometrial invasion in patients with endometrial carcinoma: a

systematic review and meta-analysis. Cancer Imaging, 2015; 14: p. 32. https://www.ncbi.nlm.nih.gov/pubmed/25608571

226. Tsili AC, Tsampoulas, C, Dalkalitsis N, Stefanou D, Paraskevaidis E, Efremidis SC, Local staging of endometrial carcinoma: role of multidetector CTEur Radiol, 2008; 18: p. 1043-8. https://www.ncbi.nlm.nih.gov/pubmed/18175120

227. Kitajima K, Suenaga Y, Ueno Y, Kanda T, Maeda T, Takahashi S, et.al. Value of fusion of PET and MRI for staging of endometrial cancer: comparison with (1)(8)F-FDG contrast-enhanced PET/CT and dynamic contrast-enhanced pelvic MRIEur J Radiol, 2013; 82: p. 1672-6. https://www.ncbi.nlm.nih.gov/pubmed/23727380

228. N. e, t, w, o, r, et.al. Clinical Practice Guidelines in Oncology: Uterine NeoplasmsNational Comprehensive Cancer Network, 2015; 2016:

229. Luomaranta A, Leminen A, Loukovaara M. Magnetic Resonance Imaging in the Assessment of High-Risk Features of Endometrial Carcinoma: A Meta-Analysis. Int J Gynecol Cancer, 2014. https://www.ncbi.nlm.nih.gov/pubmed/25010040

230. Chang MC, Chen JH. Liang JA, Yang KT, Cheng KY, Kao, C H, 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: p. 3511-7.

231. Antonsen SL, Ulrich, L, Hogdall C. Patients with atypical hyperplasia of the endometrium should be treated in oncological centers. Gynecol Oncol, 2011; 125: p. 124-8. https://www.ncbi.nlm.nih.gov/pubmed/22198048

232. Kakhki VR, Shahriari S, Treglia G, Hasanzadeh M, Zakavi S R, Yousefi Z. 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. Int J Gynecol Cancer, 2013; 23: p. 1536-43. https://www.ncbi.nlm.nih.gov/pubmed/24172090

233. B. o, k, h, m, a, et.al. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol, 1983; 15: p. 10-7. https://www.ncbi.nlm.nih.gov/pubmed/6822361

234. Board, WHO Classification of Tumours Editorial, Female Genital Tumours, 2020; 4:

235. Luchini. C, Bibeau, F, Ligtenberg, MJL, Singh, N, Nottegar, A, Bosse, T, et.al. ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. 2019; 30 (8)(8): p. 1232-1243. https://pubmed.ncbi.nlm.nih.gov/31056702/

236. Concin. N, Matias-Guiu, X, Vergote, I, Cibula, D, Mirza, MR, Marnitz, S, et.al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. 2021; 31 (1)(1): p. 12-39. https://pubmed.ncbi.nlm.nih.gov/33397713/

237. Vermij. L, Smit, V, Nout, R, Bosse, T, Incorporation of molecular characteristics into endometrial cancer management. 2020; 76 (1)(1): p. 52-63. https://pubmed.ncbi.nlm.nih.gov/31846532/

238. Soslow. RA, Tornos, C, Park, KJ, Malpica, A, Matias-Guiu, X, Oliva, E, et.al. Endometrial Carcinoma Diagnosis: Use of FIGO Grading and Genomic Subcategories in Clinical Practice: Recommendations of the International Society of Gynecological Pathologists. 2019; 38 Suppl 1: p. S64-S74. https://pubmed.ncbi.nlm.nih.gov/30550484/

239. Malpica. A, Euscher, ED, Hecht, JL, Ali-Fehmi, R, Quick, CM, Singh, N, et.al. Endometrial Carcinoma, Grossing and Processing Issues: Recommendations of the International Society of Gynecologic Pathologists. 2019; 38 Suppl 1: p. S9-S24. https://pubmed.ncbi.nlm.nih.gov/30550481/

240. Bell. DW, Ellenson, LH, Molecular Genetics of Endometrial Carcinoma. 2019; 14: p. 339-367. https://pubmed.ncbi.nlm.nih.gov/30332563/

241. Bokhman. JV, Two pathogenetic types of endometrial carcinoma. 1983; 15 (1)(1): p. 10-7. https://pubmed.ncbi.nlm.nih.gov/6822361/

242. Lax. SF, Kurman, RJ, A dualistic model for endometrial carcinogenesis based on immunohistochemical and molecular genetic analyses. 1997; 81: p. 228-32. https://pubmed.ncbi.nlm.nih.gov/9474874/

243. Lax. SF, Kurman, RJ, Pizer, ES, Wu, L, Ronnett, BM, A binary architectural grading system for uterine endometrial endometrioid carcinoma has superior reproducibility compared with FIGO grading and identifies subsets of advance-stage tumors with favorable and unfavorable prognosis. 2000; 24 (9)(9): p. 1201-8. https://pubmed.ncbi.nlm.nih.gov/10976693/

244. Lax. SF, Molecular genetic pathways in various types of endometrial carcinoma: from a phenotypical to a molecular-based classification. 2004; 444 (3)(3): p. 213-23. https://pubmed.ncbi.nlm.nih.gov/14747944/

245. Horn LC, Schnurrbusch U, Bilek K, Hentschel B, Einenkel J. Risk of progression in complex and atypical endometrial hyperplasia: clinicopathologic analysis in cases with and without progestogen treatment. Int J Gynecol Cancer, 2004; 14: p. 348-53. https://www.ncbi.nlm.nih.gov/pubmed/15086736

246. Semere. LG, Ko, E, Johnson, NR, Vitonis, AF, Phang, LJ, Cramer, DW, et.al. Endometrial intraepithelial neoplasia: clinical correlates and outcomes. 2011; 118 (1)(1): p. 21-28. https://pubmed.ncbi.nlm.nih.gov/21691159/

247. Lacey JV, Jr. Chia, V M. Endometrial hyperplasia and the risk of progression to carcinoma. Maturitas, 2009; 63: p. 39-44. https://www.ncbi.nlm.nih.gov/pubmed/19285814

248. Yuan. L, Biscotti, CV, Zhu, H, Booth, CN, Abdul-Karim, FW, Zhang, Y, Significance of atypical endometrial cells in women younger than 40 years of age. 9 (1)(1): p. 33-37. https://pubmed.ncbi.nlm.nih.gov/PMID:, 31353256/

249. Vetter. MH, Smith, B, Benedict, J, Hade, EM, Bixel, K, Copeland, LJ, et.al. Preoperative predictors of endometrial cancer at time of hysterectomy for endometrial intraepithelial neoplasia or complex atypical hyperplasia. 2020; 222 (1)(1): p. 60.e1-60.e7. https://pubmed.ncbi.nlm.nih.gov/31401259/

250. Bourdel. N, Chauvet, P, Tognazza, E, Pereira, B, Botchorishvili, R, Canis, M, Sampling in Atypical Endometrial Hyperplasia: Which Method Results in the Lowest Underestimation of Endometrial Cancer? A Systematic Review and Meta-analysis. 23 (5)(5): p. 692-701. https://pubmed.ncbi.nlm.nih.gov/27058769/

251. Smith. BQ, Boone, JD, Thomas, ED, Turner, TB, McGwin, G, Stisher, AM, et.al. The Reliability of Intraoperative Assessment on Predicting Tumor Size, Myometrial Invasion, and Cervical Involvement in Patients With a Preoperative Diagnosis of Complex Atypical Hyperplasia or (Clinical Stage I) Endometrial Cancer: A Prospective Cohort Study. 2020; 43 (2)(2): p. 122-127. https://pubmed.ncbi.nlm.nih.gov/31764025/

252. Wheeler. DT, Bell, KA, Kurman, RJ, Sherman, ME, Minimal uterine serous carcinoma: diagnosis and clinicopathologic correlation. 2000; 24 (6)(6): p. 797-806. https://pubmed.ncbi.nlm.nih.gov/10843281/

253. Trinh. VQ, Pelletier, MP, Echelard, P, Warkus, T, Sauthier, P, Gougeon, F, et.al. Distinct Histologic, Immunohistochemical and Clinical Features Associated With Serous Endometrial Intraepithelial Carcinoma Involving Polyps. 2020; 39 (2)(2): p. 128-135. https://pubmed.ncbi.nlm.nih.gov/30789501/

254. Mayr, Doris, Schmoeckel, Elisa, Höhn, Anne Kathrin, Hiller, Grit Gesine Ruth, Horn, Lars-Christian, Aktuelle WHO-Klassifikation des weiblichen Genitale, 2021; 42(3): p. 259 - 269. https://doi.org/10.1007/s00292-021-00933-w

255. Soslow. RA, High-grade endometrial carcinomas - strategies for typing. 2013; 62 (1)(1): p. 89-110. https://pubmed.ncbi.nlm.nih.gov/23240672/

256. Malpica. A, How to approach the many faces of endometrioid carcinoma. 2016; 29 Suppl 1: p. S29-44. https://pubmed.ncbi.nlm.nih.gov/26715172/

257. Murali. R, Davidson, B, Fadare, O, Carlson, JA, Crum, CP, Gilks, CB, et.al. High-grade Endometrial Carcinomas: Morphologic and Immunohistochemical Features, Diagnostic Challenges and Recommendations. 2019; 38 Suppl 1: p. S40-S63. https://pubmed.ncbi.nlm.nih.gov/30550483/

258. Hu. S, Hinson, JL, Matnani, R, Cibull, ML, Karabakhtsian, RG, Are the uterine serous carcinomas underdiagnosed? Histomorphologic and immunohistochemical correlates and clinical follow up in high-grade endometrial carcinomas initially diagnosed as high-grade endometrioid carcinoma. 2018; 31 (2)(2): p. 358-364. https://pubmed.ncbi.nlm.nih.gov/28984301/

259. Chen. W, Husain, A, Nelson, GS, Rambau, PF, Liu, S, Lee, CH, et.al. Immunohistochemical Profiling of Endometrial Serous Carcinoma. 2017; 36 (2)(2): p. 128-139. https://pubmed.ncbi.nlm.nih.gov/27167671/

260. Stewart. CJR, Crum, CP, McCluggage, WG, Park, KJ, Rutgers, JK, Oliva, E, et.al. Guidelines to Aid in the Distinction of Endometrial and Endocervical Carcinomas, and the Distinction of Independent Primary Carcinomas of the Endometrium and Adnexa From Metastatic Spread Between These and Other Sites. 2019; 38 Suppl 1: p. S75-S92. https://pubmed.ncbi.nlm.nih.gov/30550485/

261. Rabban. JT, Gilks, CB, Malpica, A, Matias-Guiu, X, Mittal, K, Mutter, GL, et.al. Issues in the Differential Diagnosis of Uterine Low-grade Endometrioid Carcinoma, Including Mixed Endometrial Carcinomas: Recommendations from the International Society of Gynecological Pathologists. 2019; 38 Suppl 1: p. S25-S39. https://pubmed.ncbi.nlm.nih.gov/30550482/

262. Lax. SF, Pathology of Endometrial Carcinoma. 2017; 943: p. 75-96. https://pubmed.ncbi.nlm.nih.gov/PMID:, 27910065/

263. Bell. DW, Ellenson, LH, Molecular Genetics of Endometrial Carcinoma. 2019; 14: p. 339-367. https://pubmed.ncbi.nlm.nih.gov/30332563/

264. Horn. LC, Höhn, AK, Krücken, I, Stiller, M, Obeck, U, Brambs, CE, Mesonephric-like adenocarcinomas of the uterine corpus: report of a case series and review of the literature indicating poor prognosis for this subtype of endometrial adenocarcinoma. 2020; 146 (4)(4): p. 971-983. https://pubmed.ncbi.nlm.nih.gov/31927619/

265. Euscher. ED, Bassett, R, Duose, DY, Lan, C, Wistuba, I, Ramondetta, L, et.al. Mesonephric-like Carcinoma of the Endometrium: A Subset of Endometrial Carcinoma With an Aggressive Behavior. 2020; 44 (4)(4): p. 429-443. https://pubmed.ncbi.nlm.nih.gov/31725471/

266. Horn LC, Dallacker M, Bilek K. [Carcinosarcomas (malignant mixed Mullerian tumors) of the uterus. Morphology, pathogenetic aspects and prognostic factors]. Pathologe, 2009; 30: p. 292-301. https://www.ncbi.nlm.nih.gov/pubmed/19495763

267. Artioli. G, Wabersich, J, Ludwig, K, Gardiman, MP, Borgato, L, Garbin, F, Rare uterine cancer: carcinosarcomas. Review from histology to treatment. 2015; 94 (1)(1): p. 98-104. https://pubmed.ncbi.nlm.nih.gov/25468677/

268. Zhao. S, Bellone, S, Lopez, S, Thakral, D, Schwab, C, English, DP, et.al. Mutational landscape of uterine and ovarian carcinosarcomas implicates histone genes in epithelial-mesenchymal transition. 2016; 113 (43)(43): p. 12238-12243. https://pubmed.ncbi.nlm.nih.gov/27791010/

269. Lopez-Garcia MA, Palacios J. Pathologic and molecular features of uterine carcinosarcomas. Semin Diagn Pathol, 2011; 27: p. 274-86. https://www.ncbi.nlm.nih.gov/pubmed/21309261

270. Denschlag D, Thiel FC, Ackermann S, Harter P. Juhasz-Boess I, Mallmann P, et.al. Sarcoma of the Uterus. Guideline of the DGGG (S2k-Level, AWMF Registry No. 015/074, August 2015). Geburtshilfe Frauenheilkd, 2015; 75: p. 1028-1042. https://www.ncbi.nlm.nih.gov/pubmed/26640293

271. Plotkin. A, Kuzeljevic, B, De Villa, V, Thompson, EF, Gilks, CB, Clarke, BA, et.al. Interlaboratory Concordance of ProMisE Molecular Classification of Endometrial Carcinoma Based on Endometrial Biopsy Specimens. 2020; 39 (6)(6): p. 537-545. https://pubmed.ncbi.nlm.nih.gov/32281774/

272. Casey. L, Singh, N, POLE, MMR, and MSI Testing in Endometrial Cancer: Proceedings of the ISGyP Companion Society Session at the USCAP 2020 Annual Meeting. 2021; 40 (1)(1): p. 5-16. https://pubmed.ncbi.nlm.nih.gov/33290350/

273. McCluggage. WG, Colgan, T, Duggan, M, Hacker, NF, Mulvany, N, Otis, C, 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. 2013; 32 (1)(1): p. 45-65. https://pubmed.ncbi.nlm.nih.gov/PMID:, 23202790/

274. Guerra. E, Matias-Guiu, X, Relevance of pathologic features in risk stratification for early-stage endometrial cancer. 2021; 32 (4)(4): p. e67. https://pubmed.ncbi.nlm.nih.gov/34085800/

275. Hirschowitz. L, Nucci, M, Zaino, RJ, Problematic issues in the staging of endometrial, cervical and vulval carcinomas. 2013; 62 (1)(1): p. 176-202. https://pubmed.ncbi.nlm.nih.gov/PMID:, 23240675/

276. Horn. LC, Hoehn, AK, Processing and Histopathological Workup of Hysterectomy Specimens. In: Alkatout I, Mettler L (Hrsg) Hysterectomy. A Comprehensive Surgical Approach. Springer International Publishing, 2018; p. 259 - 295.

277. Argani P, Cimino-Mathews A. Intraoperative Frozen Sections. Diagnostic PitfallsDemos Medical Publishing. Consultant Pathology, 2014; 5:

278. Williams JW, Hirschowitz L. 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, 2005; 25: p. 59-64. https://www.ncbi.nlm.nih.gov/pubmed/16306786

279. Liebig C, Ayala G, Wilks JA, Berger DH, Albo D. Perineural invasion in cancer: a review of the literature. Cancer, 2009; 115: p. 3379-91. https://www.ncbi.nlm.nih.gov/pubmed/19484787

280. Wittekind C, Brierley, JD, Lee A, van Eycken E. TNM Supplement: A Commentary on Uniform Use, 5th Edition, 2019. https://www.wiley.com/en-us/TNM+Supplement%3A+A+Commentary+on+Uniform+Use%2C+5th+Edition-p-9781119263920

281. Singh. N, Hirschowitz, L, Zaino, R, Alvarado-Cabrero, I, Duggan, MA, Ali-Fehmi, R, et.al. Pathologic Prognostic Factors in Endometrial Carcinoma (Other Than Tumor Type and Grade). 2019; 38 Suppl 1: p. S93-S113. https://pubmed.ncbi.nlm.nih.gov/30550486/

282. Folkins. AK, Nevadunsky, NS, Saleemuddin, A, Jarboe, EA, Muto, MG, Feltmate, CM, et.al. Evaluation of vascular space involvement in endometrial adenocarcinomas: laparoscopic vs abdominal hysterectomies. 2010; 23 (8)(8): p. 1073-9. https://pubmed.ncbi.nlm.nih.gov/20473276/

283. Wittekind. C, [Lymph nodes, tumour deposits, and TNM: are we getting better? 7th edition of UICC 2010 TNM classification of malignant tumors]. 2012; 188 (2)(2): p. 191-2. https://pubmed.ncbi.nlm.nih.gov/22231635/

284. Seifi. F, Parkash, V, Clark, M, Menderes, G, Tierney, C, Silasi, DA, et.al. Pseudovascular Invasion: Minimally Invasive Surgery for Endometrial Cancer. 23 (2)(2). https://pubmed.ncbi.nlm.nih.gov/31285650/

285. Peters. EEM, Bartosch, C, McCluggage, WG, Genestie, C, Lax, SF, Nout, R, et.al. Reproducibility of lymphovascular space invasion (LVSI) assessment in endometrial cancer. 2019; 75 (1)(1): p. 128-136. https://pubmed.ncbi.nlm.nih.gov/31155736/

286. Qian. Y, Pollom, EL, Nwachukwu, C, Seiger, K, von Eyben, R, Folkins, AK, et.al. Extent of lymphovascular space invasion may predict lymph node metastasis in uterine serous carcinoma. 2017; 147 (1)(1): p. 24-29. https://pubmed.ncbi.nlm.nih.gov/PMID:, 28709703/

287. Matsuo. K, Garcia-Sayre, J, Medeiros, F, Casabar, JK, Machida, H, Moeini, A, et.al. Impact of depth and extent of lymphovascular space invasion on lymph node metastasis and recurrence patterns in endometrial cancer. 2015; 112 (6)(6): p. 669-76. https://pubmed.ncbi.nlm.nih.gov/26391212/

288. Bosse T, Peters EE, Creutzberg CL, Jurgenliemk-Schulz IM, Jobsen JJ, Mens JW. et.al. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer--A pooled analysis of PORTEC 1 and 2 trials. Eur J Cancer, 2015; 51: p. 1742-50. https://www.ncbi.nlm.nih.gov/pubmed/26049688

289. Barnes. EA, Martell, K, Parra-Herran, C, Taggar, AS, Donovan, E, Leung, E, Substantial lymphovascular space invasion predicts worse outcomes in early-stage endometrioid endometrial cancer. 20 (3)(3): p. 527-535. https://pubmed.ncbi.nlm.nih.gov/33485810/

290. Pifer. PM, Bhargava, R, Patel, AK, Ling, DC, Vargo, JA, Orr, BC, et.al. Is the risk of substantial LVSI in stage I endometrial cancer similar to PORTEC in the North American population? - A single-institution study. 2020; 159 (1)(1): p. 23-29. https://pubmed.ncbi.nlm.nih.gov/32718729/

291. Winer. I, Ahmed, QF, Mert, I, Bandyopadhyay, S, Cote, M, Munkarah, AR, et.al. Significance of lymphovascular space invasion in uterine serous carcinoma: what matters more; extent or presence?, 2015; 34 (1)(1): p. 47-56. https://pubmed.ncbi.nlm.nih.gov/PMID:, 25473753/

292. Fader. AN, Roque, DM, Siegel, E, Buza, N, Hui, P, Abdelghany, O, et.al. Randomized Phase II Trial of Carboplatin-Paclitaxel Compared with Carboplatin-Paclitaxel-Trastuzumab in Advanced (Stage III-IV) or Recurrent Uterine Serous Carcinomas that Overexpress Her2/Neu (NCT01367002): Updated Overall Survival Analysis. 2020; 26 (15)(15): p. 3928-3935. https://pubmed.ncbi.nlm.nih.gov/32601075/

293. Buza. N, English, DP, Santin, AD, Hui, P, Toward standard HER2 testing of endometrial serous carcinoma: 4-year experience at a large academic center and recommendations for clinical practice. 2013; 26 (12)(12): p. 1605-12. https://pubmed.ncbi.nlm.nih.gov/23765245/

294. Quddus. MR, Hansen, K, Tantravahi, U, Sung, CJ, Human epidermal growth factor receptor 2 (Her2) testing for uterine serous carcinoma: Report of scenarios of unusual overexpression. 2020; 32: p. 100561. https://pubmed.ncbi.nlm.nih.gov/32258332/

295. Buza. N, HER2 Testing and Reporting in Endometrial Serous Carcinoma: Practical Recommendations for HER2 Immunohistochemistry and Fluorescent In Situ Hybridization: Proceedings of the ISGyP Companion Society Session at the 2020 USCAP Annual Meeting. 2021; 40 (1)(1): p. 17-23. https://pubmed.ncbi.nlm.nih.gov/33290351/

296. Rottmann. D, Assem, H, Matsumoto, N, Wong, S, Hui, P, Buza, N, Does Specimen Type Have an Impact on HER2 Status in Endometrial Serous Carcinoma? Discordant HER2 Status of Paired Endometrial Biopsy and Hysterectomy Specimens in the Presence of Frequent Intratumoral Heterogeneity. 2021; 40 (3)(3): p. 263-271. https://pubmed.ncbi.nlm.nih.gov/PMID:, 32897955/

297. Jamieson. A, Thompson, EF, Huvila, J, Gilks, CB, McAlpine, JN, p53abn Endometrial Cancer: understanding the most aggressive endometrial cancers in the era of molecular classification. 2021; 31 (6)(6): p. 907-913. https://pubmed.ncbi.nlm.nih.gov/33589443/

298. Jönsson. JM, Bååth, M, Björnheden, I, Sahin, ID, Måsbäck, A, Hedenfalk, I, Homologous Recombination Repair Mechanisms in Serous Endometrial Cancer. 2021; 13 (2)(2). https://pubmed.ncbi.nlm.nih.gov/33445465/

299. Ashley. CW, Da Cruz Paula, A, Kumar, R, Mandelker, D, Pei, X, Riaz, N, et.al. Analysis of mutational signatures in primary and metastatic endometrial cancer reveals distinct patterns of DNA repair defects and shifts during tumor progression. 2019; 152 (1)(1): p. 11-19. https://pubmed.ncbi.nlm.nih.gov/30415991/

300. Stephan JM, Hansen J, Samuelson, M, McDonald, M, Chin Y, Bender D. et.al. Intra-operative frozen section results reliably predict final pathology in endometrial cancer. Gynecol Oncol, 2014; 133: p. 499-505. https://www.ncbi.nlm.nih.gov/pubmed/24699308

301. Parkash. V, Matias-Guiu, X, Oliva, E, Malpica, A, McCluggage, WG, Current Practices in the Processing, Diagnosis, and Reporting of Endometrial Carcinoma: Results of a Web-based Survey by the International Society of Gynecological Pathologists (ISGyP). 2019; 38 Suppl 1: p. S3-S8. https://pubmed.ncbi.nlm.nih.gov/30550480/

302. Orezzoli JP, Sioletic S, Olawaiye A, Oliva E, del Carmen MG. Stage II endometrioid adenocarcinoma of the endometrium: clinical implications of cervical stromal invasion. Gynecol Oncol, 2009; 113: p. 316-23. https://www.ncbi.nlm.nih.gov/pubmed/19345400

303. Zaino RJ, Abendroth C, Yemelyanova A, Oliva E, Lim D, Soslow R. et.al. Endocervical involvement in endometrial adenocarcinoma is not prognostically significant and the pathologic assessment of the pattern of involvement is not reproducible. Gynecol Oncol, 2012; 128: p. 83-7. https://www.ncbi.nlm.nih.gov/pubmed/23063759

304. Şenol. T, Polat, M, Özkaya, E, Karateke, A, Misinterpretation of Frozen Section in Endometrial Cancer Cases: Does It Have Any Effect on Disease-free and Overall Survival?, 2017; 36 (6)(6): p. 550-554. https://pubmed.ncbi.nlm.nih.gov/PMID:, 28134667/

305. Blakely. M, Liu, Y, Rahaman, J, Prasad-Hayes, M, Tismenetsky, M, Wang, X, et.al. Sentinel Lymph Node Ultra-staging as a Supplement for Endometrial Cancer Intraoperative Frozen Section Deficiencies. 2019; 38 (1)(1): p. 52-58. https://pubmed.ncbi.nlm.nih.gov/28968296/

306. Strickland. SV, Rendi, MH, Garcia, RL, Norquist, BS, Pennington, KP, Kilgore, MR, Evaluation of Intraoperative Assessments in the Management of Endometrial Carcinoma: A Retrospective Quality Assurance Review. 2018; 37 (5)(5): p. 414-420. https://pubmed.ncbi.nlm.nih.gov/30102260/

307. Euscher E, Fox P, Bassett R, Al-Ghawi H, Ali-Fehmi R, Barbuto D. 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: p. 1728-36. https://www.ncbi.nlm.nih.gov/pubmed/24061515

308. Nakao Y, Yamasaki F, Yokoyama M, Aihara S, Yasunaga M, Iwasaka T. Minimal deviation endometrioid adenocarcinoma of the endometrium and its MRI findings. Eur J Gynaecol Oncol, 2014; 35: p. 185-7. https://www.ncbi.nlm.nih.gov/pubmed/24772926

309. Bartosch C, Manuel Lopes J, Oliva E. Endometrial carcinomas: a review emphasizing overlapping and distinctive morphological and immunohistochemical features. Adv Anat Pathol, 2011; 18: p. 415-37. https://www.ncbi.nlm.nih.gov/pubmed/21993268

310. Şenol. T, Polat, M, Özkaya, E, Karateke, A, Misinterpretation of Frozen Section in Endometrial Cancer Cases: Does It Have Any Effect on Disease-free and Overall Survival?, 2017; 36 (6)(6): p. 550-554. https://pubmed.ncbi.nlm.nih.gov/28134667/

311. Fotiou. S, Vlahos, N, Kondi-Pafiti, A, Zarganis, P, Papakonstantinou, K, Creatsas, G, Intraoperative gross assessment of myometrial invasion and cervical involvement in endometrial cancer: Role of tumor grade and size. 2009; 112 (3)(3): p. 517-20. https://pubmed.ncbi.nlm.nih.gov/19117598/

312. Kumar. S, Bandyopadhyay, S, Semaan, A, Shah, JP, Mahdi, H, Morris, R, et.al. The role of frozen section in surgical staging of low risk endometrial cancer. 2011; 6 (9)(9): p. e21912. https://pubmed.ncbi.nlm.nih.gov/PMID:, 21912633/

313. Takano M, Ochi H, Takei Y. Miyamoto M, Hasumi Y, Kaneta Y, et.al. Surgery for endometrial cancers with suspected cervical involvement: is radical hysterectomy needed (a GOTIC study)? Br J Cancer, 2013; 109: p. 1760-5. https://www.ncbi.nlm.nih.gov/pubmed/24002604

314. Zaino RJ, Abendroth C, Yemelyanova A, Oliva E, Lim D, Soslow R. et.al. Endocervical involvement in endometrial adenocarcinoma is not prognostically significant and the pathologic assessment of the pattern of involvement is not reproducible. Gynecol Oncol, 2012; 128: p. 83-7. https://www.ncbi.nlm.nih.gov/pubmed/23063759

315. McCluggage WG. My approach to and thoughts on the typing of ovarian carcinomas. J Clin Pathol, 2008; 61: p. 152-63.

316. McCluggage WG, Hirschowitz L, Wilson, G E, Oliva, E, Soslow RA, Zaino RJ. Significant variation in the assessment of cervical involvement in endometrial carcinoma: an interobserver variation study. Am J Surg Pathol, 2011; 35: p. 289-94. https://www.ncbi.nlm.nih.gov/pubmed/21263250

317. Horn LC, Trost M, Bilek K. Staging of endometrial carcinoma: aspects of ovarian and cervical involvement. Int J Gynecol Pathol, 2009; 29: p. 63-6. https://www.ncbi.nlm.nih.gov/pubmed/19952935

318. Morotti. M, Menada, MV, Moioli, M, Sala, P, Maffeo, I, Abete, L, et.al. Frozen section pathology at time of hysterectomy accurately predicts endometrial cancer in patients with preoperative diagnosis of atypical endometrial hyperplasia. 2012; 125 (3)(3): p. 536-40. https://pubmed.ncbi.nlm.nih.gov/PMID:, 22361087/

319. Rakha. E, Wong, SC, Soomro, I, Chaudry, Z, Sharma, A, Deen, S, et.al. Clinical outcome of atypical endometrial hyperplasia diagnosed on an endometrial biopsy: institutional experience and review of literature. 2012; 36 (11)(11): p. 1683-90. https://pubmed.ncbi.nlm.nih.gov/PMID:, 23073327/

320. Torres ML, Weaver AL, Kumar S, Uccella S, Famuyide AO, Cliby WA. et.al. Risk factors for developing endometrial cancer after benign endometrial sampling. Obstet Gynecol, 2012; 120: p. 998-1004. https://www.ncbi.nlm.nih.gov/pubmed/23090515

321. Trimble CL, Method M. Leitao M, Lu K, Ioffe O, Hampton M, et.al. Management of endometrial precancers. Obstet Gynecol, 2012; 120: p. 1160-75. https://www.ncbi.nlm.nih.gov/pubmed/23090535

322. Kumar S, Bandyopadhyay S, Semaan A, Shah JP, Mahdi H, Morris R. et.al. The role of frozen section in surgical staging of low risk endometrial cancer. PLoS One, 2011; 6: p. e21912. https://www.ncbi.nlm.nih.gov/pubmed/21912633

323. Vidal F, Rafii A. Lymph node assessment in endometrial cancer: towards personalized medicine. Obstet Gynecol Int, 2013; 2013: p. 892465. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3804440/

324. Wittekind C HJ. Meyer, TNM Klassifikation maligner TumorenWiley-VCH, 2010. http://www.wiley-vch.de/publish/dt/books/bySubjectMD00/ISBN3-527-32759-2/

325. Taraboanta. C, Britton, H, Plotkin, A, Azordegan, N, Clement, PB, Gilks, CB, Performance Characteristics of Endometrial Sampling in Diagnosis of Endometrial Carcinoma. 2020; 39 (1)(1): p. 19-25. https://pubmed.ncbi.nlm.nih.gov/31815891/

326. Emons. G, Beckmann, MW, Schmidt, D, Mallmann, P, New WHO Classification of Endometrial Hyperplasias. 2015; 75 (2)(2): p. 135-136. https://pubmed.ncbi.nlm.nih.gov/25797956/

327. Singh. S, Best, C, Dunn, S, Leyland, N, Wolfman, WL, Abnormal uterine bleeding in pre-menopausal women. 2013; 35 (5)(5): p. 473-475. https://pubmed.ncbi.nlm.nih.gov/23756279/

328. Sakhdari. A, Moghaddam, PA, Liu, Y, Endometrial Samples From Postmenopausal Women: A Proposal for Adequacy Criteria. 2016; 35 (6)(6): p. 525-530. https://pubmed.ncbi.nlm.nih.gov/26990506/

329. Juhasz-Böss,Ingolf, Ströder,Russalina, Schmidt,Gilda, Solomayer,Erich, Horn,Lars Christian, Herr,Daniel, Diagnostik und Therapie benigner und prämaligner Veränderungen des Endometriums, 2019///. 13(06): p. 511-529.

330. Phillips. V, McCluggage, WG, Results of a questionnaire regarding criteria for adequacy of endometrial biopsies. 2005; 58 (4)(4): p. 417-9. https://pubmed.ncbi.nlm.nih.gov/15790709/

331. Zaino. RJ, FIGO staging of endometrial adenocarcinoma: a critical review and proposal. 2009; 28 (1)(1): p. 1-9. https://pubmed.ncbi.nlm.nih.gov/19047915/

332. Horn. LC, Trost, M, Bilek, K, Staging of endometrial carcinoma: aspects of ovarian and cervical involvement. 2010; 29 (1)(1): p. 63-6. https://pubmed.ncbi.nlm.nih.gov/19952935/

333. Movahedi-Lankarani S, Gilks CB, Soslow R, Oliva E. Protocol for the Examination of Specimens from Patients with Carcinoma of the Endometrium, 2011;

334. R, o, b, b, o, y, et.al. Cutup – gross description and processing of specimens, in Robboy´s Pathology of the Female Reproductive Tract, Robboy Sj, Mutter GLPrat JBentley RCRussel PAnderson MC2009, Elsevier: Edinburgh, London, New York, Oxford, Philadelphia, St. Louis, Sydney, Toronto.

335. Ahmed. QF, Gattoc, L, Al-Wahab, Z, Abdulfatah, E, Ruterbusch, JJ, Cote, M, et.al. Vanishing endometrial cancer in hysterectomy specimens: a myth or a fact. 2015; 39 (2)(2): p. 221-6. https://pubmed.ncbi.nlm.nih.gov/25517962/

336. Kalyanasundaram. K, Ganesan, R, Perunovic, B, McCluggage, WG, 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. 2010; 18 (2)(2): p. 138-43. https://pubmed.ncbi.nlm.nih.gov/PMID:, 19117974/

337. Murray. SK, Young, RH, Scully, RE, Unusual epithelial and stromal changes in myoinvasive endometrioid adenocarcinoma: a study of their frequency, associated diagnostic problems, and prognostic significance. 2003; 22 (4)(4): p. 324-33. https://pubmed.ncbi.nlm.nih.gov/PMID:, 14501811/

338. Zaino R, Carinelli SG, Ellenson LH. Tumours of the uterine Corpus: epithelial Tumours and Precursors, in WHO Classification of Tumours of Female Reproductive Tract, Kurman Rj, Carcangiu MLHerrington CSYoung RH2014, IARC Press: Lyon. p. 125-126.

339. Han. G, Lim, D, Leitao, MM, Abu-Rustum, NR, Soslow, RA, Histological features associated with occult lymph node metastasis in FIGO clinical stage I, grade I endometrioid carcinoma. 2014; 64 (3)(3): p. 389-98. https://pubmed.ncbi.nlm.nih.gov/PMID:, 24215212/

340. Jorge S, Hou JY, Tergas AI, Burke WM, Huang, Y, Hu JC. et.al. Magnitude of risk for nodal metastasis associated with lymphvascular space invasion for endometrial cancer. Gynecol Oncol, 2016; 140: p. 387-93. https://www.ncbi.nlm.nih.gov/pubmed/26768835

341. Wortman. BG, Creutzberg, CL, Putter, H, Jürgenliemk-Schulz, IM, Jobsen, JJ, Lutgens, LCHW, et.al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. 2018; 119 (9)(9): p. 1067-1074. https://pubmed.ncbi.nlm.nih.gov/30356126/

342. Medeiros F, Muto MG, Lee Y, Elvin JA, Callahan MJ, Feltmate C. 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: p. 230-6. https://www.ncbi.nlm.nih.gov/pubmed/16434898

343. Höhn. AK, Brambs, CE, Erber, R, Hiller, GGR, Mayr, D, Schmidt, D, et.al. [Reporting and handling of lymphonodectomy specimens in gynecologic malignancies and sentinel lymph nodes]. 2021; 42 (3)(3): p. 319-327. https://pubmed.ncbi.nlm.nih.gov/32700061/

344. Krizova. A, Clarke, BA, Bernardini, MQ, James, S, Kalloger, SE, Boerner, SL, et.al. Histologic artifacts in abdominal, vaginal, laparoscopic, and robotic hysterectomy specimens: a blinded, retrospective review. 2011; 35 (1)(1): p. 115-26. https://pubmed.ncbi.nlm.nih.gov/21164295/

345. Delair. D, Soslow, RA, Gardner, GJ, Barakat, RR, Leitao, MM, Tumoral displacement into fallopian tubes in patients undergoing robotically assisted hysterectomy for newly diagnosed endometrial cancer. 2013; 32 (2)(2): p. 188-92. https://pubmed.ncbi.nlm.nih.gov/23370655/

346. Stewart. CJ, Doherty, DA, Havlat, M, Koay, MH, Leung, YC, Naran, A, et.al. Transtubal spread of endometrial carcinoma: correlation of intra-luminal tumour cells with tumour grade, peritoneal fluid cytology, and extra-uterine metastasis. 2013; 45 (4)(4): p. 382-7. https://pubmed.ncbi.nlm.nih.gov/23635815/

347. Singh. R, Cho, KR, Serous Tubal Intraepithelial Carcinoma or Not? Metastases to Fallopian Tube Mucosa Can Masquerade as In Situ Lesions. 2017; 141 (10)(10): p. 1313-1315. https://pubmed.ncbi.nlm.nih.gov/28968160/

348. Albright. BB, Black, JD, Passarelli, R, Gysler, S, Whicker, M, Altwerger, G, et.al. Associated characteristics and impact on recurrence and survival of free-floating tumor fragments in the lumen of fallopian tubes in Type I and Type II endometrial cancer. 2018; 23: p. 28-33. https://pubmed.ncbi.nlm.nih.gov/29387776/

349. Fedda. FA, Euscher, ED, Ramalingam, P, Malpica, A, Prophylactic Risk-reducing Hysterectomies and Bilateral Salpingo-oophorectomies in Patients With Lynch Syndrome: A Clinicopathologic Study of 29 Cases and Review of the Literature. 2020; 39 (4)(4): p. 313-320. https://pubmed.ncbi.nlm.nih.gov/31851061/

350. Downes. MR, Allo, G, McCluggage, WG, Sy, K, Ferguson, SE, Aronson, M, et.al. Review of findings in prophylactic gynaecological specimens in Lynch syndrome with literature review and recommendations for grossing. 2014; 65 (2)(2): p. 228-39. https://pubmed.ncbi.nlm.nih.gov/24495259/

351. Lachiewicz. MP, Kravochuck, SE, O'Malley, MM, Heald, B, Church, JM, Kalady, MF, et.al. Prevalence of occult gynecologic malignancy at the time of risk reducing and nonprophylactic surgery in patients with Lynch syndrome. 2014; 132 (2)(2): p. 434-7. https://pubmed.ncbi.nlm.nih.gov/24211399/

352. Karamurzin. Y, Soslow, RA, Garg, K, Histologic evaluation of prophylactic hysterectomy and oophorectomy in Lynch syndrome. 2013; 37 (4)(4): p. 579-85. https://pubmed.ncbi.nlm.nih.gov/23426126/

353. Lucas. E, Chen, H, Molberg, K, Castrillon, DH, Rivera Colon, G, Li, L, et.al. Mismatch Repair Protein Expression in Endometrioid Intraepithelial Neoplasia/Atypical Hyperplasia: Should We Screen for Lynch Syndrome in Precancerous Lesions?, 2019; 38 (6)(6): p. 533-542. https://pubmed.ncbi.nlm.nih.gov/30383610/

354. de Leeuw. WJ, Dierssen, J, Vasen, HF, Wijnen, JT, Kenter, GG, Meijers-Heijboer, H, et.al. Prediction of a mismatch repair gene defect by microsatellite instability and immunohistochemical analysis in endometrial tumours from HNPCC patients. 2000; 192 (3)(3): p. 328-35. https://pubmed.ncbi.nlm.nih.gov/11054716/

355. Nieminen. TT, Gylling, A, Abdel-Rahman, WM, Nuorva, K, Aarnio, M, Renkonen-Sinisalo, L, et.al. Molecular analysis of endometrial tumorigenesis: importance of complex hyperplasia regardless of atypia. 2009; 15 (18)(18): p. 5772-83. https://pubmed.ncbi.nlm.nih.gov/19723644/

356. Ichikawa. Y, Tsunoda, H, Takano, K, Oki, A, Yoshikawa, H, Microsatellite instability and immunohistochemical analysis of MLH1 and MSH2 in normal endometrium, endometrial hyperplasia and endometrial cancer from a hereditary nonpolyposis colorectal cancer patient. 2002; 32 (3)(3): p. 110-2. https://pubmed.ncbi.nlm.nih.gov/11956307/

357. Vierkoetter. KR, Kagami, LA, Ahn, HJ, Shimizu, DM, Terada, KY, Loss of Mismatch Repair Protein Expression in Unselected Endometrial Adenocarcinoma Precursor Lesions. 2016; 26 (2)(2): p. 228-32. https://pubmed.ncbi.nlm.nih.gov/26807560/

358. León-Castillo. A, de Boer, SM, Powell, ME, Mileshkin, LR, Mackay, HJ, Leary, A, et.al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. 2020; 38 (29)(29): p. 3388-3397. https://pubmed.ncbi.nlm.nih.gov/32749941/

359. Mills. AM, Longacre, TA, Lynch Syndrome Screening in the Gynecologic Tract: Current State of the Art. 2016; 40 (4)(4): p. e35-44. https://pubmed.ncbi.nlm.nih.gov/26872009/

360. Cho. KR, Cooper, K, Croce, S, Djordevic, B, Herrington, S, Howitt, B, et.al. International Society of Gynecological Pathologists (ISGyP) Endometrial Cancer Project: Guidelines From the Special Techniques and Ancillary Studies Group. 2019; 38 Suppl 1: p. S114-S122. https://pubmed.ncbi.nlm.nih.gov/29521846/

361. Eggink. FA, Van Gool, IC, Leary, A, Pollock, PM, Crosbie, EJ, Mileshkin, L, et.al. Immunological profiling of molecularly classified high-risk endometrial cancers identifies 6 (2)(2): p. e1264565. https://pubmed.ncbi.nlm.nih.gov/28344870/

362. Green AK, Feinberg J, Makker V. A Review of Immune Checkpoint Blockade Therapy in Endometrial Cancer. Am Soc Clin Oncol Educ Book, 2020; 40: p. 1-7. https://pubmed.ncbi.nlm.nih.gov/32213091/

363. Reijnen. C, Kü;sters-Vandevelde, HVN, Prinsen, CF, Massuger, LFAG, Snijders, MPML, Kommoss, S, et.al. Mismatch repair deficiency as a predictive marker for response to adjuvant radiotherapy in endometrial cancer. 2019; 154 (1)(1): p. 124-130. https://pubmed.ncbi.nlm.nih.gov/31103324/

364. Zakhour. M, Cohen, JG, Gibson, A, Walts, AE, Karimian, B, Baltayan, A, et.al. Abnormal mismatch repair and other clinicopathologic predictors of poor response to progestin treatment in young women with endometrial complex atypical hyperplasia and well-differentiated endometrial adenocarcinoma: a consecutive case series. 2017; 124 (10)(10): p. 1576-1583. https://pubmed.ncbi.nlm.nih.gov/28128512/

365. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft. Deutsche Krebshilfe, AWMF), S3-Leitlinie Kolorektales Karzinom, Version 2.1, Januar 2019, AWMF-Registernummer: 021/007OL, 2019. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Kolorektales_Karzinom/Version_2/LL_KRK_Langversion_2.1.pdf

366. Ryan. NAJ, McMahon, R, Tobi, S, Snowsill, T, Esquibel, S, Wallace, AJ, et.al. The proportion of endometrial tumours associated with Lynch syndrome (PETALS): A prospective cross-sectional study. 2020; 17 (9)(9): p. e1003263. https://pubmed.ncbi.nlm.nih.gov/32941469/

367. Stelloo. E, Jansen, AML, Osse, EM, Nout, RA, Creutzberg, CL, Ruano, D, et.al. Practical guidance for mismatch repair-deficiency testing in endometrial cancer. 2017; 28 (1)(1): p. 96-102. https://pubmed.ncbi.nlm.nih.gov/27742654/

368. Niu. BT, Hammond, RFL, Leen, SLS, Gilks, CB, Singh, N, Two versus four immunostains for Lynch syndrome screening in endometrial carcinoma. 2019; 75 (3)(3): p. 442-445. https://pubmed.ncbi.nlm.nih.gov/31077605/

369. Josef Rü;schoff, Gustavo Baretton, Hendrik Bläker , et al. MSI-Testung. Was ist neu? Was ist zu beachten? Der Pathologe, 2021; 42: p. 414–423.

370. Raffone. A, Travaglino, A, Cerbone, M, Gencarelli, A, Mollo, A, Insabato, L, et.al. Diagnostic Accuracy of Immunohistochemistry for Mismatch Repair Proteins as Surrogate of Microsatellite Instability Molecular Testing in Endometrial Cancer. 2020; 26 (3)(3): p. 1417-1427. https://pubmed.ncbi.nlm.nih.gov/32377987/

371. Amirkaveh Mojtahed, Iris Schrijver, James M Ford , et al. A two-antibody mismatch repair protein immunohistochemistry screening approach for colorectal carcinomas, skin sebaceous tumors, and gynecologic tract carcinomas. Modern Pathology, 2011; 24: p. 1004–1014.

372. Sari. A, Pollett, A, Eiriksson, LR, Lumsden-Johanson, B, Van de Laar, E, Kazerouni, H, et.al. Interobserver Agreement for Mismatch Repair Protein Immunohistochemistry in Endometrial and Nonserous, Nonmucinous Ovarian Carcinomas. 2019; 43 (5)(5): p. 591-600. https://pubmed.ncbi.nlm.nih.gov/30864976/

373. Stinton. C, Fraser, H, Al-Khudairy, L, Court, R, Jordan, M, Grammatopoulos, D, et.al. Testing for lynch syndrome in people with endometrial cancer using immunohistochemistry and microsatellite instability-based testing strategies - A systematic review of test accuracy. 2021; 160 (1)(1): p. 148-160. https://pubmed.ncbi.nlm.nih.gov/33190932/

374. Timmerman, S, Van Rompuy, AS, Van Gorp, T, Vanden Bempt, I, Brems, H, Van Nieuwenhuysen, E, et.al. Analysis of 108 patients with endometrial carcinoma using the PROMISE classification and additional genetic analyses for MMR-D, 2020; 157 (1)(1): p. 245-251. https://pubmed.ncbi.nlm.nih.gov/31980219/

375. Bruegl. AS, Kernberg, A, Broaddus, RR, Importance of PCR-based Tumor Testing in the Evaluation of Lynch Syndrome-associated Endometrial Cancer. 2017; 24 (6)(6): p. 372-378. https://pubmed.ncbi.nlm.nih.gov/28820751/

376. Engel. KB, Moore, HM, Effects of preanalytical variables on the detection of proteins by immunohistochemistry in formalin-fixed, paraffin-embedded tissue. 2011; 135 (5)(5): p. 537-43. https://pubmed.ncbi.nlm.nih.gov/21526952/

377. Bass. BP, Engel, KB, Greytak, SR, Moore, HM, A review of preanalytical factors affecting molecular, protein, and morphological analysis of formalin-fixed, paraffin-embedded (FFPE) tissue: how well do you know your FFPE specimen?, 2014; 138 (11)(11): p. 1520-30. https://pubmed.ncbi.nlm.nih.gov/25357115/

378. Stelloo, E, Nout, RA, Osse, EM, et al. *Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts.*. Clin Cancer Res, 2016. **22 (16):** p. 4215-24. https://pubmed.ncbi.nlm.nih.gov/27006490/

379. Kandoth, C., McLellan, M. D., Vandin, F., et al. *Mutational landscape and significance across 12 major cancer types.* Nature, 2013. **502:** p. 333-9. https://www.ncbi.nlm.nih.gov/pubmed/24132290

380. Burleigh A, Talhouk A, Gilks CB, McAlpine JN. Clinical and pathological characterization of endometrial cancer in young women: identification of a cohort without classical risk factors. Gynecol Oncol, 2015; 138: p. 141-6. https://www.ncbi.nlm.nih.gov/pubmed/25870916

381. Pilarski. R, , 2019; 11 (6)(6). https://pubmed.ncbi.nlm.nih.gov/31216739/

382. de Jonge. MM, Ritterhouse, LL, de Kroon, CD, Vreeswijk, MPG, Segal, JP, Puranik, R, et.al. Germline , 2019; 25 (24)(24): p. 7517-7526. https://pubmed.ncbi.nlm.nih.gov/31492746/

383. Vietri. MT, D'Elia, G, Caliendo, G, Casamassimi, A, Federico, A, Passariello, L, et.al. Prevalence of mutations in BRCA and MMR genes in patients affected with hereditary endometrial cancer. 2021; 38 (2)(2): p. 13. https://pubmed.ncbi.nlm.nih.gov/33484353/

384. Lawrence. J, Richer, L, Arseneau, J, Zeng, X, Chong, G, Weber, E, et.al. Mismatch Repair Universal Screening of Endometrial Cancers (MUSE) in a Canadian Cohort. 2021; 28 (1)(1): p. 509-522. https://pubmed.ncbi.nlm.nih.gov/33467402/

385. Kahn. RM, Gordhandas, S, Maddy, BP, Baltich Nelson, B, Askin, G, Christos, PJ, et.al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population?, 2019; 125 (18)(18): p. 3172-3183. https://pubmed.ncbi.nlm.nih.gov/31150123/

386. Ferguson SE, Aronson M, Pollett A, Eiriksson LR, Oza A M, Gallinger S. 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: p. 3932-9. https://www.ncbi.nlm.nih.gov/pubmed/25081409

387. Pasanen. A, Loukovaara, M, Bü;tzow, R, Clinicopathological significance of deficient DNA mismatch repair and MLH1 promoter methylation in endometrioid endometrial carcinoma. 2020; 33 (7)(7): p. 1443-1452. https://pubmed.ncbi.nlm.nih.gov/32060377/

388. Dillon. JL, Gonzalez, JL, DeMars, L, Bloch, KJ, Tafe, LJ, Universal screening for Lynch syndrome in endometrial cancers: frequency of germline mutations and identification of patients with Lynch-like syndrome. 2017; 70: p. 121-128. https://pubmed.ncbi.nlm.nih.gov/29107668/

389. Spinosa. D, Acosta, T, Wong, J, Kurtovic, K, Mewshaw, J, Collins, S, et.al. Universal screening for Lynch syndrome in uterine cancer patients: A quality improvement initiative. 2021; 160 (1)(1): p. 169-174. https://pubmed.ncbi.nlm.nih.gov/33393478/

390. Weinstein. JN, Collisson, EA, Mills, GB, Shaw, KR, Ozenberger, BA, Ellrott, K, et.al. The Cancer Genome Atlas Pan-Cancer analysis project. 2013; 45 (10)(10): p. 1113-20. https://pubmed.ncbi.nlm.nih.gov/24071849/

391. Talhouk. A, McConechy, MK, Leung, S, Li-Chang, HH, Kwon, JS, Melnyk, N, et.al. A clinically applicable molecular-based classification for endometrial cancers. 2015; 113 (2)(2): p. 299-310. https://pubmed.ncbi.nlm.nih.gov/26172027/

392. Carlson. J, McCluggage, WG, Reclassifying endometrial carcinomas with a combined morphological and molecular approach. 2019; 31 (5)(5): p. 411-419. https://pubmed.ncbi.nlm.nih.gov/31261170/

393. DeLair. DF, Burke, KA, Selenica, P, Lim, RS, Scott, SN, Middha, S, et.al. The genetic landscape of endometrial clear cell carcinomas. 2017; 243 (2)(2): p. 230-241. https://pubmed.ncbi.nlm.nih.gov/28718916/

394. Lax, Sigurd F. Pathology of Endometrial Carcinoma, in Molecular Genetics of Endometrial Carcinoma, Hedrick Ellenson, Lora , Editor, 2017; Springer International Publishing: Cham. p. 75-96. https://doi.org/10.1007/978-3-319-43139-0_3

395. Talhouk A. Hoang LN, McConechy MK, Nakonechny Q, Leo J, Cheng A, et.al. Molecular classification of endometrial carcinoma on diagnostic specimens is highly concordant with final hysterectomy: Earlier prognostic information to guide treatment. Gynecol Oncol, 2016; 143: p. 46-53. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5421949/

396. Kommoss. S, McConechy, MK, Kommoss, F, Leung, S, Bunz, A, Magrill, J, et.al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. 2018; 29 (5)(5): p. 1180-1188. https://pubmed.ncbi.nlm.nih.gov/29432521/

397. Brett. MA, Atenafu, EG, Singh, N, Ghatage, P, Clarke, BA, Nelson, GS, et.al. Equivalent Survival of p53 Mutated Endometrial Endometrioid Carcinoma Grade 3 and Endometrial Serous Carcinoma. 2021; 40 (2)(2): p. 116-123. https://pubmed.ncbi.nlm.nih.gov/32265358/

398. Wortman BG, Bosse T, Nout RA, Lutgens, Lchw, van der Steen-Banasik EM, Westerveld H. et.al. Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: Evaluation of the pilot phase of the PORTEC-4a trial. Gynecol Oncol, 2018; 151(1): p. 69-75.

399. Marnitz. S, Walter, T, Schömig-Markiefka, B, Engler, T, Kommoss, S, Brucker, SY, A Modern Approach to Endometrial Carcinoma: Will Molecular Classification Improve Precision Medicine in the Future?, 2020; 12 (9)(9). https://pubmed.ncbi.nlm.nih.gov/32927671/

400. Van Gool. IC, Rayner, E, Osse, EM, Nout, RA, Creutzberg, CL, Tomlinson, IPM, et.al. Adjuvant Treatment for , 2018; 24 (13)(13): p. 3197-3203. https://pubmed.ncbi.nlm.nih.gov/29559562/

401. Kim. SR, Cloutier, BT, Leung, S, Cochrane, D, Britton, H, Pina, A, et.al. Molecular subtypes of clear cell carcinoma of the endometrium: Opportunities for prognostic and predictive stratification. 2020; 158 (1)(1): p. 3-11. https://pubmed.ncbi.nlm.nih.gov/32331700/

402. Travaglino. A, Raffone, A, Gencarelli, A, Mollo, A, Guida, M, Insabato, L, et.al. TCGA Classification of Endometrial Cancer: the Place of Carcinosarcoma. 2020; 26 (4)(4): p. 2067-2073. https://pubmed.ncbi.nlm.nih.gov/32472441/

403. Travaglino. A, Raffone, A, Mollo, A, Borrelli, G, Alfano, P, Zannoni, GF, et.al. TCGA molecular subgroups and FIGO grade in endometrial endometrioid carcinoma. 2020; 301 (5)(5): p. 1117-1125. https://pubmed.ncbi.nlm.nih.gov/32253551/

404. Coll-de la Rubia, E, Martinez-Garcia, E, Dittmar, G, et al. *Prognostic Biomarkers in Endometrial Cancer: A Systematic Review and Meta-Analysis.*. J Clin Med, 2020. **9 (6):** https://pubmed.ncbi.nlm.nih.gov/32560580/

405. León-Castillo, A, de Boer, SM, Powell, ME, et al. *Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy.*. J Clin Oncol, 2020. **38 (29):** p. 3388-3397. https://pubmed.ncbi.nlm.nih.gov/32749941/

406. Wortman, BG, Creutzberg, CL, Putter, H, et al. *Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy.*. Br J Cancer, 2018. **119 (9):** p. 1067-1074. https://pubmed.ncbi.nlm.nih.gov/30356126/

407. Bosse, T, Nout, RA, McAlpine, JN, et al. *Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups.*. Am J Surg Pathol, 2018. **42 (5):** p. 561-568. https://pubmed.ncbi.nlm.nih.gov/29505428/

408. Van Gool. IC, Ubachs, JEH, Stelloo, E, de Kroon, CD, Goeman, JJ, Smit, VTHBM, et.al. Blinded histopathological characterisation of POLE exonuclease domain-mutant endometrial cancers: sheep in wolf's clothing. 2018; 72 (2)(2): p. 248-258. https://pubmed.ncbi.nlm.nih.gov/28795426/

409. Devereaux K, Steiner D, Ho C. A multiplex ANaPshot assay is a rapid and cost-effective method for detecting POLE mutations in endometrial carcinoma, 2020; 33 (Suppl2): p. 1040.

410. Köbel. M, Kang, EY, The Many Uses of p53 Immunohistochemistry in Gynecological Pathology: Proceedings of the ISGyP Companion Society Session at the 2020 USCAP Annual9 Meeting. 2021; 40 (1)(1): p. 32-40. https://pubmed.ncbi.nlm.nih.gov/33290354/

411. Singh. N, Piskorz, AM, Bosse, T, Jimenez-Linan, M, Rous, B, Brenton, JD, et.al. p53 immunohistochemistry is an accurate surrogate for TP53 mutational analysis in endometrial carcinoma biopsies. 2020; 250 (3)(3): p. 336-345. https://pubmed.ncbi.nlm.nih.gov/31829441/

412. Tashiro. K, Nakano, T, Honjo, T, Signal sequence trap. Expression cloning method for secreted proteins and type 1 membrane proteins. 1997; 69: p. 203-19. https://pubmed.ncbi.nlm.nih.gov/9116854/

413. Köbel. M, Ronnett, BM, Singh, N, Soslow, RA, Gilks, CB, McCluggage, WG, Interpretation of P53 Immunohistochemistry in Endometrial Carcinomas: Toward Increased Reproducibility. 2019; 38 Suppl 1: p. S123-S131. https://pubmed.ncbi.nlm.nih.gov/29517499/

414. Nastic. D, Shanwell, E, Wallin, KL, Valla, M, Måsbäck, A, Mateoiu, C, et.al. A Selective Biomarker Panel Increases the Reproducibility and the Accuracy in Endometrial Biopsy Diagnosis. 2017; 36 (4)(4): p. 339-347. https://pubmed.ncbi.nlm.nih.gov/28244894/

415. Singh. N, Piskorz, AM, Bosse, T, Jimenez-Linan, M, Rous, B, Brenton, JD, et.al. p53 immunohistochemistry is an accurate surrogate for TP53 mutational analysis in endometrial carcinoma biopsies. J Pathol, 2020; 250 (3)(3): p. 336-345. https://pubmed.ncbi.nlm.nih.gov/31829441/

416. van Esterik. M, Van Gool, IC, de Kroon, CD, Nout, RA, Creutzberg, CL, Smit, VTHBM, et.al. Limited impact of intratumour heterogeneity on molecular risk assignment in endometrial cancer. 2017; 8 (15)(15): p. 25542-25551. https://pubmed.ncbi.nlm.nih.gov/28424422/

417. Moroney. MR, Davies, KD, Wilberger, AC, Sheeder, J, Post, MD, Berning, AA, et.al. Molecular markers in recurrent stage I, grade 1 endometrioid endometrial cancers. 2019; 153 (3)(3): p. 517-520. https://pubmed.ncbi.nlm.nih.gov/30910249/

418. Costigan. DC, Dong, F, Nucci, MR, Howitt, BE, Clinicopathologic and Immunohistochemical Correlates of CTNNB1 Mutated Endometrial Endometrioid Carcinoma. 2020; 39 (2)(2): p. 119-127. https://pubmed.ncbi.nlm.nih.gov/30702464/

419. van den Heerik. ASVM, Horeweg, N, Nout, RA, Lutgens, LCHW, van der Steen-Banasik, EM, Westerveld, GH, et.al. PORTEC-4a: international randomized trial of molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer. 2020; 30 (12)(12): p. 2002-2007. https://pubmed.ncbi.nlm.nih.gov/33046573/

420. De Leo. A, de Biase, D, Lenzi, J, Barbero, G, Turchetti, D, Grillini, M, et.al. , 2021; 13 (5)(5). https://pubmed.ncbi.nlm.nih.gov/33668727/

421. Kommoss. FK, Karnezis, AN, Kommoss, F, Talhouk, A, Taran, FA, Staebler, A, et.al. L1CAM further stratifies endometrial carcinoma patients with no specific molecular risk profile. 2018; 119 (4)(4): p. 480-486. https://pubmed.ncbi.nlm.nih.gov/30050154/

422. Kandoth, C, Schultz, N, Cherniack, AD, et al. *Integrated genomic characterization of endometrial carcinoma.*. Nature, 2013. **497 (7447):** p. 67-73. https://pubmed.ncbi.nlm.nih.gov/23636398/

423. Stelloo. E, Nout, RA, Naves, LC, Ter Haar, NT, Creutzberg, CL, Smit, VT, et.al. High concordance of molecular tumor alterations between pre-operative curettage and hysterectomy specimens in patients with endometrial carcinoma. 2014; 133 (2)(2): p. 197-204. https://pubmed.ncbi.nlm.nih.gov/24556061/

424. Fumet. JD, Limagne, E, Thibaudin, M, Truntzer, C, Bertaut, A, Rederstorff, E, et.al. Precision medicine phase II study evaluating the efficacy of a double immunotherapy by durvalumab and tremelimumab combined with olaparib in patients with solid cancers and carriers of homologous recombination repair genes mutation in response or stable after olaparib treatment. 2020; 20 (1)(1): p. 748. https://pubmed.ncbi.nlm.nih.gov/32778095/

425. Sloan. EA, Ring, KL, Willis, BC, Modesitt, SC, Mills, AM, PD-L1 Expression in Mismatch Repair-deficient Endometrial Carcinomas, Including Lynch Syndrome-associated and MLH1 Promoter Hypermethylated Tumors. 2017; 41 (3)(3): p. 326-333. https://pubmed.ncbi.nlm.nih.gov/27984238/

426. Kir. G, Olgun, ZC, Soylemez, T, Aydin, A, Demircan, B, Kaya, IA, et.al. PD-L1 Expression in Mismatch Repair-deficient Endometrial Carcinoma and Tumor-associated Immune Cells: Differences Between MLH1 Methylated and Nonmethylated Subgroups. 2020; Publish Ahead of Print. https://pubmed.ncbi.nlm.nih.gov/33332859/

427. Data set for reporting of ovary, fallopian tube and primary peritoneal carcinoma: recommendations from the International Collaboration on Cancer Reporting (ICCR), 2015. https://www.ncbi.nlm.nih.gov/pubmed/26089092

428. Skala SL, Hagemann IS. Optimal sampling of grossly normal omentum in staging of gynecologic malignancies. Int J Gynecol Pathol, 2015; 34: p. 281-7. https://www.ncbi.nlm.nih.gov/pubmed/25760907

429. Gilks CB, Movahedi-Lankarani S, Baker PM, Otis CN. Protocol for the Examination of Specimens From Patients With Primary Tumors of the Ovary or Fallopian Tube, 2016;

430. McCluggage. WG, Judge, MJ, Clarke, BA, Davidson, B, Gilks, CB, Hollema, H, et.al. Data set for reporting of ovary, fallopian tube and primary peritoneal carcinoma: recommendations from the International Collaboration on Cancer Reporting (ICCR). 2015; 28 (8)(8): p. 1101-22. https://pubmed.ncbi.nlm.nih.gov/26089092/

431. Ulker. V, Tunca, A, Numanoglu, C, Akbayir, O, Akyol, A, Erim, A, et.al. Should omentectomy be a part of surgical staging in patients with endometrioid adenocarcinoma of the uterine corpus?, 2014; 77 (1)(1): p. 58-63. https://pubmed.ncbi.nlm.nih.gov/24356379/

432. Sakai K. Yamagami W, Susumu N, Nomura H, Kataoka F, Banno K, et.al. Pathological factors associated with omental metastases in endometrial cancer. Eur J Gynaecol Oncol, 2015; 36: p. 397-401. https://www.ncbi.nlm.nih.gov/pubmed/26390690

433. Horn. LC, Beckmann, MW, Follmann, M, Koch, MC, Mallmann, P, Marnitz, S, et.al. [S3 Guidelines on diagnostics and treatment of cervical cancer: Demands on pathology]. 2015; 36 (6)(6): p. 585-93. https://pubmed.ncbi.nlm.nih.gov/26483249/

434. Multinu. F, Casarin, J, Cappuccio, S, Keeney, GL, Glaser, GE, Cliby, WA, et.al. Ultrastaging of negative pelvic lymph nodes to decrease the true prevalence of isolated para-aortic dissemination in endometrial cancer. 2019; 154 (1)(1): p. 60-64. https://pubmed.ncbi.nlm.nih.gov/31126637/

435. Ignatov. A, Lebius, C, Ignatov, T, Ivros, S, Knueppel, R, Papathemelis, T, et.al. Lymph node micrometastases and outcome of endometrial cancer. 2019; 154 (3)(3): p. 475-479. https://pubmed.ncbi.nlm.nih.gov/31345606/

436. Plante. M, Stanleigh, J, Renaud, MC, Sebastianelli, A, Grondin, K, Grégoire, J, Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter?, 2017; 146 (2)(2): p. 240-246. https://pubmed.ncbi.nlm.nih.gov/28577885/

437. García Pineda. V, Hernández Gutiérrez, A, Gracia Segovia, M, Siegrist Ridruejo, J, Diestro Tejeda, MD, Zapardiel, I, Low-Volume Nodal Metastasis in Endometrial Cancer: Risk Factors and Prognostic Significance. 2020; 9 (6)(6). https://pubmed.ncbi.nlm.nih.gov/32630498/

438. Rossi. EC, Kowalski, LD, Scalici, J, Cantrell, L, Schuler, K, Hanna, RK, et.al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. 2017; 18 (3)(3): p. 384-392. https://pubmed.ncbi.nlm.nih.gov/28159465/

439. Bogani. G, Murgia, F, Ditto, A, Raspagliesi, F, Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. 2019; 153 (3)(3): p. 676-683. https://pubmed.ncbi.nlm.nih.gov/30952370/

440. Zanfagnin. V, Huang, Y, Mc Gree, ME, Weaver, AL, Casarin, J, Multinu, F, et.al. Predictors of extensive lymphatic dissemination and recurrences in node-positive endometrial cancer. 2019; 154 (3)(3): p. 480-486. https://pubmed.ncbi.nlm.nih.gov/31324453/

441. McCluggage WG, Colgan T, Duggan M, Hacker NF, Mulvany N, Otis C. 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, 2012; 32: p. 45-65. https://www.ncbi.nlm.nih.gov/pubmed/23202790

442. Euscher. ED, Malpica, A, Gynaecological malignancies and sentinel lymph node mapping: an update. 2020; 76 (1)(1): p. 139-150. https://pubmed.ncbi.nlm.nih.gov/31846525/

443. Abu-Rustum. NR, Sentinel lymph node mapping for endometrial cancer: a modern approach to surgical staging. 2014; 12 (2)(2): p. 288-97. https://pubmed.ncbi.nlm.nih.gov/24586087/

444. Euscher. E, Sui, D, Soliman, P, Westin, S, Ramalingam, P, Bassett, R, et.al. Ultrastaging of Sentinel Lymph Nodes in Endometrial Carcinoma According to Use of 2 Different Methods. 2018; 37 (3)(3): p. 242-251. https://pubmed.ncbi.nlm.nih.gov/28700425/

445. Burg. LC, Hengeveld, EM, In 't Hout, J, Bulten, J, Bult, P, Zusterzeel, PLM, Ultrastaging methods of sentinel lymph nodes in endometrial cancer - a systematic review. 2021; 31 (5)(5): p. 744-753. https://pubmed.ncbi.nlm.nih.gov/33187974/

446. Holloway. RW, Abu-Rustum, NR, Backes, FJ, Boggess, JF, Gotlieb, WH, Jeffrey Lowery, W, et.al. Sentinel lymph node mapping and staging in endometrial cancer: A Society of Gynecologic Oncology literature review with consensus recommendations. 2017; 146 (2)(2): p. 405-415. https://pubmed.ncbi.nlm.nih.gov/28566221/

447. Tu. H, Gu, HF, Huang, H, Liu, KJ, Yun, JP, Chen, JP, et.al. Sectioning protocol determines accuracy of intraoperative pathological examination of sentinel lymph node in cervical cancer: A systematic review and meta-analysis. 2020; 158 (2)(2): p. 489-497. https://pubmed.ncbi.nlm.nih.gov/32507651/

448. Abu-Rustum. NR, Yashar, CM, Bradley, K, Campos, SM, Chino, J, Chon, HS, et.al. NCCN Guidelines® Insights: Uterine Neoplasms, Version 3.2021. 2021; 19 (8)(8): p. 888-895. https://pubmed.ncbi.nlm.nih.gov/34416706/

449. Pacaut. C, Bourmaud, A, Rivoirard, R, Moriceau, G, Guy, JB, Collard, O, et.al. Uterine and ovary carcinosarcomas: outcome, prognosis factors, and adjuvant therapy. 2015; 38 (3)(3): p. 272-7. https://pubmed.ncbi.nlm.nih.gov/23751320/

450. Oz. M, Korkmaz, V, Meydanli, MM, Sari, ME, Cuylan, ZF, Gungor, T, Is Tumor Size Really Important for Prediction of Lymphatic Dissemination in Grade 1 Endometrial Carcinoma With Superficial Myometrial Invasion?, 2017; 27 (7)(7): p. 1393-1398. https://pubmed.ncbi.nlm.nih.gov/28604451/

451. Tejerizo-Garcia A, Jimenez-Lopez JS, Munoz-Gonzalez JL, Bartolome-Sotillos, S, Marqueta-Marques, L, Lopez-Gonzalez G. et.al. Overall survival and disease-free survival in endometrial cancer: prognostic factors in 276 patients. Onco Targets Ther, 2013; 9: p. 1305-13. https://www.ncbi.nlm.nih.gov/pubmed/24092993

452. Morice. P, Leary, A, Creutzberg, C, Abu-Rustum, N, Darai, E, Endometrial cancer. 2016; 387 (10023)(10023): p. 1094-1108. https://pubmed.ncbi.nlm.nih.gov/26354523/

453. Kihara. A, Yoshida, H, Watanabe, R, Takahashi, K, Kato, T, Ino, Y, et.al. Clinicopathologic Association and Prognostic Value of Microcystic, Elongated, and Fragmented (MELF) Pattern in Endometrial Endometrioid Carcinoma. 2017; 41 (7)(7): p. 896-905. https://pubmed.ncbi.nlm.nih.gov/28418994/

454. Joehlin-Price. AS, McHugh, KE, Stephens, JA, Li, Z, Backes, FJ, Cohn, DE, et.al. The Microcystic, Elongated, and Fragmented (MELF) Pattern of Invasion: A Single Institution Report of 464 Consecutive FIGO Grade 1 Endometrial Endometrioid Adenocarcinomas. 2017; 41 (1)(1): p. 49-55. https://pubmed.ncbi.nlm.nih.gov/27740968/

455. Rau. TT, Bettschen, E, Büchi, C, Christe, L, Rohner, A, Müller, MD, et.al. Prognostic impact of tumor budding in endometrial carcinoma within distinct molecular subgroups. 2021; 34 (1)(1): p. 222-232. https://pubmed.ncbi.nlm.nih.gov/32728223/

456. Steiner E, Einenkel J, Schmidt D, Horn LC. Prädiktive und prognostische Marker beim Endometriumkarzinom. Der Onkologe, 2012. https://www.researchgate.net/publication/257455370_Pradiktive_und_prognostische_Marker_beim_Endometriumkarzinom

457. Zhang. Y, Zhao, D, Gong, C, Zhang, F, He, J, Zhang, W, et.al. Prognostic role of hormone receptors in endometrial cancer: a systematic review and meta-analysis. 2015; 13: p. 208. https://pubmed.ncbi.nlm.nih.gov/26108802/

458. Creutzberg CL, van Stiphout RG, Nout RA, Lutgens, L C, Jurgenliemk-Schulz IM, Jobsen JJ. et.al. Nomograms for prediction of outcome with or without adjuvant radiation therapy for patients with endometrial cancer: a pooled analysis of PORTEC-1 and PORTEC-2 trials. Int J Radiat Oncol Biol Phys, 2015; 91: p. 530-9. https://www.ncbi.nlm.nih.gov/pubmed/25680597

459. Miller. MD, Salinas, EA, Newtson, AM, Sharma, D, Keeney, ME, Warrier, A, et.al. An integrated prediction model of recurrence in endometrial endometrioid cancers. 2019; 11: p. 5301-5315. https://pubmed.ncbi.nlm.nih.gov/31239780/

460. Salinas. EA, Miller, MD, Newtson, AM, Sharma, D, McDonald, ME, Keeney, ME, et.al. A Prediction Model for Preoperative Risk Assessment in Endometrial Cancer Utilizing Clinical and Molecular Variables. 2019; 20 (5)(5). https://pubmed.ncbi.nlm.nih.gov/30857319/

461. Travaglino, A, Raffone, A, Saccone, G, et al. *Significant risk of occult cancer in complex non-atypical endometrial hyperplasia..* Arch Gynecol Obstet, 2019. **300 (5):** p. 1147-1154. https://pubmed.ncbi.nlm.nih.gov/31531779/

462. Antonsen SL, Ulrich, L, Hogdall C. Patients with atypical hyperplasia of the endometrium should be treated in oncological centers. Gynecol Oncol, 2011; 125: p. 124-8. https://www.ncbi.nlm.nih.gov/pubmed/22198048

463. Chan JK, Wu H, Cheung MK, Shin JY, Osann, K, Kapp DS. The outcomes of 27,063 women with unstaged endometrioid uterine cancer. Gynecol Oncol, 2007; 106: p. 282-8. https://www.ncbi.nlm.nih.gov/pubmed/17662377

464. Trimble CL, Method M. Leitao M, Lu K, Ioffe O, Hampton M, et.al. Management of endometrial precancers. Obstet Gynecol, 2012; 120: p. 1160-75. https://www.ncbi.nlm.nih.gov/pubmed/23090535

465. S3-Leitlinie Indikation und Methodik der Hysterektomie bei benignen Erkrankungen, Langversion 1.2, 2015. https://www.awmf.org/leitlinien/detail/ll/015-070.html

466. Polcher M, Hauptmann S, Fotopoulou C, Schmalfeldt B, Meinhold-Heerlein I, Mustea A, et.al. Opportunistic salpingectomies for the prevention of a high-grade serous carcinoma: a statement by the Kommission Ovar of the AGOArch Gynecol Obstet, 2015; 292: p. 231-4. https://www.ncbi.nlm.nih.gov/pubmed/25914073

467. Sun C, Chen G, Yang Z, Jiang J, Yang X, Li N. et.al. Safety of ovarian preservation in young patients with early-stage endometrial cancer: a retrospective study and meta-analysis. Fertil Steril, 2013; 100: p. 782-7. https://www.ncbi.nlm.nih.gov/pubmed/23830105

468. Gu Y, Zhou X, Zhang SL. Meta-analysis of an association of codon 72 polymorphisms of the p53 gene with increased endometrial cancer risk. Genet Mol Res, 2011; 10: p. 3609-19.

469. Gunderson, C. C., Fader, A. N., Carson, K. A., 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:** p. 477-82. https://www.ncbi.nlm.nih.gov/pubmed/22245711

470. Luo, L., Luo, B., Zheng, Y., et al. *Levonorgestrel-releasing intrauterine system for atypical endometrial hyperplasia.* Cochrane Database Syst Rev, 2013. **6:** p. CD009458. https://www.ncbi.nlm.nih.gov/pubmed/23737032

471. Gallos, I. D., Yap, J., Rajkhowa, M., 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:** p. 266.e1-12. https://www.ncbi.nlm.nih.gov/pubmed/23021687

472. Baker, J., Obermair, A., Gebski, V., 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:** p. 263-70. https://www.ncbi.nlm.nih.gov/pubmed/22196499

473. Koskas, M., Uzan, J., Luton, D., 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:** p. 785-94. https://www.ncbi.nlm.nih.gov/pubmed/24388202

474. Luo L, Luo B, Zheng Y, Zhang H, Li J, Sidell N. Levonorgestrel-releasing intrauterine system for atypical endometrial hyperplasia. Cochrane Database Syst Rev, 2013; 6: p. CD009458. https://www.ncbi.nlm.nih.gov/pubmed/23737032

475. Gunderson CC, Fader AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. Gynecol Oncol, 2012; 125: p. 477-82. https://www.ncbi.nlm.nih.gov/pubmed/22245711

476. Gallos ID, Yap J, Rajkhowa M, Luesley, D M, Coomarasamy A, Gupta J K. 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: p. 266.e1-12. https://www.ncbi.nlm.nih.gov/pubmed/23021687

477. Baker J, Obermair A, Gebski V, Janda M. 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: p. 263-70. https://www.ncbi.nlm.nih.gov/pubmed/22196499

478. Koskas M, Uzan J, Luton D, Rouzier R, Darai E. 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: p. 785-94. https://www.ncbi.nlm.nih.gov/pubmed/24388202

479. Mandelbaum. RS, Ciccone, MA, Nusbaum, DJ, Khoshchehreh, M, Purswani, H, Morocco, EB, et.al. Progestin therapy for obese women with complex atypical hyperplasia: levonorgestrel-releasing

intrauterine device vs systemic therapy. 2020; 223 (1)(1): p. 103.e1-103.e13. https://pubmed.ncbi.nlm.nih.gov/31978437/

480. Clement. NS, Oliver, TR, Shiwani, H, Sanner, JR, Mulvaney, CA, Atiomo, W, Metformin for endometrial hyperplasia. 2017; 10: p. CD012214. https://pubmed.ncbi.nlm.nih.gov/29077194/

481. Tehranian. A, Ghahghaei-Nezamabadi, A, Arab, M, Khalagi, K, Aghajani, R, Sadeghi, S, The impact of adjunctive metformin to progesterone for the treatment of non-atypical endometrial hyperplasia in a randomized fashion, a placebo-controlled, double blind clinical trial. 2021; 50 (6)(6): p. 101863. https://pubmed.ncbi.nlm.nih.gov/32652300/

482. Matsuo. K, Mandelbaum, RS, Ciccone, M, Khoshchehreh, M, Pursuwani, H, Morocco, EB, et.al. Route-specific association of progestin therapy and concurrent metformin use in obese women with complex atypical hyperplasia. 2020; 30 (9)(9): p. 1331-1339. https://pubmed.ncbi.nlm.nih.gov/32376736/

483. Yang. BY, Gulinazi, Y, Du, Y, Ning, CC, Cheng, YL, Shan, WW, et.al. Metformin plus megestrol acetate compared with megestrol acetate alone as fertility-sparing treatment in patients with atypical endometrial hyperplasia and well-differentiated endometrial cancer: a randomised controlled trial. 2020; 127 (7)(7): p. 848-857. https://pubmed.ncbi.nlm.nih.gov/31961463/

484. Chan, J. K., Wu, H., Cheung, M. K., et al. *The outcomes of 27,063 women with unstaged endometrioid uterine cancer.* Gynecol Oncol, 2007. **106:** p. 282-8. https://www.ncbi.nlm.nih.gov/pubmed/17662377

485. Walsh C, Holschneider C, Hoang Y, Tieu K, Karlan B, Cass I. Coexisting ovarian malignancy in young women with endometrial cancer. Obstet Gynecol, 2005; 106: p. 693-9. https://www.ncbi.nlm.nih.gov/pubmed/16199623

486. Williams MG, Bandera EV, Demissie K, Rodriguez-Rodriguez L. Synchronous primary ovarian and endometrial cancers: a population-based assessment of survival. Obstet Gynecol, 2009; 113: p. 783-9. https://www.ncbi.nlm.nih.gov/pubmed/19305320

487. Oranratanaphan S, Manchana T, Sirisabya N. 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: p. 403-7. https://www.ncbi.nlm.nih.gov/pubmed/18990010

488. Akbayir O, Kuru O, Goksedef P, Numanoglu C, Corbacioglu A. Cetin A, Coexisting ovarian malignancy in patients with clinical stage I endometrial carcinoma. Arch Gynecol Obstet, 2012; 286: p. 1241-5. https://www.ncbi.nlm.nih.gov/pubmed/22688443

489. Duska LR, Garrett A, Rueda BR, Haas J, Chang Y, Fuller A F. Endometrial cancer in women 40 years old or younger. Gynecol Oncol, 2001; 83: p. 388-93. https://www.ncbi.nlm.nih.gov/pubmed/11606102

490. Dogan A, Schultheis B, Rezniczek GA, Hilal Z, Cetin C, Hausler G. et.al. Synchronous Endometrial and Ovarian Cancer in Young Women: Case Report and Review of the Literature. Anticancer Res, 2017; 37: p. 969-978. https://www.ncbi.nlm.nih.gov/pubmed/28314254

491. Anglesio MS, Wang YK, Maassen M, Horlings HM, Bashashati A, Senz J. et.al. Synchronous Endometrial and Ovarian Carcinomas: Evidence of Clonality. J Natl Cancer Inst, 2016; 108: p. djv428. https://www.ncbi.nlm.nih.gov/pubmed/26832771

492. Goyal A. Masand RP, Roma A A, 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, 2015; 35: p. 167-75. https://www.ncbi.nlm.nih.gov/pubmed/26352548

493. Batte BA, Bruegl, A S, Daniels MS, Ring KL, Dempsey KM, Djordjevic B. et.al. Consequences of universal MSI/IHC in screening ENDOMETRIAL cancer patients for Lynch syndrome. Gynecol Oncol, 2014; 134: p. 319-25. https://www.ncbi.nlm.nih.gov/pubmed/24933100

494. Ruiz. MP, Huang, Y, Hou, JY, Tergas, AI, Burke, WM, Ananth, CV, et.al. All-cause mortality in young women with endometrial cancer receiving progesterone therapy. 2017; 217 (6)(6): p. 669.e1-669.e13. https://pubmed.ncbi.nlm.nih.gov/28844824/

495. Gonthier. C, Trefoux-Bourdet, A, Koskas, M, Impact of Conservative Managements in Young Women With Grade 2 or 3 Endometrial Adenocarcinoma Confined to the Endometrium. 2017; 27 (3)(3): p. 493-499. https://pubmed.ncbi.nlm.nih.gov/28187090/

496. Greenwald. ZR, Huang, LN, Wissing, MD, Franco, EL, Gotlieb, WH, Does hormonal therapy for fertility preservation affect the survival of young women with early-stage endometrial cancer?, 2017; 123 (9)(9): p. 1545-1554. https://pubmed.ncbi.nlm.nih.gov/28026855/

497. Guillon. S, Popescu, N, Phelippeau, J, Koskas, M, A systematic review and meta-analysis of prognostic factors for remission in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma. 2019; 146 (3)(3): p. 277-288. https://pubmed.ncbi.nlm.nih.gov/31197826/

498. Raffone. A, Travaglino, A, Saccone, G, Insabato, L, Mollo, A, De Placido, G, et.al. Endometrial hyperplasia and progression to cancer: which classification system stratifies the risk better? A systematic review and meta-analysis. 2019; 299 (5)(5): p. 1233-1242. https://pubmed.ncbi.nlm.nih.gov/30810881/

499. Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A. 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: p. 1736-44. https://www.ncbi.nlm.nih.gov/pubmed/10561210

500. Lentz SS, Brady MF, Major, F J, Reid GC, Soper, J T. High-dose megestrol acetate in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol, 1996; 14: p. 357-61. https://www.ncbi.nlm.nih.gov/pubmed/8636744

501. Liu, T, Tu, H, Li, Y, et al. *Impact of Radical Hysterectomy Versus Simple Hysterectomy on Survival of Patients with Stage 2 Endometrial Cancer: A Meta-analysis.*. Ann Surg Oncol, 2019. **26 (9):** p. 2933-2942. https://pubmed.ncbi.nlm.nih.gov/31147990/

502. Cohn DE, Woeste, E M, Cacchio S, Zanagnolo VL, Havrilesky, L J, Mariani A. et.al. Clinical and pathologic correlates in surgical stage II endometrial carcinoma. Obstet Gynecol, 2007; 109: p. 1062-7. https://www.ncbi.nlm.nih.gov/pubmed/17470583

503. Tamussino KF. Reich O, Gucer, F, Moser, F, Zivkovic, F, Lang PF, et.al. Parametrial spread in patients with endometrial carcinoma undergoing radical hysterectomy. Int J Gynecol Cancer, 2001; 10: p. 313-317. https://www.ncbi.nlm.nih.gov/pubmed/11240692

504. Frost, J. A., Webster, K. E., Bryant, A., et al. *Lymphadenectomy for the management of endometrial cancer.* Cochrane Database Syst Rev, 2017. **10 (10):** p. Cd007585.

505. Sueoka K, Umayahara K, Abe A, Usami T, Yamamoto A, Nomura H. et.al. Prognosis for endometrial cancer patients treated with systematic pelvic and para-aortic lymphadenectomy followed by platinum-based chemotherapy. Int J Gynecol Cancer, 2014; 25: p. 81-6. https://www.ncbi.nlm.nih.gov/pubmed/25347094

506. Sirisabya N, Manchana T. Worasethsin P, Khemapech N, Lertkhachonsuk R, Sittisomwong T, et.al. Is complete surgical staging necessary in clinically early-stage endometrial carcinoma? Int J Gynecol Cancer, 2009; 19: p. 1057-61. https://www.ncbi.nlm.nih.gov/pubmed/19820368

507. Garg G, Morris RT, Solomon L, Toy EP, Kruger M, Clary K. et.al. Evaluating the significance of location of lymph node metastasis and extranodal disease in women with stage IIIC endometrial cancer. Gynecol Oncol, 2011; 123: p. 208-13. https://www.ncbi.nlm.nih.gov/pubmed/21821278

508. Kapp DS, Kiet TK. Chan JK, Prognostic discrimination of subgrouping node-positive endometrioid uterine cancer: location vs nodal extent. Br J Cancer, 2011; 105: p. 1137-43. https://www.ncbi.nlm.nih.gov/pubmed/21915131

509. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller, P B. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer, 1987; 60: p. 2035-41. https://www.ncbi.nlm.nih.gov/pubmed/3652025

510. Frost JA, Webster KE, Bryant, A, Morrison J. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev, 2017; 10(10): p. Cd007585.

511. Kitchener H, Swart AM, Qian Q, Amos C, Parmar, M K. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet, 2008; 373: p. 125-36. https://www.ncbi.nlm.nih.gov/pubmed/19070889

512. Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G. et.al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst, 2008; 100: p. 1707-16. https://www.ncbi.nlm.nih.gov/pubmed/19033573

513. Frost JA, Webster KE, Bryant, A, Morrison J. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev, 2015; 2015(9): p. Cd007585.

514. Eltabbakh GH. Piver MS, Hempling RE, Shin KH, Excellent long-term survival and absence of vaginal recurrences in 332 patients with low-risk stage I endometrial adenocarcinoma treated with hysterectomy and vaginal brachytherapy without formal staging lymph node sampling: report of a prospective trial. Int J Radiat Oncol Biol Phys, 1997; 38: p. 373-80. https://www.ncbi.nlm.nih.gov/pubmed/9226326

515. Mariani A, Webb MJ, Keeney GL, Haddock MG, Calori, G, Podratz KC. Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary? Am J Obstet Gynecol, 2000; 182: p. 1506-19. https://www.ncbi.nlm.nih.gov/pubmed/10871473

516. Dowdy SC, Borah BJ, Bakkum-Gamez, J N, Weaver AL, McGree ME, Haas, L R. et.al. Prospective assessment of survival, morbidity, and cost associated with lymphadenectomy in low-risk endometrial cancer. Gynecol Oncol, 2012; 127: p. 5-10. https://www.ncbi.nlm.nih.gov/pubmed/22771890

517. Bendifallah S, Koskas M, Ballester M, Genin AS, Darai E, Rouzier R. The survival impact of systematic lymphadenectomy in endometrial cancer with the use of propensity score matching analysis. Am J Obstet Gynecol, 2012; 206: p. 500.e1-11. https://www.ncbi.nlm.nih.gov/pubmed/22546083

518. Mariani A, Dowdy SC, Cliby WA, Gostout BS, Jones MB, Wilson TO. et.al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol, 2008; 109: p. 11-8. https://www.ncbi.nlm.nih.gov/pubmed/18304622

519. Johnson N, Bryant A, Miles T, Hogberg T, Cornes P. Adjuvant chemotherapy for endometrial cancer after hysterectomy. Cochrane Database Syst Rev, 2011; p. Cd003175. https://www.ncbi.nlm.nih.gov/pubmed/21975736

520. Kim HS. Suh DH, Kim MK, Chung HH, Park NH, Song YS, Systematic lymphadenectomy for survival in patients with endometrial cancer: a meta-analysis. Jpn J Clin Oncol, 2012; 42: p. 405-12. https://www.ncbi.nlm.nih.gov/pubmed/22396619

521. Smith DC, Macdonald OK. Lee, C M, Gaffney DK, Survival impact of lymph node dissection in endometrial adenocarcinoma: a surveillance, epidemiology, and end results analysis. Int J Gynecol Cancer, 2007; 18: p. 255-61. https://www.ncbi.nlm.nih.gov/pubmed/17624991

522. Body, N, Grégoire, J, Renaud, MC, et al. *Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer.*. Gynecol Oncol, 2018. **150 (2):** p. 267-273. https://pubmed.ncbi.nlm.nih.gov/29909967/

523. Lambrou NC, Gomez-Marin O, Mirhashemi R, Beach H, Salom E, Almeida-Parra Z. et.al. Optimal surgical cytoreduction in patients with Stage III and Stage IV endometrial carcinoma: a study of morbidity and survival. Gynecol Oncol, 2004; 93: p. 653-8. https://www.ncbi.nlm.nih.gov/pubmed/15196860

524. Shih KK, Yun E, Gardner GJ, Barakat RR, Chi DS, Leitao MM. Jr. Surgical cytoreduction in stage IV endometrioid endometrial carcinoma. Gynecol Oncol, 2011; 122: p. 608-11. https://www.ncbi.nlm.nih.gov/pubmed/21664663

525. Setiawan VW, Yang HP, Pike MC, McCann SE, Yu H, Xiang YB. et.al. Type I and II endometrial cancers: have they different risk factors? J Clin Oncol, 2013; 31: p. 2607-18. https://www.ncbi.nlm.nih.gov/pubmed/23733771

526. Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet, 2010; 375: p. 1165-72. https://www.ncbi.nlm.nih.gov/pubmed/20188410

527. Bodurtha Smith, AJ, Fader, AN, Tanner, EJ. *Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis.*. Am J Obstet Gynecol, 2017. **216 (5):** p. 459-476.e10. https://pubmed.ncbi.nlm.nih.gov/27871836/

528. Bogani, G, Casarin, J, Leone Roberti Maggiore, U, et al. *Survival outcomes in endometrial cancer patients having lymphadenectomy, sentinel node mapping followed by lymphadectomy and sentinel node mapping alone: Long-term results of a propensity-matched analysis.*. Gynecol Oncol, 2020. **158 (1):** p. 77-83. https://pubmed.ncbi.nlm.nih.gov/32389376/

529. Kogan, L, Matanes, E, Wissing, M, et al. *The added value of sentinel node mapping in endometrial cancer.*. Gynecol Oncol, 2020. **158 (1):** p. 84-91. https://pubmed.ncbi.nlm.nih.gov/32349874/

530. Guo, W, Cai, J, Li, M, et al. *Survival benefits of pelvic lymphadenectomy versus pelvic and para-aortic lymphadenectomy in patients with endometrial cancer: A meta-analysis.*. Medicine (Baltimore), 2018. **97 (1):** p. e9520. https://pubmed.ncbi.nlm.nih.gov/29505525/

531. Odagiri T, Watari H, Kato T, Mitamura T, Hosaka M, Sudo S. 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: p. 2755-61. https://www.ncbi.nlm.nih.gov/pubmed/24705578

532. Alay I, Turan T, Ureyen I, Karalok A. Tasci T, Ozfuttu A, et.al. Lymphadenectomy should be performed up to the renal vein in patients with intermediate-high risk endometrial cancer. Pathol Oncol Res, 2015; 21: p. 803-10. https://www.ncbi.nlm.nih.gov/pubmed/25564000

533. Cosgrove. CM, Cohn, DE, Rhoades, J, Felix, AS, The prognostic significance of aortic lymph node metastasis in endometrial cancer: Potential implications for selective aortic lymph node assessment. 2019; 153 (3)(3): p. 505-510. https://pubmed.ncbi.nlm.nih.gov/30935714/

534. Cantrell LA, Blank SV, Duska LR. Uterine carcinosarcoma: A review of the literature. Gynecol Oncol, 2015; 137: p. 581-8. https://www.ncbi.nlm.nih.gov/pubmed/25805398

535. Nemani D, Mitra N, Guo M, Lin L. Assessing the effects of lymphadenectomy and radiation therapy in patients with uterine carcinosarcoma: a SEER analysis. Gynecol Oncol, 2008; 111: p. 82-8. https://www.ncbi.nlm.nih.gov/pubmed/18674808

536. Versluis. MAC, Pielsticker, C, van der Aa, MA, de Bruyn, M, Hollema, H, Nijman, HW, Lymphadenectomy and Adjuvant Therapy Improve Survival with Uterine Carcinosarcoma: A Large Retrospective Cohort Study. 2018; 95 (2)(2): p. 100-108. https://pubmed.ncbi.nlm.nih.gov/29791913/

537. Torne A, Pahisa J, Vidal-Sicart S, Martinez-Roman S, Paredes P, Puerto B. et.al. Transvaginal ultrasound-guided myometrial injection of radiotracer (TUMIR): a new method for sentinel lymph node detection in endometrial cancer. Gynecol Oncol, 2013; 128: p. 88-94. https://www.ncbi.nlm.nih.gov/pubmed/23085461

538. Lopez-De la Manzanara Cano C. Cordero Garcia JM, Martin-Francisco C, Pascual-Ramirez J, Parra C P, Cespedes Casas C, Sentinel lymph node detection using 99mTc combined with methylene blue cervical injection for endometrial cancer surgical management: a prospective study. Int J Gynecol Cancer, 2014; 24: p. 1048-53. https://www.ncbi.nlm.nih.gov/pubmed/24927249

539. Ballester M, Dubernard G, Lecuru F, Heitz D, Mathevet P, Marret H. et.al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). Lancet Oncol, 2011; 12: p. 469-76. https://www.ncbi.nlm.nih.gov/pubmed/21489874

540. Ballester M, Naoura I, Chereau E, Seror J, Bats AS, Bricou A. et.al. Sentinel node biopsy upstages patients with presumed low- and intermediate-risk endometrial cancer: results of a multicenter study. Ann Surg Oncol, 2012; 20: p. 407-12. https://www.ncbi.nlm.nih.gov/pubmed/23054119

541. Koskas M, Chereau E, Ballester M, Dubernard G, Lecuru F, Heitz D. et.al. Accuracy of a nomogram for prediction of lymph-node metastasis detected with conventional histopathology and ultrastaging in endometrial cancer. Br J Cancer, 2013; 108: p. 1267-72. https://www.ncbi.nlm.nih.gov/pubmed/23481184

542. Darai E, Dubernard G, Bats AS, Heitz D, Mathevet P, Marret H. et.al. Sentinel node biopsy for the management of early stage endometrial cancer: long-term results of the SENTI-ENDO study. Gynecol Oncol, 2014; 136: p. 54-9. https://www.ncbi.nlm.nih.gov/pubmed/25450151

543. Cormier B, Rozenholc AT, Gotlieb W, Plante M, Giede C. Sentinel lymph node procedure in endometrial cancer: A systematic review and proposal for standardization of future research. Gynecol Oncol, 2015; 138: p. 478-85. https://www.ncbi.nlm.nih.gov/pubmed/26047592

544. Mueller. JJ, Pedra Nobre, S, Braxton, K, Alektiar, KM, Leitao, MM, Aghajanian, C, et.al. Incidence of pelvic lymph node metastasis using modern FIGO staging and sentinel lymph node mapping with ultrastaging in surgically staged patients with endometrioid and serous endometrial carcinoma. 2020; 157 (3)(3): p. 619-623. https://pubmed.ncbi.nlm.nih.gov/32247604/

545. Imboden. S, Mereu, L, Siegenthaler, F, Pellegrini, A, Papadia, A, Tateo, S, et.al. Oncological safety and perioperative morbidity in low-risk endometrial cancer with sentinel lymph-node dissection. 2019; 45 (9)(9): p. 1638-1643. https://pubmed.ncbi.nlm.nih.gov/31229377/

546. Zheng. Y, Yang, X, Liang, Y, Zhang, T, Chen, J, Li, Y, et.al. Effects of lymphadenectomy among women with stage IA endometrial cancer: a SEER database analysis. 2019; 15 (19)(19): p. 2251-2266. https://pubmed.ncbi.nlm.nih.gov/31094582/

547. Ouldamer. L, Bendifallah, S, Body, G, Canlorbe, G, Touboul, C, Graesslin, O, et.al. Call for Surgical Nodal Staging in Women with ESMO/ESGO/ESTRO High-Intermediate Risk Endometrial Cancer: A Multicentre Cohort Analysis from the FRANCOGYN Study Group. 2017; 24 (6)(6): p. 1660-1666. https://pubmed.ncbi.nlm.nih.gov/28058558/

548. Colombo N, Creutzberg C, Amant F, Bosse T, Gonzalez-Martin A, Ledermann J. et.al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. Int J Gynecol Cancer, 2015; 26: p. 2-30. https://www.ncbi.nlm.nih.gov/pubmed/26634381

549. Bogani. G, Dowdy, SC, Cliby, WA, Ghezzi, F, Rossetti, D, Mariani, A, Role of pelvic and para-aortic lymphadenectomy in endometrial cancer: current evidence. 2014; 40 (2)(2): p. 301-11. https://pubmed.ncbi.nlm.nih.gov/24472047/

550. Papadia. A, Gasparri, ML, Buda, A, Mueller, MD, Sentinel lymph node mapping in endometrial cancer: comparison of fluorescence dye with traditional radiocolloid and blue. 2017; 143 (10)(10): p. 2039-2048. https://pubmed.ncbi.nlm.nih.gov/28828528/

551. Sinno. AK, Peijnenburg, E, Fader, AN, Temkin, SM, Stone, R, Levinson, K, et.al. Reducing overtreatment: A comparison of lymph node assessment strategies for endometrial cancer. 2016; 143 (2)(2): p. 281-286. https://pubmed.ncbi.nlm.nih.gov/27568279/

552. Cusimano. MC, Vicus, D, Pulman, K, Maganti, M, Bernardini, MQ, Bouchard-Fortier, G, et.al. Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging. 2021; 156 (2)(2): p. 157-164. https://pubmed.ncbi.nlm.nih.gov/33175109/

553. Schlappe. BA, Weaver, AL, McGree, ME, Ducie, J, Zahl Eriksson, AG, Dowdy, SC, et.al. Multicenter study comparing oncologic outcomes after lymph node assessment via a sentinel lymph node algorithm versus comprehensive pelvic and para-aortic lymphadenectomy in patients with serous and clear cell endometrial carcinoma. 2020; 156 (1)(1): p. 62-69. https://pubmed.ncbi.nlm.nih.gov/31776037/

554. Ditto. A, Casarin, J, Pinelli, C, Perrone, AM, Scollo, P, Martinelli, F, et.al. Corrigendum to "Hysteroscopic versus cervical injection for sentinel node detection in endometrial cancer: A multicenter prospective randomised controlled trial from the Multicenter Italian Trials in Ovarian cancer (MITO) study group" [European Journal of Cancer. Volume 140, November 2020, Pages 1-10]. 2021; 144: p. 399. https://pubmed.ncbi.nlm.nih.gov/33342624/

555. Persson. J, Salehi, S, Bollino, M, Lönnerfors, C, Falconer, H, Geppert, B, Pelvic Sentinel lymph node detection in High-Risk Endometrial Cancer (SHREC-trial)-the final step towards a paradigm shift in surgical staging. 2019; 116: p. 77-85. https://pubmed.ncbi.nlm.nih.gov/31181536/

556. Galaal, K, Donkers, H, Bryant, A, et al. *Laparoscopy versus laparotomy for the management of early stage endometrial cancer.*. Cochrane Database Syst Rev, 2018. **10 ():** p. CD006655. https://pubmed.ncbi.nlm.nih.gov/30379327/

557. Asher, R, Obermair, A, Janda, M, et al. *Disease-Free and Survival Outcomes for Total Laparoscopic Hysterectomy Compared With Total Abdominal Hysterectomy in Early-Stage Endometrial Carcinoma: A Meta-analysis.*. Int J Gynecol Cancer, 2018. **28 (3):** p. 529-538. https://pubmed.ncbi.nlm.nih.gov/29369119/

558. Galaal, K., Bryant, A., Fisher, A. D., et al. *Laparoscopy versus laparotomy for the management of early stage endometrial cancer.* Cochrane Database Syst Rev, 2012. **9:** p. Cd006655. https://www.ncbi.nlm.nih.gov/pubmed/22972096

559. Walker JL, Piedmonte MR, Spirtos NM, Eisenkop SM, Schlaerth JB, Mannel, R S. et.al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. J Clin Oncol, 2009; 27: p. 5331-6. https://www.ncbi.nlm.nih.gov/pubmed/19805679

560. Walker JL, Piedmonte MR, Spirtos NM, Eisenkop SM, Schlaerth JB, Mannel, R S. et.al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical

staging of uterine cancer: Gynecologic Oncology Group LAP2 Study. J Clin Oncol, 2012; 30: p. 695-700. https://www.ncbi.nlm.nih.gov/pubmed/22291074

561. Zullo F, Falbo A, Palomba S. Safety of laparoscopy vs laparotomy in the surgical staging of endometrial cancer: a systematic review and metaanalysis of randomized controlled trials. Am J Obstet Gynecol, 2012; 207: p. 94-100. https://www.ncbi.nlm.nih.gov/pubmed/22340944

562. Philp. L, Tannenbaum, S, Haber, H, Saini, A, Laurent, JS, James, K, et.al. Effect of surgical approach on risk of recurrence after vaginal brachytherapy in early-stage high-intermediate risk endometrial cancer. 2021; 160 (2)(2): p. 389-395. https://pubmed.ncbi.nlm.nih.gov/33358198/

563. Padilla-Iserte P, Lago V, Tauste C, Díaz-Feijoo B, Gil-Moreno A, Oliver R. et.al. Impact of uterine manipulator on oncological outcome in endometrial cancer surgery. Am J Obstet Gynecol, 2021; 224(1): p. 65.e1-65.e11.

564. Cusimano, MC, Simpson, AN, Dossa, F, et al. *Laparoscopic and robotic hysterectomy in endometrial cancer patients with obesity: a systematic review and meta-analysis of conversions and complications.*. Am J Obstet Gynecol, 2019. **221 (5):** p. 410-428.e19. https://pubmed.ncbi.nlm.nih.gov/31082383/

565. Wang, L, Liu, F. *Meta-analysis of laparoscopy sentinel lymph node mapping in endometrial cancer.*. Arch Gynecol Obstet, 2018. **298 (3):** p. 505-510. https://pubmed.ncbi.nlm.nih.gov/30008031/

566. Ind, T, Laios, A, Hacking, M, et al. *A comparison of operative outcomes between standard and robotic laparoscopic surgery for endometrial cancer: A systematic review and meta-analysis.*. Int J Med Robot, 2017. **13 (4):** https://pubmed.ncbi.nlm.nih.gov/28762635/

567. Wright JD, Burke WM, Wilde ET, Lewin SN, Charles AS, Kim JH. et.al. Comparative effectiveness of robotic versus laparoscopic hysterectomy for endometrial cancer. J Clin Oncol, 2012; 30: p. 783-91. https://www.ncbi.nlm.nih.gov/pubmed/22291073

568. Ran L, Jin J, Xu Y, Bu Y, Song F. Comparison of robotic surgery with laparoscopy and laparotomy for treatment of endometrial cancer: a meta-analysis. PLoS One, 2014; 9: p. e108361. https://www.ncbi.nlm.nih.gov/pubmed/25259856

569. Chan JK, Gardner AB, Taylor, K, Thompson CA, Blansit, K, Yu X. et.al. Robotic versus laparoscopic versus open surgery in morbidly obese endometrial cancer patients - a comparative analysis of total charges and complication rates. Gynecol Oncol, 2015; 139: p. 300-5. https://www.ncbi.nlm.nih.gov/pubmed/26363212

570. O'Malley DM. Smith B, Fowler JM, The role of robotic surgery in endometrial cancer. J Surg Oncol, 2015; 112: p. 761-8. https://www.ncbi.nlm.nih.gov/pubmed/26385835

571. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet, 2015; 387: p. 1094-108. https://www.ncbi.nlm.nih.gov/pubmed/26354523

572. de Lange, NM, Ezendam, NPM, Kwon, JS, et al. *Neoadjuvant chemotherapy followed by surgery for advanced-stage endometrial cancer.*. Curr Oncol, 2019. **26 (2):** p. e226-e232. https://pubmed.ncbi.nlm.nih.gov/31043831/

573. Tanner, E. J., Leitao, M. M., Jr., Garg, K., et al. *The role of cytoreductive surgery for newly diagnosed advanced-stage uterine carcinosarcoma.* Gynecol Oncol, 2011. **123:** p. 548-52. https://www.ncbi.nlm.nih.gov/pubmed/21945551

574. Barlin, J. N., Puri, I., Bristow, R. E.. *Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis.* Gynecol Oncol, 2010. **118:** p. 14-8. https://www.ncbi.nlm.nih.gov/pubmed/20434198

575. Kong A. Johnson N, Kitchener HC, Lawrie TA, Adjuvant radiotherapy for stage I endometrial cancer. Cochrane Database Syst Rev, 2012; 4: p. CD003916. https://www.ncbi.nlm.nih.gov/pubmed/22513918

576. Kong A. Johnson N, Kitchener HC, Lawrie TA, Adjuvant radiotherapy for stage I endometrial cancer: an updated Cochrane systematic review and meta-analysis. J Natl Cancer Inst, 2012; 104: p. 1625-34. https://www.ncbi.nlm.nih.gov/pubmed/22962693

577. Klopp A, Smith BD, Alektiar K, Cabrera A, Damato A L, Erickson B. et.al. The role of postoperative radiation therapy for endometrial cancer: executive summary of an American society for radiation oncology evidence-based guideline (Provisional abstract). Database of Abstracts of Reviews of Effects, 2014; p. 137-144. https://www.ncbi.nlm.nih.gov/pubmed/24766678

578. TNM-Klassifikation maligner Tumoren. EndometriumkarzinomWiley-VCHTNM-Klassifikation maligner Tumoren, 2010;

579. C. . , W, i, t, et.al. TNM-Klassifikation maligner Tumoren, 2017;

580. Nout RA, van de Poll-Franse LV, Lybeert ML, Warlam-Rodenhuis CC, Jobsen JJ, Mens JW. 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: p. 1692-700. https://www.ncbi.nlm.nih.gov/pubmed/21444867

581. Creutzberg CL, Nout RA, Lybeert ML, Warlam-Rodenhuis CC, Jobsen JJ, Mens JW. et.al. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. Int J Radiat Oncol Biol Phys, 2011; 81: p. e631-8. https://www.ncbi.nlm.nih.gov/pubmed/21640520

582. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol, 1980; 56: p. 419-27. https://www.ncbi.nlm.nih.gov/pubmed/6999399

583. Onsrud M, Cvancarova M, Hellebust TP, Trope CG, Kristensen, G B, Lindemann K. Long-term outcomes after pelvic radiation for early-stage endometrial cancer. J Clin Oncol, 2013; 31: p. 3951-6. https://www.ncbi.nlm.nih.gov/pubmed/24019546

584. Wiltink LM. Nout RA, Fiocco, M, Meershoek-Klein Kranenbarg E, Jurgenliemk-Schulz IM, Jobsen JJ, et.al. No Increased Risk of Second Cancer After Radiotherapy in Patients Treated for Rectal or Endometrial Cancer in the Randomized TME, PORTEC-1, and PORTEC-2 Trials. J Clin Oncol, 2014; 33: p. 1640-6. https://www.ncbi.nlm.nih.gov/pubmed/25534376

585. Creutzberg CL. van Putten WL, Warlam-Rodenhuis CC, van den Bergh AC, de Winter KA, Koper PC, et.al. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the Postoperative Radiation Therapy in Endometrial Carcinoma Trial. J Clin Oncol, 2004; 22: p. 1234-41. https://www.ncbi.nlm.nih.gov/pubmed/15051771

586. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD. et.al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol, 2004; 92: p. 744-51. https://www.ncbi.nlm.nih.gov/pubmed/14984936

587. T, h, e, ,, , A, et.al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN5 randomised trials): pooled trial results, systematic review, and meta-analysis, 2009; 373: p. 137-146. https://www.ncbi.nlm.nih.gov/pubmed/19070891

588. Scholten AN, van Putten WL. Beerman H, Smit VT, Koper PC, Lybeert ML, et.al. Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys, 2005; 63: p. 834-8. https://www.ncbi.nlm.nih.gov/pubmed/15927414

589. Bosse T, Peters EE, Creutzberg CL, Jurgenliemk-Schulz IM, Jobsen JJ, Mens JW. et.al. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer--A pooled analysis of PORTEC 1 and 2 trials. Eur J Cancer, 2015; 51: p. 1742-50. https://www.ncbi.nlm.nih.gov/pubmed/26049688

590. Klopp, A., Smith, B. D., Alektiar, K., et al. *The role of postoperative radiation therapy for endometrial cancer: executive summary of an American society for radiation oncology evidence-based guideline (Provisional abstract).* Database of Abstracts of Reviews of Effects, 2014. p. 137-144. https://www.ncbi.nlm.nih.gov/pubmed/24766678

591. Ortoft, G., Hansen, E. S., Bertelsen, K.. *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:** p. 1429-37. https://www.ncbi.nlm.nih.gov/pubmed/24257557

592. AlHilli, M, Amarnath, S, Elson, P, et al. *Impact of vaginal brachytherapy on survival in stage I endometrioid endometrial carcinoma..* Int J Gynecol Cancer, 2020. **30 (6):** p. 789-796. https://pubmed.ncbi.nlm.nih.gov/32184268/

593. Nout, R. A., van de Poll-Franse, L. V., Lybeert, M. L., 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:** p. 1692-700. https://www.ncbi.nlm.nih.gov/pubmed/21444867

594. Nout, R. A., Putter, H., Jurgenliemk-Schulz, I. M., 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:** p. 3547-56. https://www.ncbi.nlm.nih.gov/pubmed/19546404

595. Nout, R. A., Smit, V. T., Putter, H., 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:** p. 816-23. https://www.ncbi.nlm.nih.gov/pubmed/20206777

596. de Boer, SM, Powell, ME, Mileshkin, L, et al. *Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial..* Lancet Oncol, 2016. **17 (8):** p. 1114-1126. https://pubmed.ncbi.nlm.nih.gov/27397040/

597. de Boer, SM, Powell, ME, Mileshkin, L, et al. *Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial..* Lancet Oncol, 2019. **20 (9):** p. 1273-1285. https://pubmed.ncbi.nlm.nih.gov/31345626/

598. de Boer, SM, Powell, ME, Mileshkin, L, et al. *Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial..* Lancet Oncol, 2018. **19 (3):** p. 295-309. https://pubmed.ncbi.nlm.nih.gov/29449189/

599. Nout, R. A., Putter, H., Jurgenliemk-Schulz, I. M., 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:** p. 3547-56. https://www.ncbi.nlm.nih.gov/pubmed/19546404

600. Nout, R. A., Smit, V. T., Putter, H., 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:** p. 816-23. https://www.ncbi.nlm.nih.gov/pubmed/20206777

601. Ørtoft, G, Høgdall, C, Hansen, ES, et al. *Survival and recurrence in stage II endometrial cancers in relation to uterine risk stratification after introduction of lymph node resection and omission of postoperative radiotherapy: a Danish Gynecological Cancer Group Study.*. J Gynecol Oncol, 2020. **31 (2):** p. e22. https://pubmed.ncbi.nlm.nih.gov/31912677/

602. Narasimhulu, DM, Cope, A, Riaz, IB, et al. *External beam radiotherapy versus vaginal brachytherapy in patients with stage II endometrial cancer: a systematic review and meta-analysis.*. Int J Gynecol Cancer, 2020. **30 (6):** p. 797-805. https://pubmed.ncbi.nlm.nih.gov/32221021/

603. Bertelsen K, Ortoft G, Hansen ES. Survival of Danish patients with endometrial cancer in the intermediate-risk group not given postoperative radiotherapy: the Danish Endometrial Cancer Study (DEMCA). Int J Gynecol Cancer, 2011; 21: p. 1191-9. https://www.ncbi.nlm.nih.gov/pubmed/21885985

604. Nagar H, Boothe D. Parikh A, Yondorf M, Parashar B, Gupta D, et.al. Administration of concurrent vaginal brachytherapy during chemotherapy for treatment of endometrial cancer. Int J Radiat Oncol Biol Phys, 2013; 87: p. 665-9. https://www.ncbi.nlm.nih.gov/pubmed/24138915

605. Sorbe B, Nordstrom B, Maenpaa J, Kuhelj J, Kuhelj D, Okkan S. et.al. Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer: a controlled randomized study. Int J Gynecol Cancer, 2009; 19: p. 873-8. https://www.ncbi.nlm.nih.gov/pubmed/19574776

606. Rydzewski. NR, Strohl, AE, Donnelly, ED, Kanis, MJ, Lurain, JR, Nieves-Neira, W, et.al. Receipt of vaginal brachytherapy is associated with improved survival in women with stage I endometrioid adenocarcinoma of the uterus: A National Cancer Data Base study. 2016; 122 (23)(23): p. 3724-3731. https://pubmed.ncbi.nlm.nih.gov/27509082/

607. Ortoft G, Hansen ES, Bertelsen K. 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: p. 1429-37. https://www.ncbi.nlm.nih.gov/pubmed/24257557

608. Matei. D, Filiaci, V, Randall, ME, Mutch, D, Steinhoff, MM, DiSilvestro, PA, et.al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. 2019; 380 (24)(24): p. 2317-2326. https://pubmed.ncbi.nlm.nih.gov/31189035/

609. Maggi R, Lissoni A, Spina F, Melpignano M, Zola P, Favalli G. et.al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. Br J Cancer, 2006; 95: p. 266-71. https://www.ncbi.nlm.nih.gov/pubmed/16868539

610. Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J. et.al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol, 2005; 24: p. 36-44. https://www.ncbi.nlm.nih.gov/pubmed/16330675

611. Hogberg T, Signorelli M, de Oliveira CF, Fossati R, Lissoni AA, Sorbe B. et.al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer, 2010; 46: p. 2422-31. https://www.ncbi.nlm.nih.gov/pubmed/20619634

612. Xiang. M, English, DP, Kidd, EA, Defining the survival benefit of adjuvant pelvic radiotherapy and chemotherapy versus chemotherapy alone in stages III-IVA endometrial carcinoma. 2019; 154 (3)(3): p. 487-494. https://pubmed.ncbi.nlm.nih.gov/31257010/

613. Goodman. CR, Hatoum, S, Seagle, BL, Donnelly, ED, Barber, EL, Shahabi, S, et.al. Association of chemotherapy and radiotherapy sequence with overall survival in locoregionally advanced endometrial cancer. 2019; 153 (1)(1): p. 41-48. https://pubmed.ncbi.nlm.nih.gov/30660345/

614. Mitra D, Klopp AH, Viswanathan AN. Pros and cons of vaginal brachytherapy after external beam radiation therapy in endometrial cancer. Gynecol Oncol, 2015; 140: p. 167-75. https://www.ncbi.nlm.nih.gov/pubmed/26432041

615. Randall ME, Filiaci V, McMeekin DS, von Gruenigen V, Huang H, Yashar CM. et.al. Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. J Clin Oncol, 2019; 37(21): p. 1810-1818.

616. Lin Y, Zhou J. Cheng Y, Zhao L, Yang Y, Wang J, Comparison of Survival Benefits of Combined Chemotherapy and Radiotherapy Versus Chemotherapy Alone for Uterine Serous Carcinoma: A Meta-analysis. Int J Gynecol Cancer, 2016; 27: p. 93-101. https://www.ncbi.nlm.nih.gov/pubmed/28005619

617. van der Steen-Banasik E, Christiaens M, Shash E, Coens C, Casado A, Herrera FG. et.al. Systemic review: Radiation therapy alone in medical non-operable endometrial carcinoma. Eur J Cancer, 2016; 65: p. 172-81. https://www.ncbi.nlm.nih.gov/pubmed/27501506

618. Reed, N. S., Mangioni, C., Malmstrom, H., 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:** p. 808-18. https://www.ncbi.nlm.nih.gov/pubmed/18378136

619. Reed NS, Mangioni C, Malmstrom H, Scarfone G, Poveda A, Pecorelli, 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: p. 808-18. https://www.ncbi.nlm.nih.gov/pubmed/18378136

620. Wolfson AH, Brady MF, Rocereto T, Mannel RS, Lee YC, Futoran RJ. et.al. A gynecologic oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV carcinosarcoma (CS) of the uterus. Gynecol Oncol, 2007; 107: p. 177-85. https://www.ncbi.nlm.nih.gov/pubmed/17822748

621. Sampath S, Schultheiss TE, Ryu JK, Wong JY. The role of adjuvant radiation in uterine sarcomas. Int J Radiat Oncol Biol Phys, 2009; 76: p. 728-34. https://www.ncbi.nlm.nih.gov/pubmed/19700247

622. Wright JD, Seshan VE, Shah M, Schiff PB, Burke WM, Cohen CJ. et.al. The role of radiation in improving survival for early-stage carcinosarcoma and leiomyosarcoma. Am J Obstet Gynecol, 2008; 199: p. 536 e1-8. https://www.ncbi.nlm.nih.gov/pubmed/18511017

623. Nemani D, Mitra N, Guo M, Lin L. Assessing the effects of lymphadenectomy and radiation therapy in patients with uterine carcinosarcoma: a SEER analysis. Gynecol Oncol, 2008; 111: p. 82-8. https://www.ncbi.nlm.nih.gov/pubmed/18674808

624. Vordermark. D, Medenwald, D, Izaguirre, V, Sieker, F, Marnitz, S, The Role of Postoperative Radiotherapy for Carcinosarcoma of the Uterus. 2020; 12 (12)(12). https://pubmed.ncbi.nlm.nih.gov/33265910/

625. L. e, i, t, l, i, et.al. S3-Leitlinie Supportive Therapie bei onkologischen PatientInnen, Langversion 1.1 – April 2017, AWMF-Registernummer: 032/054OL, 2017. https://www.leitlinienprogramm-onkologie.de/leitlinien/supportive-therapie/

626. E. u, r, o, p, e, et.al. PUBLIC SUMMARY OF POSITIVE OPINION FOR ORPHAN DESIGNATION OF sodium butyrate (rectal use) for the prevention of radiation proctitis, 2005. https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/05/284-public-summary-positive-opinion-orphan-designation-sodium-butyrate-rectal-use-prevention_en.pdf

627. Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman T H. et.al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol, 2008; 27: p. 127-45. https://www.ncbi.nlm.nih.gov/pubmed/19018081

628. Martin-Hirsch, P. P. L., Bryant, Andrew, Keep Sarah, L., et al. *Adjuvant progestagens for endometrial cancer.* Cochrane Database of Systematic Reviews, 2011. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4238061/

629. Martin-Hirsch PPL, Bryant, Andrew, Keep Sarah, L, Kitchener Henry C. Lilford, Richard, Adjuvant progestagens for endometrial cancerJohn Wiley & Sons, Ltd. Cochrane Database of Systematic Reviews, 2011. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4238061/

630. Galaal, K., Al Moundhri, M., Bryant, A., et al. *Adjuvant chemotherapy for advanced endometrial cancer.* Cochrane Database Syst Rev, 2014. **5:** p. Cd010681. https://www.ncbi.nlm.nih.gov/pubmed/24832785

631. de Boer, P., Adam, J. A., Buist, M. R., et al. *Role of MRI in detecting involvement of the uterine internal os in uterine cervical cancer: systematic review of diagnostic test accuracy.* Eur J Radiol, 2013. **82:** p. e422-8.

632. Nomura, H, Aoki, D, Michimae, H, et al. *Effect of Taxane Plus Platinum Regimens vs Doxorubicin Plus Cisplatin as Adjuvant Chemotherapy for Endometrial Cancer at a High Risk of Progression: A Randomized Clinical Trial..* JAMA Oncol, 2019. **5 (6):** p. 833-840. https://pubmed.ncbi.nlm.nih.gov/30896757/

633. Miller, D. S., Filiaci, V. L., Mannel, R. S., et al. *Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209).* J Clin Oncol, 2020. **38 (33):** p. 3841-3850. https://pubmed.ncbi.nlm.nih.gov/33078978/

634. Miller. DS, Filiaci, VL, Mannel, RS, Cohn, DE, Matsumoto, T, Tewari, KS, et.al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). 2020; 38 (33)(33): p. 3841-3850. https://pubmed.ncbi.nlm.nih.gov/33078978/

635. van den Heerik. ASVM, Horeweg, N, Nout, RA, Lutgens, LCHW, van der Steen-Banasik, EM, Westerveld, GH, et.al. PORTEC-4a: international randomized trial of molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer. 2020; 30 (12)(12): p. 2002-2007. https://pubmed.ncbi.nlm.nih.gov/33046573/

636. Cantrell, L. A., Havrilesky, L., Moore, D. T., et al. *A multi-institutional cohort study of adjuvant therapy in stage I-II uterine carcinosarcoma.* Gynecol Oncol, 2012. **127:** p. 22-6. https://www.ncbi.nlm.nih.gov/pubmed/22727985

637. Galaal, K., van der Heijden, E., Godfrey, K., et al. *Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma.* Cochrane Database Syst Rev, 2013. **2:** p. Cd006812. https://www.ncbi.nlm.nih.gov/pubmed/23450572

638. Sutton, G., Brunetto, V. L., Kilgore, L., 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:** p. 147-53. https://www.ncbi.nlm.nih.gov/pubmed/11063636

639. Homesley, H. D., Filiaci, V., Markman, M., 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:** p. 526-31. https://www.ncbi.nlm.nih.gov/pubmed/17290061

640. Cantrell LA. Havrilesky L, Moore DT, O'Malley D, Liotta M, Secord, A A, et.al. A multi-institutional cohort study of adjuvant therapy in stage I-II uterine carcinosarcoma. Gynecol Oncol, 2012; 127: p. 22-6. https://www.ncbi.nlm.nih.gov/pubmed/22727985

641. Cantrell LA, Blank SV, Duska LR. Uterine carcinosarcoma: A review of the literature. Gynecol Oncol, 2015; 137: p. 581-8. https://www.ncbi.nlm.nih.gov/pubmed/25805398

642. Sutton G. Brunetto VL, Kilgore, L, Soper JT, McGehee R, Olt 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: p. 147-53. https://www.ncbi.nlm.nih.gov/pubmed/11063636

643. Homesley HD, Filiaci V, Markman M, Bitterman P, Eaton L, Kilgore L C. 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: p. 526-31. https://www.ncbi.nlm.nih.gov/pubmed/17290061

644. Galaal K, van der Heijden E, Godfrey K, Naik R, Kucukmetin A. Bryant A, et.al. Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma. Cochrane Database Syst Rev, 2013; 2: p. Cd006812. https://www.ncbi.nlm.nih.gov/pubmed/23450572

645. Powell. Matthew A, Filiaci, Virginia L, Hensley, Martee Leigh, Huang, Helen Q, Moore, Kathleen N, Tewari, Krishnansu Sujata, et.al. A randomized phase 3 trial of paclitaxel (P) plus carboplatin (C) versus paclitaxel plus ifosfamide (I) in chemotherapy-naive patients with stage I-IV, persistent or recurrent carcinosarcoma of the uterus or ovary: An NRG Oncology trial. Wolters Kluwer. Journal of Clinical Oncology, 2019; 37(15_suppl): p. 5500 - 5500. https://doi.org/10.1200/JCO.2019.37.15_suppl.5500

646. Fung-Kee-Fung, M., Dodge, J., Elit, L., et al. *Follow-up after primary therapy for endometrial cancer: a systematic review.* Gynecol Oncol, 2006. **101:** p. 520-9. https://www.ncbi.nlm.nih.gov/pubmed/16556457

647. Gadducci, A., Cosio, S., Fanucchi, A., et al. *An intensive follow-up does not change survival of patients with clinical stage I endometrial cancer.* Anticancer Res, 2000. **20:** p. 1977-84. https://www.ncbi.nlm.nih.gov/pubmed/10928137

648. Sartori, E., Pasinetti, B., Carrara, L., et al. *Pattern of failure and value of follow-up procedures in endometrial and cervical cancer patients.* Gynecol Oncol, 2007. **107:** p. S241-7. https://www.ncbi.nlm.nih.gov/pubmed/17826824

649. Smith, C. J., Heeren, M., Nicklin, J. L., et al. *Efficacy of routine follow-up in patients with recurrent uterine cancer.* Gynecol Oncol, 2007. **107:** p. 124-9. https://www.ncbi.nlm.nih.gov/pubmed/17655917

650. Carrara, L., Gadducci, A., Landoni, F., 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:** p. 1013-9. https://www.ncbi.nlm.nih.gov/pubmed/22706226

651. Creutzberg, C. L., van Putten, W. L., Koper, P. C., et al. *Survival after relapse in patients with endometrial cancer: results from a randomized trial.* Gynecol Oncol, 2003. **89:** p. 201-9. https://www.ncbi.nlm.nih.gov/pubmed/12713981

652. Reddoch, J. M., Burke, T. W., Morris, M., et al. *Surveillance for recurrent endometrial carcinoma: development of a follow-up scheme.* Gynecol Oncol, 1995. **59:** p. 221-5. https://www.ncbi.nlm.nih.gov/pubmed/7590477

653. Bristow, R. E., Purinton, S. C., Santillan, A., et al. *Cost-effectiveness of routine vaginal cytology for endometrial cancer surveillance.* Gynecologic Oncology, 2006. **103:** p. 709-713. https://www.ncbi.nlm.nih.gov/pubmed/16797686

654. Salani, R., Nagel, C. I., Drennen, E., et al. *Recurrence patterns and surveillance for patients with early stage endometrial cancer.* Gynecol Oncol, 2011. **123:** p. 205-7. https://www.ncbi.nlm.nih.gov/pubmed/21820709

655. Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol, 2006; 101: p. 520-9. https://www.ncbi.nlm.nih.gov/pubmed/16556457

656. Carrara L. Gadducci A, Landoni F, Maggino T, Scambia G, Galletto 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: p. 1013-9. https://www.ncbi.nlm.nih.gov/pubmed/22706226

657. Yalamanchi P, Shabason JE, Zhang X, Ko, E M, Lin LL. Use of Aggressive Surveillance for Locoregional Endometrial Cancer After Local Therapy. Int J Gynecol Cancer, 2018; 28(7): p. 1264-1270. https://pubmed.ncbi.nlm.nih.gov/30036223/

658. Nomura H, Aoki D, Susumu N, Mizuno M. Nakai H, Arai M, et.al. Analysis of the relapse patterns and risk factors of endometrial cancer following postoperative adjuvant chemotherapy in a phase III randomized clinical trial. Gynecol Oncol, 2019; 155(3): p. 413-419. https://pubmed.ncbi.nlm.nih.gov/31601493/

659. Testa AC, Fruscella E, Ludovisi M, De Vincenzo R, Malaggese M, Corrado G. et.al. The role of sonographic examination in the follow-up of gynecological neoplasms. Gynecol Oncol, 2005; 99: p. 696-703. https://www.ncbi.nlm.nih.gov/pubmed/16140365

660. Zola P, Fuso L, Mazzola S, Gadducci A, Landoni F, Maggino T. et.al. Follow-up strategies in gynecological oncology: searching appropriateness. Int J Gynecol Cancer, 2007; 17(6): p. 1186-93. https://pubmed.ncbi.nlm.nih.gov/17466042/

661. Beaver. K, Williamson, S, Sutton, C, Hollingworth, W, Gardner, A, Allton, B, et.al. Comparing hospital and telephone follow-up for patients treated for stage-I endometrial cancer (ENDCAT trial): a randomised, multicentre, non-inferiority trial. 2017; 124 (1)(1): p. 150-160. https://pubmed.ncbi.nlm.nih.gov/27062690/

662. Jeppesen. MM, Jensen, PT, Hansen, DG, Christensen, RD, Mogensen, O, Patient-initiated follow up affects fear of recurrence and healthcare use: a randomised trial in early-stage endometrial cancer. 2018; 125 (13)(13): p. 1705-1714. https://pubmed.ncbi.nlm.nih.gov/29978593/

663. Morrison. V, Spencer, LH, Totton, N, Pye, K, Yeo, ST, Butterworth, C, et.al. Trial of Optimal Personalised Care After Treatment-Gynaecological Cancer (TOPCAT-G): A Randomized Feasibility Trial. 2018; 28 (2)(2): p. 401-411. https://pubmed.ncbi.nlm.nih.gov/29324539/

664. Høeg BL, Bidstrup PE, Karlsen RV, Friberg AS, Albieri, V, Dalton, S O. et.al. Follow-up strategies following completion of primary cancer treatment in adult cancer survivors. Cochrane Database Syst Rev, 2019; 2019(11). https://pubmed.ncbi.nlm.nih.gov/31750936/

665. Nicolaije. KA, Ezendam, NP, Vos, MC, Pijnenborg, JM, Boll, D, Boss, EA, et.al. Impact of an Automatically Generated Cancer Survivorship Care Plan on Patient-Reported Outcomes in Routine Clinical Practice: Longitudinal Outcomes of a Pragmatic, Cluster Randomized Trial. 2015; 33 (31)(31): p. 3550-9. https://pubmed.ncbi.nlm.nih.gov/26304900/

666. Kadkhodayan, S., Shahriari, S., Treglia, G., 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:** p. 397-404. https://www.ncbi.nlm.nih.gov/pubmed/23107613

667. Kadkhodayan S, Shahriari S, Treglia G, Yousefi Z, Sadeghi R. 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: p. 397-404. https://www.ncbi.nlm.nih.gov/pubmed/23107613

668. Bollineni VR, Ytre-Hauge S. Bollineni-Balabay O, Salvesen HB, Haldorsen IS, High Diagnostic Value of 18F-FDG PET/CT in Endometrial Cancer: Systematic Review and Meta-Analysis of the Literature. J Nucl Med, 2016; 57(6): p. 879-85. https://pubmed.ncbi.nlm.nih.gov/26823564/

669. Wright JD, Seshan VE, Shah M, Schiff PB, Burke WM, Cohen CJ. et.al. The role of radiation in improving survival for early-stage carcinosarcoma and leiomyosarcoma. Am J Obstet Gynecol, 2008; 199: p. 536 e1-8. https://www.ncbi.nlm.nih.gov/pubmed/18511017

670. Creutzberg CL, van Putten WL, Koper PC. Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC, et.al. Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol, 2003; 89: p. 201-9. https://www.ncbi.nlm.nih.gov/pubmed/12713981

671. Vargo JA, Kim H, Houser CJ, Berhane H, Sukumvanich P, Olawaiye, A B. et.al. Definitive salvage for vaginal recurrence of endometrial cancer: the impact of modern intensity-modulated-radiotherapy with image-based HDR brachytherapy and the interplay of the PORTEC 1 risk stratification. Radiother Oncol, 2014; 113: p. 126-31. https://www.ncbi.nlm.nih.gov/pubmed/25241996

672. Hardarson HA, Heidemann LN, dePont Christensen R, Mogensen O, Jochumsen KM. Vaginal vault recurrences of endometrial cancer in non-irradiated patients - Radiotherapy or surgery. Gynecol Oncol Rep, 2015; 11: p. 26-30. https://www.ncbi.nlm.nih.gov/pubmed/26076091

673. Jereczek-Fossa B, Badzio A, Jassem J. Recurrent endometrial cancer after surgery alone: results of salvage radiotherapy. Int J Radiat Oncol Biol Phys, 2000; 48: p. 405-13. https://www.ncbi.nlm.nih.gov/pubmed/10974454

674. Ng TY, Perrin LC, Nicklin JL, Cheuk R, Crandon AJ. Local recurrence in high-risk node-negative stage I endometrial carcinoma treated with postoperative vaginal vault brachytherapy. Gynecol Oncol, 2000; 79: p. 490-4. https://www.ncbi.nlm.nih.gov/pubmed/11104626

675. Chapman CH, Maghsoudi K, Littell RD, Chen LM, Hsu IC. Salvage high-dose-rate brachytherapy and external beam radiotherapy for isolated vaginal recurrences of endometrial cancer with no prior adjuvant therapy. Brachytherapy, 2017; 16(6): p. 1152-1158. https://pubmed.ncbi.nlm.nih.gov/28802913/

676. Ang C, Bryant A, Barton DP, Pomel C, Naik R. Exenterative surgery for recurrent gynaecological malignancies. Cochrane Database Syst Rev, 2014; 2: p. Cd010449. https://www.ncbi.nlm.nih.gov/pubmed/24497188

677. Andikyan V, Khoury-Collado F, Sonoda Y, Gerst SR, Alektiar KM, Sandhu JS. et.al. Extended pelvic resections for recurrent or persistent uterine and cervical malignancies: an update on out of the box surgery. Gynecol Oncol, 2012; 125: p. 404-8. https://www.ncbi.nlm.nih.gov/pubmed/22285844

678. Chiantera V. Rossi M, De Iaco P, Koehler C, Marnitz S, Gallotta V, et.al. Pelvic exenteration for recurrent endometrial adenocarcinoma: a retrospective multi-institutional study about 21 patients. Int J Gynecol Cancer, 2014; 24: p. 880-4. https://www.ncbi.nlm.nih.gov/pubmed/24685828

679. Chiantera V, Rossi M, De Iaco P, Koehler C, Marnitz S, Fagotti A. et.al. Morbidity after pelvic exenteration for gynecological malignancies: a retrospective multicentric study of 230 patients. Int J Gynecol Cancer, 2013; 24: p. 156-64. https://www.ncbi.nlm.nih.gov/pubmed/24362721

680. Bhambhvani HP, Zhou O, Cattle C, Taiwo R, Diver E, Hayden Gephart M. Brain Metastases from Endometrial Cancer: Clinical Characteristics, Outcomes, and Review of the Literature. World Neurosurg, 2021; 147: p. e32-e39. https://pubmed.ncbi.nlm.nih.gov/33321250/

681. Beucler N, Sellier A. Bernard C, Joubert C, Desse N, Dagain A, Brain metastases in endometrial cancer: A systematic review of the surgical prognostic factors. Eur J Obstet Gynecol Reprod Biol, 2021; 258: p. 240-252.

682. Ethier, JL, Desautels, DN, Amir, E, et al. *Is hormonal therapy effective in advanced endometrial cancer? A systematic review and meta-analysis..* Gynecol Oncol, 2017. **147 (1):** p. 158-166. https://pubmed.ncbi.nlm.nih.gov/28689667/

683. Jerzak, KJ, Duska, L, MacKay, HJ. *Endocrine therapy in endometrial cancer: An old dog with new tricks..* Gynecol Oncol, 2019. **153 (1):** p. 175-183. https://pubmed.ncbi.nlm.nih.gov/30616900/

684. Thigpen, J. T., Brady, M. F., Alvarez, R. D., 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:** p. 1736-44. https://www.ncbi.nlm.nih.gov/pubmed/10561210

685. Kokka, F., Brockbank, E., Oram, D., et al. *Hormonal therapy in advanced or recurrent endometrial cancer.* Cochrane Database Syst Rev, 2010. p. Cd007926. https://www.ncbi.nlm.nih.gov/pubmed/21154390

686. Covens, A. L., Filiaci, V., Gersell, D., et al. *Phase II study of fulvestrant in recurrent/metastatic endometrial carcinoma: a Gynecologic Oncology Group study.* Gynecol Oncol, 2010. **120:** p. 185-8. https://www.ncbi.nlm.nih.gov/pubmed/21075433

687. Kokka F, Brockbank E, Oram D, Gallagher C, Bryant A. Hormonal therapy in advanced or recurrent endometrial cancer. Cochrane Database Syst Rev, 2010; p. Cd007926. https://www.ncbi.nlm.nih.gov/pubmed/21154390

688. Roncolato F, Lindemann K, Willson ML, Martyn J, Mileshkin, L. PI3K/AKT/mTOR inhibitors for advanced or recurrent endometrial cancer. Cochrane Database Syst Rev, 2019; 10(10): p. Cd012160. https://pubmed.ncbi.nlm.nih.gov/31588998/

689. Vale, C. L., Tierney, J., Bull, S. J., et al. *Chemotherapy for advanced, recurrent or metastatic endometrial carcinoma.* Cochrane Database Syst Rev, 2012. **8:** p. CD003915. https://www.ncbi.nlm.nih.gov/pubmed/22895938

690. Vale CL, Tierney J, Bull SJ, Symonds PR. Chemotherapy for advanced, recurrent or metastatic endometrial carcinoma. Cochrane Database Syst Rev, 2012; 8: p. CD003915. https://www.ncbi.nlm.nih.gov/pubmed/22895938

691. Nagao S, Nishio S, Okada S, Otsuki T, Fujiwara K, Tanabe H. et.al. What is an appropriate second-line regimen for recurrent endometrial cancer? Ancillary analysis of the SGSG012/GOTIC004/Intergroup study. Cancer Chemother Pharmacol, 2015; 76: p. 335-42. https://www.ncbi.nlm.nih.gov/pubmed/26092322

692. Makker, V, Colombo, N, Casado Herráez, A, et al. *Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer..* N Engl J Med, 2022. **386 (5):** p. 437-448. https://pubmed.ncbi.nlm.nih.gov/35045221/

693. Makker, V, Taylor, MH, Aghajanian, C, et al. *Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer..* J Clin Oncol, 2020. **38 (26):** p. 2981-2992. https://pubmed.ncbi.nlm.nih.gov/32167863/

694. Le, DT, Durham, JN, Smith, KN, et al. *Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade..* Science, 2017. **357 (6349):** p. 409-413. https://pubmed.ncbi.nlm.nih.gov/28596308/

695. Marabelle, A, Le, DT, Ascierto, PA, et al. *Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study..* J Clin Oncol, 2020. **38 (1):** p. 1-10. https://pubmed.ncbi.nlm.nih.gov/31682550/

696. Oaknin, A, Tinker, AV, Gilbert, L, et al. *Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial..* JAMA Oncol, 2020. **6 (11):** p. 1766-1772. https://pubmed.ncbi.nlm.nih.gov/33001143/

697. Konstantinopoulos. PA, Luo, W, Liu, JF, Gulhan, DC, Krasner, C, Ishizuka, JJ, et.al. Phase II Study of Avelumab in Patients With Mismatch Repair Deficient and Mismatch Repair Proficient Recurrent/Persistent Endometrial Cancer. 2019; 37 (30)(30): p. 2786-2794. https://pubmed.ncbi.nlm.nih.gov/31461377/

698. Lee, Y. K., Chung, H. H., Kim, J. W., et al. *Vaginal pH-balanced gel for the control of atrophic vaginitis among breast cancer survivors: a randomized controlled trial.* Obstet Gynecol, 2011. **117:** p. 922-7. https://www.ncbi.nlm.nih.gov/pubmed/21422866

699. Morris L, Do V, Chard J, Brand AH. Radiation-induced vaginal stenosis: current perspectives. Int J Womens Health, 2017; 9: p. 273-279. https://pubmed.ncbi.nlm.nih.gov/28496367/

700. Lester J, Pahouja G, Andersen B, Lustberg M. Atrophic vaginitis in breast cancer survivors: a difficult survivorship issue. J Pers Med, 2015; 5: p. 50-66. https://www.ncbi.nlm.nih.gov/pubmed/25815692

701. G. u, i, d, o, z, et.al. Estrogen therapy in gynecological cancer survivors. Climacteric, 2013; 16: p. 611-7. https://www.ncbi.nlm.nih.gov/pubmed/23952524

702. Shim SH, Lee SJ, Kim SN. Effects of hormone replacement therapy on the rate of recurrence in endometrial cancer survivors: a meta-analysis. Eur J Cancer, 2014; 50(9): p. 1628-37. https://pubmed.ncbi.nlm.nih.gov/24685478/

703. Simon J, Nachtigall L, Ulrich L G, Eugster-Hausmann M, Gut R. Endometrial safety of ultra-low-dose estradiol vaginal tablets. Obstet Gynecol, 2010; 116(4): p. 876-883. https://pubmed.ncbi.nlm.nih.gov/20859151/

704. Lester J, Pahouja G, Andersen B, Lustberg M. Atrophic vaginitis in breast cancer survivors: a difficult survivorship issue. J Pers Med, 2015; 5: p. 50-66. https://www.ncbi.nlm.nih.gov/pubmed/25815692

705. Lee YK, Chung HH, Kim JW, Park NH, Song YS, Kang, S B. Vaginal pH-balanced gel for the control of atrophic vaginitis among breast cancer survivors: a randomized controlled trial. Obstet Gynecol, 2011; 117: p. 922-7. https://www.ncbi.nlm.nih.gov/pubmed/21422866

706. Pitkin RM, VanVoorhis LW. Postirradiation vaginitis. An evaluation of prophylaxis with topical estrogen. Radiology, 1971; 99: p. 417-21. https://www.ncbi.nlm.nih.gov/pubmed/5553582

707. Denton AS, Maher EJ. Interventions for the physical aspects of sexual dysfunction in women following pelvic radiotherapy. Cochrane Database Syst Rev, 2003; p. CD003750. https://www.ncbi.nlm.nih.gov/pubmed/12535485

708. Hintz BL, Kagan AR, Gilbert HA, Rao AR, Chan P, Nussbaum H. Systemic absorption of conjugated estrogenic cream by the irradiated vagina. Gynecol Oncol, 1981; 12: p. 75-82. https://www.ncbi.nlm.nih.gov/pubmed/6268486

709. Bartl W, Breitenecker G. Kemeter P, Tatra G, [The absorption of conjugated oestrogens from the irradiated and non-irradiated vagina (author's transl)]. Geburtshilfe Frauenheilkd, 1980; 40(4): p. 319-25. https://pubmed.ncbi.nlm.nih.gov/6247239/

710. G. u, i, d, o, z, et.al. Estrogen therapy in gynecological cancer survivors. Climacteric, 2013; 16: p. 611-7. https://www.ncbi.nlm.nih.gov/pubmed/23952524

711. Singh P, Oehler MK. Hormone replacement after gynaecological cancer. Maturitas, 2009; 65: p. 190-7. https://www.ncbi.nlm.nih.gov/pubmed/20018467

712. Edey KA, Rundle S, Hickey M. Hormone replacement therapy for women previously treated for endometrial cancer. Cochrane Database Syst Rev, 2018; 5(5): p. Cd008830. https://pubmed.ncbi.nlm.nih.gov/29763969/

713. Nout RA, Putter H, Jurgenliemk-Schulz IM. Jobsen JJ, Lutgens LC, van der Steen-Banasik EM, et.al. Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data. Eur J Cancer, 2011; 48: p. 1638-48. https://www.ncbi.nlm.nih.gov/pubmed/22176868

714. Miles T, Johnson N. Vaginal dilator therapy for women receiving pelvic radiotherapy. Cochrane Database Syst Rev, 2014; 9: p. CD007291. https://www.ncbi.nlm.nih.gov/pubmed/20824858

715. N. a, t, i, o, n, et.al. NCCN Guideline - Uterine Neoplasms, 2020. https://www.nccn.org/guidelines/nccn-guidelines/guidelines-detail?category=1&id=1473

716. Akbaba S, Oelmann-Avendano JT, Krug D, Arians N, Bostel, T, Hoerner-Rieber J. et.al. The impact of vaginal dilator use on vaginal stenosis and sexual quality of life in women treated with adjuvant radiotherapy for endometrial cancer. Strahlenther Onkol, 2019; 195(10): p. 902-912. https://pubmed.ncbi.nlm.nih.gov/30997541/

717. Stahl JM, Qian JM, Tien CJ, Carlson DJ, Chen Z, Ratner ES. et.al. Extended duration of dilator use beyond 1<PLACEHOLDER_0/>year may reduce vaginal stenosis after intravaginal high-dose-rate brachytherapy. Support Care Cancer, 2019; 27(4): p. 1425-1433. https://pubmed.ncbi.nlm.nih.gov/30187220/

718. Cerentini TM, Schlöttgen J, Viana da Rosa P. La Rosa VL, Vitale SG, Giampaolino P, et.al. Clinical and Psychological Outcomes of the Use of Vaginal Dilators After Gynaecological Brachytherapy: a Randomized Clinical Trial. Adv Ther, 2019; 36(8): p. 1936-1949. https://pubmed.ncbi.nlm.nih.gov/31209699/

719. Hanlon A, Small W, Jr. Strauss J, Lin LL, Hanisch, L. Huang, L, et.al. Dilator Use After Vaginal Brachytherapy for Endometrial Cancer: A Randomized Feasibility and Adherence Study. Cancer Nurs, 2018; 41(3): p. 200-209. https://pubmed.ncbi.nlm.nih.gov/28437283/

720. Perrone AM, Tesei, M, Ferioli, M, De Terlizzi F, Della Gatta AN, Boussedra S. et.al. Results of a Phase I-II Study on Laser Therapy for Vaginal Side Effects after Radiotherapy for Cancer of Uterine Cervix or Endometrium. Cancers (Basel), 2020; 12(6). https://pubmed.ncbi.nlm.nih.gov/32575821/

721. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft. Deutsche Krebshilfe, AWMF), Erweiterte S3-Leitlinie Palliativmedizin für Patienten mit einer nicht-heilbaren Krebserkrankung, Langversion 2.2, 2020, AWMF-Registernummer: 128/001OL, 2020. http://leitlinienprogramm-onkologie.de/Palliativmedizin.80.0.html

722. ten Broeke, S. W., Brohet, R. M., Tops, C. M., et al. *Lynch syndrome caused by germline PMS2 mutations: delineating the cancer risk.* J Clin Oncol, 2014. **33:** p. 319-25. https://www.ncbi.nlm.nih.gov/pubmed/25512458

723. Buchanan, D. D., Tan, Y. Y., Walsh, M. 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, 2013. **32:** p. 90-100. https://www.ncbi.nlm.nih.gov/pubmed/24323032

724. Carcangiu, M. L., Radice, P., Casalini, P., 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, 2009. **18:** p. 21-6. https://www.ncbi.nlm.nih.gov/pubmed/19443869

725. Dowty, J. G., Win, A. K., Buchanan, D. D., et al. *Cancer risks for MLH1 and MSH2 mutation carriers.* Hum Mutat, 2012. **34:** p. 490-7. https://www.ncbi.nlm.nih.gov/pubmed/23255516

726. Egoavil, C., Alenda, C., Castillejo, A., et al. *Prevalence of Lynch syndrome among patients with newly diagnosed endometrial cancers.* PLoS One, 2013. **8:** p. e79737. https://www.ncbi.nlm.nih.gov/pubmed/24244552

727. Hampel, H., Frankel, W., Panescu, J., et al. *Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients.* Cancer Res, 2006. **66:** p. 7810-7. https://www.ncbi.nlm.nih.gov/pubmed/16885385

728. Leenen, C. H., van Lier, M. G., van Doorn, H. C., et al. *Prospective evaluation of molecular screening for Lynch syndrome in patients with endometrial cancer </= 70 years.* Gynecol Oncol, 2012. **125:** p. 414-20. https://www.ncbi.nlm.nih.gov/pubmed/22306203

729. Lu, K. H., Schorge, J. O., Rodabaugh, K. J., et al. *Prospective determination of prevalence of lynch syndrome in young women with endometrial cancer.* J Clin Oncol, 2007. **25:** p. 5158-64. https://www.ncbi.nlm.nih.gov/pubmed/17925543

730. Westin, S. N., Lacour, R. A., Urbauer, D. L., et al. *Carcinoma of the lower uterine segment: a newly described association with Lynch syndrome.* J Clin Oncol, 2008. **26:** p. 5965-71. https://www.ncbi.nlm.nih.gov/pubmed/19001318

731. Win, A. K., Lindor, N. M., Winship, I., et al. *Risks of colorectal and other cancers after endometrial cancer for women with Lynch syndrome.* J Natl Cancer Inst, 2013. **105:** p. 274-9. https://www.ncbi.nlm.nih.gov/pubmed/23385444

732. ten Broeke SW, Brohet RM, Tops CM, van der Klift HM, Velthuizen, M E, Bernstein I. et.al. Lynch syndrome caused by germline PMS2 mutations: delineating the cancer risk. J Clin Oncol, 2014; 33: p. 319-25. https://www.ncbi.nlm.nih.gov/pubmed/25512458

733. Dowty JG, Win AK, Buchanan DD, Lindor NM, Macrae FA, Clendenning, M. et.al. Cancer risks for MLH1 and MSH2 mutation carriers. Hum Mutat, 2012; 34: p. 490-7. https://www.ncbi.nlm.nih.gov/pubmed/23255516

734. Westin SN, Lacour RA, Urbauer DL, Luthra R, Bodurka DC, Lu KH. et.al. Carcinoma of the lower uterine segment: a newly described association with Lynch syndrome. J Clin Oncol, 2008; 26: p. 5965-71. https://www.ncbi.nlm.nih.gov/pubmed/19001318

735. Hampel. H, de la Chapelle, A, The search for unaffected individuals with Lynch syndrome: do the ends justify the means?, 2011; 4 (1)(1): p. 1-5. https://pubmed.ncbi.nlm.nih.gov/21205737/

736. Win. AK, Jenkins, MA, Dowty, JG, Antoniou, AC, Lee, A, Giles, GG, et.al. Prevalence and Penetrance of Major Genes and Polygenes for Colorectal Cancer. 2017; 26 (3)(3): p. 404-412. https://pubmed.ncbi.nlm.nih.gov/27799157/

737. Nelen MR, Kremer H, Konings IB, Schoute F, van Essen AJ, Koch, R. et.al. Novel PTEN mutations in patients with Cowden disease: absence of clear genotype-phenotype correlations. Eur J Hum Genet, 1999; 7: p. 267-73. https://www.ncbi.nlm.nih.gov/pubmed/10234502

738. Ryan. NAJ, Glaire, MA, Blake, D, Cabrera-Dandy, M, Evans, DG, Crosbie, EJ, The proportion of endometrial cancers associated with Lynch syndrome: a systematic review of the literature and meta-analysis. 2019; 21 (10)(10): p. 2167-2180. https://pubmed.ncbi.nlm.nih.gov/31086306/

739. Snowsill. TM, Ryan, NAJ, Crosbie, EJ, Frayling, IM, Evans, DG, Hyde, CJ, Cost-effectiveness analysis of reflex testing for Lynch syndrome in women with endometrial cancer in the UK setting. 2019; 14 (8)(8): p. e0221419. https://pubmed.ncbi.nlm.nih.gov/31469860/

740. Dominguez-Valentin. M, Sampson, JR, Seppälä, TT, Ten Broeke, SW, Plazzer, JP, Nakken, S, et.al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. 2020; 22 (1)(1): p. 15-25. https://pubmed.ncbi.nlm.nih.gov/31337882/

741. Riegert-Johnson DL, Gleeson FC, Roberts M. Tholen K, Youngborg, L, Bullock M, et.al. Cancer and Lhermitte-Duclos disease are common in Cowden syndrome patients. Hered Cancer Clin Pract, 2010; 8: p. 6. https://www.ncbi.nlm.nih.gov/pubmed/20565722

742. Tan MH, Mester JL, Ngeow J, Rybicki, L A, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res, 2012; 18: p. 400-7. https://www.ncbi.nlm.nih.gov/pubmed/22252256

743. Hampel H, Frankel W, Panescu J, Lockman J, Sotamaa K, Fix D. et.al. Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. Cancer Res, 2006; 66: p. 7810-7. https://www.ncbi.nlm.nih.gov/pubmed/16885385

744. Leenen CH, van Lier MG, van Doorn, H C, van Leerdam ME, Kooi SG, de Waard J. et.al. Prospective evaluation of molecular screening for Lynch syndrome in patients with endometrial cancer = 70 years. Gynecol Oncol, 2012; 125: p. 414-20. https://www.ncbi.nlm.nih.gov/pubmed/22306203

745. Bubien V, Bonnet F, Brouste V, Hoppe S, Barouk-Simonet E, David A. et.al. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. J Med Genet, 2013; 50: p. 255-63. https://www.ncbi.nlm.nih.gov/pubmed/23335809

746. Clarke BA, Cooper K. Identifying Lynch syndrome in patients with endometrial carcinoma: shortcomings of morphologic and clinical schemas. Adv Anat Pathol, 2012; 19: p. 231-8. https://www.ncbi.nlm.nih.gov/pubmed/22692286

747. Lamberti C, Mangold E, Pagenstecher C, Jungck M. Schwering D, Bollmann M, et.al. Frequency of hereditary non-polyposis colorectal cancer among unselected patients with colorectal cancer in Germany. Digestion, 2006; 74: p. 58-67. https://www.ncbi.nlm.nih.gov/pubmed/17095871

748. Chen S. Wang W, Lee S, Nafa K, Lee J, Romans K, et.al. Prediction of germline mutations and cancer risk in the Lynch syndrome. JAMA, 2006; 296: p. 1479-87. https://www.ncbi.nlm.nih.gov/pubmed/17003396

749. Hampel, Heather, Panescu, Jenny, Lockman, Janet, Sotamaa, Kaisa, Fix, Daniel, Comeras, Ilene, et.al. Comment on: Screening for Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer) among Endometrial Cancer Patients. Cancer Research, 2007; 67: p. 9603-9603. http://cancerres.aacrjournals.org/content/66/15/7810.short

750. Buchanan DD, Tan YY, Walsh MD, Clendenning M, Metcalf AM, Ferguson K. 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, 2013; 32: p. 90-100. https://www.ncbi.nlm.nih.gov/pubmed/24323032

751. Egoavil C, Alenda C, Castillejo A, Paya A, Peiro G, Sanchez-Heras A B. et.al. Prevalence of Lynch syndrome among patients with newly diagnosed endometrial cancers. PLoS One, 2013; 8: p. e79737. https://www.ncbi.nlm.nih.gov/pubmed/24244552

752. Lu KH, Schorge JO, Rodabaugh KJ, Daniels MS, Sun CC, Soliman PT. et.al. Prospective determination of prevalence of lynch syndrome in young women with endometrial cancer. J Clin Oncol, 2007; 25: p. 5158-64. https://www.ncbi.nlm.nih.gov/pubmed/17925543

753. Lynch HT, Harris RE, Lynch PM, Guirgis HA. Lynch JF, Bardawil WA, Role of heredity in multiple primary cancer. Cancer, 1977; 40: p. 1849-54. https://www.ncbi.nlm.nih.gov/pubmed/907988

754. Barrow E, Hill J, Evans DG. Cancer risk in Lynch Syndrome. Fam Cancer, 2013; 12: p. 229-40. https://www.ncbi.nlm.nih.gov/pubmed/23604856

755. Mecklin JP, Jarvinen HJ. Clinical features of colorectal carcinoma in cancer family syndrome. Dis Colon Rectum, 1986; 29: p. 160-4. https://www.ncbi.nlm.nih.gov/pubmed/3943429

756. Win AK, Lindor NM, Winship I, Tucker, K M, Buchanan DD, Young JP. et.al. Risks of colorectal and other cancers after endometrial cancer for women with Lynch syndrome. J Natl Cancer Inst, 2013; 105: p. 274-9. https://www.ncbi.nlm.nih.gov/pubmed/23385444

757. Lu KH, Dinh M, Kohlmann W, Watson P, Green J, Syngal S. et.al. Gynecologic cancer as a "sentinel cancer" for women with hereditary nonpolyposis colorectal cancer syndrome. Obstet Gynecol, 2005; 105: p. 569-74. https://www.ncbi.nlm.nih.gov/pubmed/15738026

758. Ferguson SE, Aronson M, Pollett A, Eiriksson LR, Oza A M, Gallinger S. 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: p. 3932-9. https://www.ncbi.nlm.nih.gov/pubmed/25081409

759. N. c, c, n, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2016, 2016; 2. https://www.genomeweb.com/sites/default/files/nccn_2017.pdf

760. N. c, c, n, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Genetic/Familial High-Risk Assessment: Colorectal, Version 1.2016, 2016;

761. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. 1998. https://www.ncbi.nlm.nih.gov/pubmed/9809732

762. Tabor A, Watt HC, Wald NJ. Endometrial thickness as a test for endometrial cancer in women with postmenopausal vaginal bleeding. Obstet Gynecol, 2002; 99: p. 663-70. https://www.ncbi.nlm.nih.gov/pubmed/12039131

763. Carcangiu ML, Radice P. Casalini P, Bertario, L, Merola M, Sala P, Lynch syndrome--related endometrial carcinomas show a high frequency of nonendometrioid types and of high FIGO grade endometrioid types. Int J Surg Pathol, 2009; 18: p. 21-6. https://www.ncbi.nlm.nih.gov/pubmed/19443869

764. Pagon RA, Adam MP, Ardinger HH. Wallace SE, Amemiya, A, Bean LJH, et.al. GeneReviewsUniversity of Washington, Seattle, 1993;

765. Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Ruschoff J. et.al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst, 2004; 96: p. 261-8. https://www.ncbi.nlm.nih.gov/pubmed/14970275

766. Vasen HF, Mecklin JP, Khan, P M, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). Dis Colon Rectum, 1991; 34: p. 424-5. https://www.ncbi.nlm.nih.gov/pubmed/2022152

767. Steinke V, Holzapfel S, Loeffler M, Holinski-Feder E, Morak M, Schackert HK. et.al. Evaluating the performance of clinical criteria for predicting mismatch repair gene mutations in Lynch syndrome: a comprehensive analysis of 3,671 families. Int J Cancer, 2014; 135: p. 69-77. https://www.ncbi.nlm.nih.gov/pubmed/24493211

768. Barrow P, Khan M, Lalloo F, Evans DG, Hill J. Systematic review of the impact of registration and screening on colorectal cancer incidence and mortality in familial adenomatous polyposis and Lynch syndrome. Br J Surg, 2013; 100: p. 1719-31. https://www.ncbi.nlm.nih.gov/pubmed/24227356

769. Barrow P, Green K, Clancy T, Lalloo F, Hill J, Evans DG. Improving the uptake of predictive testing and colorectal screening in Lynch syndrome: a regional primary care survey. Clin Genet, 2015; 87: p. 517-24. https://www.ncbi.nlm.nih.gov/pubmed/25652327

770. Backes FJ, Mitchell E. Hampel H, Cohn DE, Endometrial cancer patients and compliance with genetic counseling: room for improvement. Gynecol Oncol, 2011; 123: p. 532-6. https://www.ncbi.nlm.nih.gov/pubmed/21968342

771. Aktan-Collan K, Kaariainen H, Jarvinen H, Peltomaki P. Pylvanainen K, Mecklin JP, et.al. Psychosocial consequences of predictive genetic testing for Lynch syndrome and associations to surveillance behaviour in a 7-year follow-up study. Fam Cancer, 2013; 12: p. 639-46. https://www.ncbi.nlm.nih.gov/pubmed/23512527

772. Eliezer D, Hadley D W, Koehly LM. Exploring psychological responses to genetic testing for Lynch Syndrome within the family context. Psychooncology, 2014; 23: p. 1292-9. https://www.ncbi.nlm.nih.gov/pubmed/24872228

773. Esplen MJ, Wong, J, Aronson M, Butler K. Rothenmund H, Semotiuk K, et.al. Long-term psychosocial and behavioral adjustment in individuals receiving genetic test results in Lynch syndrome. Clin Genet, 2014; 87: p. 525-32. https://www.ncbi.nlm.nih.gov/pubmed/25297893

774. Galiatsatos P, Rothenmund H, Aubin S, Foulkes WD. Psychosocial Impact of Lynch Syndrome on Affected Individuals and Families. Dig Dis Sci, 2015; 60: p. 2246-50. https://www.ncbi.nlm.nih.gov/pubmed/25786861

775. Hirschberg AM, Chan-Smutko G, Pirl WF. Psychiatric implications of cancer genetic testing. Cancer, 2014; 121: p. 341-60. https://www.ncbi.nlm.nih.gov/pubmed/25234846

776. H. o, l, t, h, a, et.al. Psychische Aspekte im Zusammenhang mit tumorgenetischer Beratung. PSYCH up2date, 2014; 8: p. 225-240. https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0034-1370167

777. K. e, l, l, e, r, et.al. Erbliche Tumorerkrankungen - psychosoziale und familiäre Aspekte. Psychotherapie im Dialog, 2010; p. 151-154.

778. Landsbergen KM, Prins JB, Brunner HG, Kraaimaat FW, Hoogerbrugge N. Genetic testing for Lynch syndrome in the first year of colorectal cancer: a review of the psychological impact. Fam Cancer, 2009; 8: p. 325-37. https://www.ncbi.nlm.nih.gov/pubmed/19330464

779. Landsbergen KM, Prins JB, Brunner HG, van Duijvendijk P, Nagengast FM, van Krieken JH. et.al. Psychological distress in newly diagnosed colorectal cancer patients following microsatellite instability testing for Lynch syndrome on the pathologist's initiative. Fam Cancer, 2012; 11: p. 259-67. https://www.ncbi.nlm.nih.gov/pubmed/22311584

780. Gesetz über genetische Untersuchungen bei Menschen (Gendiagnostikgesetz - GenDG), 2010. http://www.gesetze-im-internet.de/gendg/

781. R, o, b, e, r, t, et.al. Richtlinien der Gendiagnostik-Kommission (GEKO) zur genetischen Untersuchung bei nicht-einwilligungsfähigen Personen nach § 14 in Verbindung mit § 23 Abs. 2 Nr. 1c GenDGBundesgesundheitsbl, 2011; 54: p. 1248–1256. https://www.rki.de/DE/Content/Kommissionen/GendiagnostikKommission/Richtlinien/Richtlinien_node.html

782. Duncan RE, Gillam L, Savulescu J, Williamson R, Rogers J G, Delatycki MB. The challenge of developmentally appropriate care: predictive genetic testing in young people for familial adenomatous polyposis. Fam Cancer, 2009; 9: p. 27-35. https://www.ncbi.nlm.nih.gov/pubmed/19760114

783. Snowsill, T., Huxley, N., Hoyle, M., et al. *A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome.* Health Technol Assess, 2014. **18:** p. 1-406. https://www.ncbi.nlm.nih.gov/pubmed/25244061

784. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt, R W. et.al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res, 1998; 58: p. 5248-57. https://www.ncbi.nlm.nih.gov/pubmed/9823339

785. Hegde M, Ferber M, Mao R, Samowitz W, Ganguly A. ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis). Genet Med, 2013; 16: p. 101-16. https://www.ncbi.nlm.nih.gov/pubmed/24310308

786. Backes FJ, Leon ME, Ivanov I, Suarez A, Frankel WL, Hampel H. et.al. Prospective evaluation of DNA mismatch repair protein expression in primary endometrial cancer. Gynecol Oncol, 2009; 114: p. 486-90. https://www.ncbi.nlm.nih.gov/pubmed/19515405

787. Moline J, Mahdi H, Yang B. Biscotti C, Roma AA, Heald B, et.al. Implementation of tumor testing for lynch syndrome in endometrial cancers at a large academic medical center. Gynecol Oncol, 2013; 130: p. 121-6. https://www.ncbi.nlm.nih.gov/pubmed/23612316

788. Gausachs M, Mur P, Corral J, Pineda M, Gonzalez S, Benito L. et.al. MLH1 promoter hypermethylation in the analytical algorithm of Lynch syndrome: a cost-effectiveness study. Eur J Hum Genet, 2012; 20: p. 762-8. https://www.ncbi.nlm.nih.gov/pubmed/22274583

789. Deng G, Bell I, Crawley S, Gum J, Terdiman J P, Allen BA. et.al. BRAF mutation is frequently present in sporadic colorectal cancer with methylated hMLH1, but not in hereditary nonpolyposis colorectal cancer. Clin Cancer Res, 2004; 10: p. 191-5. https://www.ncbi.nlm.nih.gov/pubmed/14734469

790. Kawaguchi M. Yanokura M, Banno K, Kobayashi Y, Kuwabara Y, Kobayashi M, et.al. Analysis of a correlation between the BRAF V600E mutation and abnormal DNA mismatch repair in patients with sporadic endometrial cancer. Int J Oncol, 2009; 34: p. 1541-7. https://www.ncbi.nlm.nih.gov/pubmed/19424571

791. Bellido. F, Pineda, M, Aiza, G, Valdés-Mas, R, Navarro, M, Puente, DA, et.al. POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance. 2016; 18 (4)(4): p. 325-32. https://pubmed.ncbi.nlm.nih.gov/26133394/

792. Snowsill T, Huxley N, Hoyle M, Jones-Hughes T, Coelho H, Cooper C. et.al. A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. Health Technol Assess, 2014; 18: p. 1-406. https://www.ncbi.nlm.nih.gov/pubmed/25244061

793. Richtlinien zur prädiktiven genetischen Diagnostik, 2003;

794. Zertifizierte medizinische Fortbildung: Indikationen zur molekulargenetischen Diagnostik bei erblichen Krankheiten, 2006. https://www.aerzteblatt.de/archiv/50438/Zertifizierte-medizinische-Fortbildung-Indikationen-zur-molekulargenetischen-Diagnostik-bei-erblichen-Krankheiten

795. Plon. SE, Eccles, DM, Easton, D, Foulkes, WD, Genuardi, M, Greenblatt, MS, et.al. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. 2008; 29 (11)(11): p. 1282-91. https://pubmed.ncbi.nlm.nih.gov/18951446/

796. Burn. J, Sheth, H, Elliott, F, Reed, L, Macrae, F, Mecklin, JP, et.al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. 2020; 395 (10240)(10240): p. 1855-1863. https://pubmed.ncbi.nlm.nih.gov/32534647/

797. Auranen, A., Joutsiniemi, T.. *A systematic review of gynecological cancer surveillance in women belonging to hereditary nonpolyposis colorectal cancer (Lynch syndrome) families.* Acta Obstet Gynecol Scand, 2011. **90:** p. 437-44. https://www.ncbi.nlm.nih.gov/pubmed/21306348

798. Lecuru, F., Le Frere Belda, M. A., Bats, A. S., 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:** p. 1326-31. https://www.ncbi.nlm.nih.gov/pubmed/18217965

799. Lu KH, Daniels M. Endometrial and ovarian cancer in women with Lynch syndrome: update in screening and prevention. Fam Cancer, 2013; 12: p. 273-7. https://www.ncbi.nlm.nih.gov/pubmed/23765559

800. Auranen A, Joutsiniemi T. A systematic review of gynecological cancer surveillance in women belonging to hereditary nonpolyposis colorectal cancer (Lynch syndrome) families. Acta Obstet Gynecol Scand, 2011; 90: p. 437-44. https://www.ncbi.nlm.nih.gov/pubmed/21306348

801. Dove-Edwin I, Boks D, Goff S, Kenter GG, Carpenter R, Vasen HF. et.al. The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. Cancer, 2002; 94: p. 1708-12. https://www.ncbi.nlm.nih.gov/pubmed/11920532

802. Rijcken FE, Mourits MJ, Kleibeuker, J H, Hollema, H, van der Zee AG. Gynecologic screening in hereditary nonpolyposis colorectal cancer. Gynecol Oncol, 2003; 91: p. 74-80. https://www.ncbi.nlm.nih.gov/pubmed/14529665

803. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome, 2006. https://www.ncbi.nlm.nih.gov/pubmed/17096354

804. Lecuru F, Le Frere Belda MA, Bats, A S. Tulpin L, Metzger U, Olschwang, S, 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: p. 1326-31. https://www.ncbi.nlm.nih.gov/pubmed/18217965

805. Manchanda R, Saridogan E. Abdelraheim A, Johnson M, Rosenthal A N, Benjamin E, et.al. Annual outpatient hysteroscopy and endometrial sampling (OHES) in HNPCC/Lynch syndrome (LS). Arch Gynecol Obstet, 2012; 286: p. 1555-62. https://www.ncbi.nlm.nih.gov/pubmed/22865035

806. Helder-Woolderink JM, De Bock GH, Sijmons RH, Hollema, H, Mourits, M J. The additional value of endometrial sampling in the early detection of endometrial cancer in women with Lynch syndrome. Gynecol Oncol, 2013; 131: p. 304-8. https://www.ncbi.nlm.nih.gov/pubmed/23769810

807. Möller. P, Seppälä, T, Bernstein, I, Holinski-Feder, E, Sala, P, Evans, DG, et.al. Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. 2017; 66 (3)(3): p. 464-472. https://pubmed.ncbi.nlm.nih.gov/26657901/

808. Schmeler KM, Lynch HT, Chen LM, Munsell, M F, Soliman PT, Clark, M B. et.al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med, 2006; 354: p. 261-9. https://www.ncbi.nlm.nih.gov/pubmed/16421367

809. Helder-Woolderink. JM, Blok, EA, Vasen, HF, Hollema, H, Mourits, MJ, De Bock, GH, Ovarian cancer in Lynch syndrome; a systematic review. 2016; 55: p. 65-73. https://pubmed.ncbi.nlm.nih.gov/26773421/

810. Seppälä. T, Pylvänäinen, K, Evans, DG, Järvinen, H, Renkonen-Sinisalo, L, Bernstein, I, et.al. Colorectal cancer incidence in path_MLH1 carriers subjected to different follow-up protocols: a Prospective Lynch Syndrome Database report, 2017; 15: p. 18. https://pubmed.ncbi.nlm.nih.gov/29046738/

811. L. e, i, t, l, i, et.al. S3-Leitlinie Psychoonkologische Diagnostik, Beratung und Behandlung von erwachsenen Krebspatienten, Version 1.1, Januar 2014, AWMF-Registernummer: 032/051OL, 2014. https://www.leitlinienprogramm-onkologie.de/leitlinien/psychoonkologie/

812. Reuter K, Raugust S, Marschner N, Harter M. Differences in prevalence rates of psychological distress and mental disorders in inpatients and outpatients with breast and gynaecological cancer. Eur J Cancer Care (Engl), 2007; 16: p. 222-30. https://www.ncbi.nlm.nih.gov/pubmed/17508941

813. Steele R, Fitch MI. Supportive care needs of women with gynecologic cancer. Cancer Nurs, 2008; 31: p. 284-91. https://www.ncbi.nlm.nih.gov/pubmed/18600115

814. Mehnert A, Brahler E, Faller H. Harter M, Keller M, Schulz H, et.al. Four-week prevalence of mental disorders in patients with cancer across major tumor entities. J Clin Oncol, 2014; 32: p. 3540-6. https://www.ncbi.nlm.nih.gov/pubmed/25287821

815. Roth AJ; Carter, J; Nelson CJ, Sexuality After Cancer, in Psycho-Oncology, Jimmie CHolland, William SBreitbart, Paul BJacobsen, Matthew J Loscalzo, Ruth McCorkle, and Phyllis NButow , Editor, 2010; Oxford University Press: New York. p. 245-250.

816. Brown LF, Kroenke K. Cancer-related fatigue and its associations with depression and anxiety: a systematic review. Psychosomatics, 2009; 50: p. 440-7. https://www.ncbi.nlm.nih.gov/pubmed/19855028

817. Hodgkinson. K, Butow, P, Fuchs, A, Hunt, GE, Stenlake, A, Hobbs, KM, et.al. Long-term survival from gynecologic cancer: psychosocial outcomes, supportive care needs and positive outcomes. 2007; 104 (2)(2): p. 381-9. https://pubmed.ncbi.nlm.nih.gov/17027072/

818. Mehnert A, Lehmann C, Cao P, Koch U. Die Erfassung psychosozialer Belastungen und Ressourcen in der Onkologie - Ein Literaturüberblick zu Screeningmethoden und Entwicklungstrends [Assessment of psychosocial distress and resources in oncology - a literature review about screening measures and current developments]. Psychother Psychosom Med Psychol, 2006; 56: p. 462-79.

819. Singer S, Schwarz R. [Psychosocial aftercare of patients with endometrial or cervical cancer]. Zentralbl Gynakol, 2002; 124: p. 64-70. https://www.ncbi.nlm.nih.gov/pubmed/11873318

820. Sporn. NJ, Smith, KB, Pirl, WF, Lennes, IT, Hyland, KA, Park, ER, Sexual health communication between cancer survivors and providers: how frequently does it occur and which providers are preferred?, 2015; 24 (9)(9): p. 1167-73. https://pubmed.ncbi.nlm.nih.gov/25534170/

821. Donovan KA, Boyington, A R, Judson PL, Wyman JF. Bladder and bowel symptoms in cervical and endometrial cancer survivors. Psychooncology, 2014; 23: p. 672-8. https://www.ncbi.nlm.nih.gov/pubmed/24481859

822. Jeppesen MM, Mogensen O, Dehn P, Jensen P T. Needs and priorities of women with endometrial and cervical cancer. J Psychosom Obstet Gynaecol, 2015; 36: p. 122-32. https://www.ncbi.nlm.nih.gov/pubmed/26123123

823. Karabuga H, Gultekin M, Tulunay G, Yuce K, Ayhan A, Yuce D. et.al. Assessing the Quality of Life in Patients With Endometrial Cancer Treated With Adjuvant Radiotherapy. Int J Gynecol Cancer, 2015; 25: p. 1526-33. https://www.ncbi.nlm.nih.gov/pubmed/26207785

824. Lee WL. Lee FK, Su WH, Tsui, K H, Kuo CD, Hsieh SL, et.al. Hormone therapy for younger patients with endometrial cancer. Taiwan J Obstet Gynecol, 2013; 51: p. 495-505. https://www.ncbi.nlm.nih.gov/pubmed/23276551

825. Honerlaw KR, Rumble ME, Rose SL, Coe CL, Costanzo, E S. Biopsychosocial predictors of pain among women recovering from surgery for endometrial cancer. Gynecol Oncol, 2015; 140: p. 301-6. https://www.ncbi.nlm.nih.gov/pubmed/26363211

826. Erekson EA, Sung VW, DiSilvestro PA, Myers DL. Urinary symptoms and impact on quality of life in women after treatment for endometrial cancer. Int Urogynecol J Pelvic Floor Dysfunct, 2008; 20: p. 159-63. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2887706/

827. Wiggins DL, Wood R, Granai CO, Dizon DS. Sex, intimacy, and the gynecologic oncologists: survey results of the New England Association of Gynecologic Oncologists (NEAGO). J Psychosoc Oncol, 2007; 25: p. 61-70. https://www.ncbi.nlm.nih.gov/pubmed/18032265

828. Klee M, Thranov I, Machin Prof D. The patients' perspective on physical symptoms after radiotherapy for cervical cancer. Gynecol Oncol, 2000; 76: p. 14-23. https://www.ncbi.nlm.nih.gov/pubmed/10620435

829. Deutsches Institut für Medizinische Dokumentation und Information (DIMDI), ICD-10-GM 2018 Systematisches Verzeichnis : Internationale statistische Klassifikation der Krankheiten und verwandter GesundheitsproblemeDeutscher Ärzte-Verlag, 2017; im Druck.

830. Sanjida, Saira, Kissane, David, McPhail, Steven M. Obermair, Andreas, Janda, Monika, Anxiety and depression in patients with early stage endometrial cancer: A longitudinal analysis from before surgery to 6-month post-surgery. Journal of Psychosocial Oncology Research and Practice, 2019; 1(3). https://journals.lww.com/jporp/Fulltext/2019/12000/Anxiety_and_depression_in_patients_with_early.1.aspx

831. Sanjida. S, Obermair, A, Gebski, V, Armfield, N, Janda, M, Long-term quality of life outcomes of women treated for early-stage endometrial cancer. 2021; 31 (4)(4): p. 530-536. https://pubmed.ncbi.nlm.nih.gov/33361459/

832. Rowlands IJ, Lee C, Beesley VL, Webb PM. Predictors of sexual well-being after endometrial cancer: results of a national self-report survey. Support Care Cancer, 2014; 22: p. 2715-23. https://www.ncbi.nlm.nih.gov/pubmed/24798754

833. Rowlands IJ, Lee C, Janda M. Nagle C M, Obermair A, Webb PM, Predicting positive and negative impacts of cancer among long-term endometrial cancer survivors. Psychooncology, 2012; 22: p. 1963-71. https://www.ncbi.nlm.nih.gov/pubmed/23239462

834. Nouri K, Reinthaller A. Fertilitätserhalt bei prämenopausalen Frauen mit Endometriumkarzinom im frühen, niedriggradigen Stadium. Speculum, 2015; 33: p. 12-16. https://www.kup.at/kup/pdf/12731.pdf

835. Hurria A, Li D, Hansen K, Patil S, Gupta R, Nelson C. et.al. Distress in older patients with cancer. J Clin Oncol, 2009; 27: p. 4346-51. https://www.ncbi.nlm.nih.gov/pubmed/19652074

836. Köhler. N, Götze, H, Mehnert, A, Psychische Belastung und psychosoziale Unterstützung älterer Krebspatienten. Der Onkologe, 2015; 21(6): p. 518-522. https://www.springermedizin.de/psychische-belastung-und-psychosoziale-unterstuetzung-aelterer-k/8665544

837. Kornblith AB, Powell M, Regan M M, Bennett S, Krasner C, Moy, B. et.al. Long-term psychosocial adjustment of older vs younger survivors of breast and endometrial cancer. Psychooncology, 2007; 16: p. 895-903. https://www.ncbi.nlm.nih.gov/pubmed/17245695

838. Rowlands IJ, Janda M, McKinnon L. Webb PM, Beesley VL, Prevalence, predictors, and correlates of supportive care needs among women 3-5 years after a diagnosis of endometrial cancer. Support Care Cancer, 2014; 23: p. 1205-14. https://www.ncbi.nlm.nih.gov/pubmed/25304121

839. 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. http://www.leitlinienprogramm-onkologie.de/leitlinien/psychoonkologie/

840. 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. http://www.leitlinienprogramm-onkologie.de/leitlinien/zervixkarzinom/

841. Rowlands IJ, Janda M, McKinnon L. Webb PM, Beesley VL, Prevalence, predictors, and correlates of supportive care needs among women 3-5 years after a diagnosis of endometrial cancer. Support Care Cancer, 2014; 23: p. 1205-14. https://www.ncbi.nlm.nih.gov/pubmed/25304121

842. de Rooij. BH, Ezendam, NPM, Vos, MC, Pijnenborg, JMA, Boll, D, Kruitwagen, RFPM, et.al. Patients' information coping styles influence the benefit of a survivorship care plan in the ROGY Care Trial: New insights for tailored delivery. 2019; 125 (5)(5): p. 788-797. https://pubmed.ncbi.nlm.nih.gov/30500067/

843. Rowlands IJ, Lee C, Janda M. Nagle C M, Obermair A, Webb PM, Predicting positive and negative impacts of cancer among long-term endometrial cancer survivors. Psychooncology, 2012; 22: p. 1963-71. https://www.ncbi.nlm.nih.gov/pubmed/23239462

844. Geue K, Sowa E, Kuhnt S. Körperliche Beschwerden und psychosoziale Folgen nach einer Zervixkarzinomerkrankung. Der Onkologe, 2016; 22: p. 780-784.

845. Weis, J, Giesler JM. Standards in der psychosozialen Versorgung von Krebspatienten. Der Onkologe, 2016; 22(3): p. 198-205. http://link.springer.com/article/10.1007/s00761-015-2938-9

846. Herschbach P, Weis J. Screeningverfahren in der PsychoonkologieDeutsche Krebsgesellschaft, 2010;

847. Beesley V, Eakin E, Steginga S, Aitken J, Dunn J, Battistutta D. Unmet needs of gynaecological cancer survivors: implications for developing community support services. Psychooncology, 2007; 17: p. 392-400. https://www.ncbi.nlm.nih.gov/pubmed/17680554

848. Chan YM, Lee PW, Fong DY. Fung AS, Wu LY, Choi AY, et.al. Effect of individual psychological intervention in Chinese women with gynecologic malignancy: a randomized controlled trial. J Clin Oncol, 2005; 23: p. 4913-24. https://www.ncbi.nlm.nih.gov/pubmed/15939927

849. Faller. H, Schuler, M, Richard, M, Heckl, U, Weis, J, Kü;ffner, R, Effects of psycho-oncologic interventions on emotional distress and quality of life in adult patients with cancer: systematic review and meta-analysis. 2013; 31 (6)(6): p. 782-93. https://pubmed.ncbi.nlm.nih.gov/23319686/

850. Manne. SL, Virtue, SM, Ozga, M, Kashy, D, Heckman, C, Kissane, D, et.al. A comparison of two psychological interventions for newly-diagnosed gynecological cancer patients. 2017; 144 (2)(2): p. 354-362. https://pubmed.ncbi.nlm.nih.gov/27887806/

851. Buchanan. A, Roddy, M, Badr, H, Patient-reported outcomes of non-pharmacological interventions for endometrial cancer survivors: a systematic review. 2021; 15 (4)(4): p. 526-535. https://pubmed.ncbi.nlm.nih.gov/33140266/

852. Gilbert E, Ussher JM, Perz J. Sexuality after gynaecological cancer: a review of the material, intrapsychic, and discursive aspects of treatment on women's sexual-wellbeing. Maturitas, 2011; 70: p. 42-57. https://www.ncbi.nlm.nih.gov/pubmed/15939927

853. Hasenburg A, Roxana Schwab R, Farthmann J. Sexualität nach gynäko-onkologischen ErkrankungenDe Gruyter, 2020;

854. Dadak. C, Sohlmann, S, Sexualität nach einer Krebserkrankung. Der Gynäkologe, 2014; 47(2): p. 99-103. https://www.springermedizin.de/sexualitaet-nach-einer-krebserkrankung/8105692

855. Faubion. SS, MacLaughlin, KL, Long, ME, Pruthi, S, Casey, PM, Surveillance and Care of the Gynecologic Cancer Survivor. 2015; 24 (11)(11): p. 899-906. https://pubmed.ncbi.nlm.nih.gov/26208166/

856. White. ID, Sangha, A, Lucas, G, Wiseman, T, Assessment of sexual difficulties associated with multi-modal treatment for cervical or endometrial cancer: A systematic review of measurement instruments. 2016; 143 (3)(3): p. 664-673. https://pubmed.ncbi.nlm.nih.gov/27671030/

857. Baser. RE, Li, Y, Carter, J, Psychometric validation of the Female Sexual Function Index (FSFI) in cancer survivors. 2012; 118 (18)(18): p. 4606-18. https://pubmed.ncbi.nlm.nih.gov/22359250/

858. Neijenhuijs. KI, Hooghiemstra, N, Holtmaat, K, Aaronson, NK, Groenvold, M, Holzner, B, et.al. The Female Sexual Function Index (FSFI)-A Systematic Review of Measurement Properties. 2019; 16 (5)(5): p. 640-660. https://pubmed.ncbi.nlm.nih.gov/30956110/

859. MMBerner LKriston H-PZahradnik, MHärter ARohde, Überprüfung der Gültigkeit und Zuverlässigkeit des deutschen Female Sexual Function Index (FSFI-d). Geburtshilfe Frauenheilkd, 2004; 64(3): p. 293-303.

860. S3-Leitlinie Mammakarzinom. Langversion 4.3, AWMF-Registernummer: 032 – 045OL, 2020. https://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/

861. 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. http://www.leitlinienprogramm-onkologie.de/leitlinien/prostatakarzinom/

862. Gilligan. T, Coyle, N, Frankel, RM, Berry, DL, Bohlke, K, Epstein, RM, et.al. Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline. 2017; 35 (31)(31): p. 3618-3632. https://pubmed.ncbi.nlm.nih.gov/28892432/

863. Gysels. M, Higginson, IJ, Interactive technologies and videotapes for patient education in cancer care: systematic review and meta-analysis of randomised trials. 2007; 15 (1)(1): p. 7-20. https://pubmed.ncbi.nlm.nih.gov/17024500/

864. Nilsen. ES, Myrhaug, HT, Johansen, M, Oliver, S, Oxman, AD, Methods of consumer involvement in developing healthcare policy and research, clinical practice guidelines and patient information material. 2006; (3)(3): p. CD004563. https://pubmed.ncbi.nlm.nih.gov/16856050/

865. Wofford. JL, Smith, ED, Miller, DP, The multimedia computer for office-based patient education: a systematic review. 2005; 59 (2)(2): p. 148-57. https://pubmed.ncbi.nlm.nih.gov/16257619/

866. Bundesgesundheitsblatt, 2013;

867. N. h, s, Effective Health Care: Informing, communicating and sharing decision with people who have cancerLatimer Trend & Company Ltd. 2000. https://www.ncbi.nlm.nih.gov/pubmed/11533427

868. Wright EB. Holcombe C, Salmon P, Doctors' communication of trust, care, and respect in breast cancer: qualitative study. BMJ, 2004; 328: p. 864. https://www.ncbi.nlm.nih.gov/pubmed/15054034

869. Jansen SJ, Otten W, Baas-Thijssen MC, van de Velde, C J, Nortier, J W, Stiggelbout AM. Explaining differences in attitude toward adjuvant chemotherapy between experienced and inexperienced breast cancer patients. J Clin Oncol, 2005; 23: p. 6623-30. https://www.ncbi.nlm.nih.gov/pubmed/16170169

870. Katz SJ, Lantz PM, Janz NK, Fagerlin A, Schwartz, K, Liu L. et.al. Patient involvement in surgery treatment decisions for breast cancer. J Clin Oncol, 2005; 23: p. 5526-33. https://www.ncbi.nlm.nih.gov/pubmed/16110013

871. Wagner K, Koller M, Keil A, Trott D, Engenhart-Cabillic R. Pfab R, et.al. [Radiotherapy in surgical and nonsurgical patients. Therapy expectations, quality of life and physician assessment]. Chirurg, 1998; 69: p. 252-8. https://www.ncbi.nlm.nih.gov/pubmed/9576035

872. Weis J, Giesler J M. Subjective dimensions of patient competence: relationships with selected healthcare usage behaviors and general features of self-rated competence. Patient Educ Couns, 2008; 73: p. 511-8. https://www.ncbi.nlm.nih.gov/pubmed/18952394

873. Albert US, Schulz KD, Alt, D, Beck V, Doherty J, Holsteg K. et.al. [A guideline for guidelines--methodological report and use of the guideline women's information]. Zentralbl Gynakol, 2004; 125: p. 484-93. https://www.ncbi.nlm.nih.gov/pubmed/14755359

874. Klemperer D. Lang B, Koch K, Bastian H, Brunsmann F, M, Burkhardt, et.al. Die Gute Praxis Gesundheitsinformation. ZEFQ, 2010; 104: p. 66-68. https://www.ebm-netzwerk.de/pdf/publikationen/gpgi2.pdf

875. O'Connor AM, Fiset V, DeGrasse C, Graham ID, Evans W, Stacey, D. et.al. Decision aids for patients considering options affecting cancer outcomes: evidence of efficacy and policy implications. J Natl Cancer Inst Monogr, 2000; p. 67-80. https://www.ncbi.nlm.nih.gov/pubmed/10854460

876. Dissemination, NHS Centre for Reviews and, Effective Health Care: Informing, communicating and sharing decisions with people who have cancerLatimer Trend & Company Ltd, 2000; 6:

877. Bundesministerium für Justiz, Patientenrechtegesetz, Gesetz zur Verbesserung der Rechte von Patientinnen und PatientenDeutscher Bundestag, 20. Februar 2013. Jahrgang 2013: p. 277-282. https://www.bgbl.de/xaver/bgbl/start.xav?startbk=Bundesanzeiger_BGBl&jumpTo=bgbl113s0277.pdf#__bgbl__%2F%2F*%5B%40attr_id%3D%27bgbl113s0277.pdf%27%5D__1489429188064

878. Cherny. NI, Radbruch, L, European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. 2009; 23 (7)(7): p. 581-93. https://pubmed.ncbi.nlm.nih.gov/19858355/

879. L. e, i, t, l, i, et.al. Palliativmedizin für Patienten mit einer nicht heilbaren Krebserkrankung, Langversion 1.0, 2015, AWMF-Registernummer: 128/001OL, 2015. https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/

880. GJBauerschmitz MHellriegel, GEmons, Palliative Konzepte beim Endometrium-, Zervix- und Vulvakarzinom. Der Gynäkologe, 2017; 12:

881. L, e, i, et al. *Komplementärmedizin in der Behandlung von onkologischen PatientInnen.* Langversion, Registernummer: 032/055OL, 2021. **Version 1.1:** https://www.leitlinienprogramm-onkologie.de/leitlinien/komplementaermedizin/

882. Berger. AM, Abernethy, AP, Atkinson, A, Barsevick, AM, Breitbart, WS, Cella, D, et.al. NCCN Clinical Practice Guidelines Cancer-related fatigue. 2010; 8 (8)(8): p. 904-31. https://pubmed.ncbi.nlm.nih.gov/20870636/

883. Fabi. A, Bhargava, R, Fatigoni, S, Guglielmo, M, Horneber, M, Roila, F, et.al. Cancer-related fatigue: ESMO Clinical Practice Guidelines for diagnosis and treatment. 2020; 31 (6)(6): p. 713-723. https://pubmed.ncbi.nlm.nih.gov/32173483/

884. Greer JA. Smith, A L, Arya, L A, Pelvic floor muscle training for urgency urinary incontinence in women: a systematic review. Int Urogynecol J, 2012; 23: p. 687-97. https://www.ncbi.nlm.nih.gov/pubmed/22246576

885. Hartmann KE, McPheeters ML, Biller DH, Ward RM, McKoy JN. Jerome RN, et.al. Treatment of overactive bladder in women. Evid Rep Technol Assess (Full Rep), 2009; p. 1-120, v. https://www.ncbi.nlm.nih.gov/pubmed/19947666

886. Berghmans B, van Waalwijk van Doorn E, Nieman F, de Bie R, van den Brandt P. Van Kerrebroeck P, Efficacy of physical therapeutic modalities in women with proven bladder overactivity. Eur Urol, 2002; 41: p. 581-7. https://www.ncbi.nlm.nih.gov/pubmed/12074773

887. Wang AC. Wang YY, Chen MC, Single-blind, randomized trial of pelvic floor muscle training, biofeedback-assisted pelvic floor muscle training, and electrical stimulation in the management of overactive bladder. Urology, 2004; 63: p. 61-6. https://www.ncbi.nlm.nih.gov/pubmed/14751349

888. Dumoulin C, Hay-Smith J. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev, 2010; p. CD005654. https://www.ncbi.nlm.nih.gov/pubmed/24823491

889. Hay-Smith EJ, Herderschee R, Dumoulin C, Herbison GP. Comparisons of approaches to pelvic floor muscle training for urinary incontinence in women. Cochrane Database Syst Rev, 2011; p. CD009508. https://www.ncbi.nlm.nih.gov/pubmed/22161451

890. Imamura M, Abrams P, Bain C, Buckley B, Cardozo L, Cody J. et.al. Systematic review and economic modelling of the effectiveness and cost-effectiveness of non-surgical treatments for women with stress urinary incontinence. Health Technol Assess, 2010; 14: p. 1-188, iii-iv. https://www.ncbi.nlm.nih.gov/pubmed/20738930

891. Choi H, Palmer MH, Park J. Meta-analysis of pelvic floor muscle training: randomized controlled trials in incontinent women. Nurs Res, 2007; 56: p. 226-34. https://www.ncbi.nlm.nih.gov/pubmed/17625461

892. Lo, Sing Kai, Naidu, Jaya, Cao, Yuelong, Additive Effect of Interferential Therapy Over Pelvic Floor Exercise Alone in the Treatment of Female Urinary Stress and Urge Incontinence: A Randomized Controlled Trial. Hong Kong Physiotherapy Journal, 2003; 21: p. 37-42. https://www.sciencedirect.com/science/article/pii/S1013702509700387

893. Patil SP, Nagrale AV, Ganvir SD. Additive effect of interferential therapy over pelvic floor exercises. International Journal of Therapy & Rehabilitation, 2010; 17: p. 596-602. https://www.magonlinelibrary.com/doi/abs/10.12968/ijtr.2010.17.11.79540

894. Hosker G, Cody JD, Norton CC. Electrical stimulation for faecal incontinence in adults. Cochrane Database Syst Rev, 2007; p. CD001310. https://www.cochrane.org/CD001310/INCONT_electrical-stimulation-for-faecal-incontinence-in-adults

895. Norton C, Cody JD. Biofeedback and/or sphincter exercises for the treatment of faecal incontinence in adults. Cochrane Database Syst Rev, 2012; p. CD002111. https://www.ncbi.nlm.nih.gov/pubmed/22786479

896. Le Borgne G, Mercier M, Woronoff AS, Guizard AV, Abeilard E, Caravati-Jouvenceaux A. et.al. Quality of life in long-term cervical cancer survivors: a population-based study. Gynecol Oncol, 2013; 129: p. 222-8. https://www.ncbi.nlm.nih.gov/pubmed/23280088

897. Devoogdt N. Christiaens MR, Geraerts I, Truijen S, Smeets A, Leunen K, et.al. Effect of manual lymph drainage in addition to guidelines and exercise therapy on arm lymphoedema related to breast cancer: randomised controlled trial. BMJ, 2011; 343: p. d5326. https://www.ncbi.nlm.nih.gov/pubmed/21885537

898. Hayes SC, Reul-Hirche H, Turner J. Exercise and secondary lymphedema: safety, potential benefits, and research issues. Med Sci Sports Exerc, 2009; 41: p. 483-9. https://www.ncbi.nlm.nih.gov/pubmed/19204604

899. Sagen A. Karesen R, Risberg MA, Physical activity for the affected limb and arm lymphedema after breast cancer surgery. A prospective, randomized controlled trial with two years follow-up. Acta Oncol, 2009; 48: p. 1102-10. https://www.ncbi.nlm.nih.gov/pubmed/19863217

900. Ahmed Omar MT, Abd-El-Gayed Ebid A, El Morsy A M. Treatment of post-mastectomy lymphedema with laser therapy: double blind placebo control randomized study. J Surg Res, 2010; 165: p. 82-90. https://www.ncbi.nlm.nih.gov/pubmed/20538293

901. Kozanoglu E, Basaran S, Paydas S, Sarpel T. Efficacy of pneumatic compression and low-level laser therapy in the treatment of postmastectomy lymphoedema: a randomized controlled trial. Clin Rehabil, 2009; 23: p. 117-24. https://www.ncbi.nlm.nih.gov/pubmed/19164399

902. Tsai HJ, Hung HC, Yang, J L, Huang, C S, Tsauo, J Y. Could Kinesio tape replace the bandage in decongestive lymphatic therapy for breast-cancer-related lymphedema? A pilot study. Support Care Cancer, 2009; 17: p. 1353-60. https://www.ncbi.nlm.nih.gov/pubmed/19199105

903. Mohile, SG, Dale, W, Somerfield, MR, et al. *Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology.*. J Clin Oncol, 2018. **36 (22):** p. 2326-2347. https://pubmed.ncbi.nlm.nih.gov/29782209/

904. Decoster, L, Van Puyvelde, K, Mohile, S, et al. *Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†.*. Ann Oncol, 2015. **26 (2):** p. 288-300. https://pubmed.ncbi.nlm.nih.gov/24936581/

905. Nadaraja, S, Jørgensen, TL, Matzen, LE, et al. *Impact of Age, Comorbidity, and FIGO Stage on Treatment Choice and Mortality in Older Danish Patients with Gynecological Cancer: A Retrospective Register-Based Cohort Study.* Drugs Real World Outcomes, 2018. **5 (4):** p. 225-235. https://pubmed.ncbi.nlm.nih.gov/30460662/

906. Bourgin, C, Saidani, M, Poupon, C, et al. *Endometrial cancer in elderly women: Which disease, which surgical management? A systematic review of the literature.* Eur J Surg Oncol, 2016. **42 (2):** p. 166-75. https://pubmed.ncbi.nlm.nih.gov/26647302/

907. Driver, JA, Viswanathan, AN. *Frailty measure is more predictive of outcomes after curative therapy for endometrial cancer than traditional risk factors in women 60 and older.* Gynecol Oncol, 2017. **145 (3):** p. 526-530. https://pubmed.ncbi.nlm.nih.gov/28359689/

908. Ahmed, A, Deng, W, Tew, W, et al. *Pre-operative assessment and post-operative outcomes of elderly women with gynecologic cancers, primary analysis of NRG CC-002: An NRG oncology group/gynecologic oncology group study.* Gynecol Oncol, 2018. **150 (2):** p. 300-305. https://pubmed.ncbi.nlm.nih.gov/29807694/

909. Bauer, J, Denkinger, M , Freiberger, E., et al. *S1-Leitlinie "Geriatrisches Assessment der Stufe 2.* 2019. https://www.awmf.org/leitlinien/detail/ll/084-002.html

910. B. e, c, k, m, a, et.al. Gynäkologische Krebszentren – Kompetenzbündelung zur Qualitätsverbesserung. Frauenheilkunde up2date, 2009; 3: p. 71-74.

911. Wesselmann S, Beckmann MW, Winter A. The concept of the certification system of the German Cancer Society and its impact on gynecological cancer care. Arch Gynecol Obstet, 2013; 289: p. 7-12. https://www.ncbi.nlm.nih.gov/pubmed/24220845

912. Kowalski C, Wesselmann S, Ansmann L, Kreienberg R, Pfaff H. Zertifizierte Brustkrebszentren aus Sicht der Zentrumsleitungen: Ergebnisse einer Schlüsselpersonenbefragung. Geburtsh Frauenheilk, 2012; 72: p. 235-242.

913. Huthmann D, Seufferlein T, Post S. Benz S, Stinner B, Wesselmann S, Zertifizierte Darmkrebszentren aus Sicht der Zentrumsleitungen: Ergebnisse einer Schlüsselpersonenbefragung. Gastroenterol, 2012; 50: p. 753-759.

914. Kowalski C, Wesselmann S, Ansmann L, Kreienberg R, Pfaff H. Zertifizierte Brustkrebszentren aus Sicht der Patientinnen: Stärken und Verbesserungspotenziale. Geburtsh Frauenheilk, 2012; 71: p. 137-143.

915. Thiel FC, Scharl A, Hildebrandt T, Kotziabassis E, Schrauder MG, Bani MR. et.al. Financing of certified centers: a willingness-to-pay analysis. Arch Gynecol Obstet, 2012; 287: p. 495-509. https://www.ncbi.nlm.nih.gov/pubmed/23080545

916. Lux MP, Fasching, P A, Bani MR, Schrauder M. Marketing von Brust- und Perinatalzentren – Sind Patientinnen mit dem Produkt "zertifiziertes Zentrum" vertraut? Geburtsh Frauenheilk, 2009; 69: p. 321-327.

917. Wesselmann S. Winter A, Ferencz J, Seufferlein T, Post S, Documented quality of care in certified colorectal cancer centers in Germany: German Cancer Society benchmarking report for 2013. Int J Colorectal Dis, 2014; 29: p. 511-8. https://www.ncbi.nlm.nih.gov/pubmed/24584335

918. Beckmann MW, Adler G, Albers P, Bruns J. Dreistufenmodell optimiert Behandlung unter Kostendeckung Wie die künftigen Strukturen der onkologischen Versorgung in Deutschland aussehen sollten. Dtsch Arztebl, 2007; 104: p. 3004-3009. https://www.aerzteblatt.de/archiv/57409/Onkologie-Dreistufenmodell-optimiert-Behandlung-unter-Kostendeckung-Wie-die-kuenftigen-Strukturen-der-onkologischen-Versorgung-in-Deutschland-aussehen-sollten

919. Onkozert et.al. Kennzahlenauswertung 2020 - Jahresbericht der zertifizierten Gynäkologischen Krebszentren - Auditjahr 2019 / Kennzahlenjahr 2018, 2020. https://www.onkozert.de/wordpress/wp-content/uploads/2020/04/qualitaetsindikatoren_gynaekologische-krebserkrankungen_2020-A1_200402.pdf?v=44353574

920. Roland PY, Kelly FJ, Kulwicki CY, Blitzer P, Curcio M, Orr, J W. Jr. The benefits of a gynecologic oncologist: a pattern of care study for endometrial cancer treatment. Gynecol Oncol, 2004; 93: p. 125-30. https://www.ncbi.nlm.nih.gov/pubmed/15047225

921. Macdonald OK. Sause WT, Lee RJ, Dodson MK, Zempolich, K, Gaffney DK, Does oncologic specialization influence outcomes following surgery in early stage adenocarcinoma of the endometrium? Gynecol Oncol, 2005; 99: p. 730-5. https://www.ncbi.nlm.nih.gov/pubmed/16139348

922. Chan JK, Sherman AE, Kapp DS, Zhang R, Osann, K E, Maxwell L. et.al. Influence of gynecologic oncologists on the survival of patients with endometrial cancer. J Clin Oncol, 2011; 29: p. 832-8. https://www.ncbi.nlm.nih.gov/pubmed/21263082

923. Beckmann MW. et al. Der neue Schwerpunkt Gynäkologische Onkologie: nationale und internationale Chance? Geburtsh Frauenheilk, 2006; 66: p. 123-127.

924. Ioka A. Tsukuma H, Ajiki W, Oshima A, Influence of hospital procedure volume on uterine cancer survival in Osaka, Japan. Cancer Sci, 2005; 96: p. 689-94. https://www.ncbi.nlm.nih.gov/pubmed/16232201

925. Diaz-Montes TP, Zahurak ML, Giuntoli RL, 2nd, Gardner GJ, Bristow RE. Uterine cancer in Maryland: impact of surgeon case volume and other prognostic factors on short-term mortality. Gynecol Oncol, 2006; 103: p. 1043-7. https://www.ncbi.nlm.nih.gov/pubmed/16876234

926. Elit LM, O'Leary EM, Pond GR, Seow HY. Impact of wait times on survival for women with uterine cancer. J Clin Oncol, 2013; 32: p. 27-33. https://www.ncbi.nlm.nih.gov/pubmed/24276779

927. Beckmann MW. et.al. Frauenarzt/-ärztin der Zukunft: müssen die Kliniken neu strukturiert werden? Der Gynäkologe, 2010; 43: p. 748-756. https://www.springermedizin.de/frauenarzt-aerztin-der-zukunft-muessen-die-kliniken-neu-struktur/8104622

928. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). Entwicklung von leitlinienbasierten Qualitätsindikatoren. Methodenpapier für das Leitlinienprogramm OnkologieLeitlinienprogramm Onkologie, 2017; 2017.

https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Methodik/QIEP_OL_2017_Version_2.1.pdf