Interdisciplinary Diagnosis, Therapy and Follow-up of Patients with Endometrial Cancer. Guideline (S3-Level, AWMF Registry Nummer 032/034-OL, April 2018) – Part 1 with Recommendations on the Epidemiology, Screening, Diagnosis and Hereditary Factors of Endometrial Cancer

Interdisziplinäre Diagnostik, Therapie und Nachsorge der Patientinnen mit Endometriumkarzinom. Leitlinie (S3-Level, AWMF-Register-Nummer 032/034-OL, April 2018) – Teil 1 mit Empfehlungen zur Epidemiologie, Früherkennung, Diagnostik und hereditären Faktoren des Endometriumkarzinoms

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Key words
dometrical cancer, epidemiology, genetics, guideline, screening, hereditary factors

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

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

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

Recommendations Part 1 of this short version of the guideline presents recommendations on epidemiology, screening, diagnosis and hereditary factors, The epidemiology of endometrial cancer and the risk factors for developing endometrial cancer are presented. The options for screening and the methods used to diagnose endometrial cancer including the pathology of the cancer are outlined. Recommendations are given for the prevention, diagnosis, and therapy of hereditary forms of endometrial cancer.
I Guideline Information

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

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

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

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Guideline documents
The complete long version together with a summary of the conflicts of interest of all of the authors, a short version, the guideline report, and the search for external literature are available in German on the homepage of the Oncology Guidelines Program under: https://www.leitlinienprogramm-onkologie.de/leitlinien/endometriumkarzinom/, last accessed on 13.08.2018.

Guideline authors
The working groups who contributed to this guideline consisted of members of the guideline steering committee (Table 1), specialists nominated by participating professional societies and organizations (Table 2), and experts invited to participate by the steering committee (Table 3), and they are the authors of this guideline. Only mandate holders nominated by participating professional societies and organizations were eligible to vote on a chapter-by-chapter basis during the voting process (consensus

| Participating professional societies and organizations | Mandate holder | Deputy |
|--------------------------------------------------------|----------------|--------|
| ADT (Association of German Tumor Centers [AG Deutscher Tumorzentren]) | Prof. Dr. med. Olaf Ortmann, Regensburg |        |
| AET (DKG Working Group for Hereditary Tumor Disease [AG Erbliche Tumorerkrankungen der DKG]) | Prof. Dr. med. Stefan Aretz, Bonn | Prof. Dr. med. Rita Katharina Schmutzler, Köln Prof. Dr. med. Alfons Meindl, Munich (only once in 06/2015) |
| AGO (Gynecological Oncology Working Group of the DGGG and DKG [Arbeitsgemeinschaft Gynäkologische Onkologie in der DGGG und DKG]) | Prof. Dr. med. Peter Mallmann, Cologne |        |
| AGO Study Group (Arbeitsgemeinschaft Gynäkologische Onkologie [AGO] Studiengruppe) | PD Dr. med. Christian Kuzedez, Basel | Prof. Dr. med. Felix Hilpert, Hamburg |
| AIO (Internal Oncology Working Group [Arbeitsgemeinschaft Internistische Onkologie der DKG]) | Dr. med. Volker Hagen, Dortmund | PD Dr. med. Anne Letsch, Berlin |
| APM (Palliative Medicine Working Group of the German Cancer Society [Arbeitsgemeinschaft Palliativmedizin der Deutschen Krebsgesellschaft]) | Prof. Dr. med. Birgitt van Oorschot, Würzburg | Dr. med. Joan Elisabeth Panke, Essen |
| ARO (Radiological Oncology Working Group [Arbeitsgemeinschaft Radiologische Onkologie der DKG]) | Prof. Dr. med. Stefan Höcht, Saarlouis | Prof. Dr. med. Vratislav Strnad, Erlangen |
| ASORS (Supportive Measures in Oncology, Rehabilitation and Social Medicine Working Group [AG Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin der DKG]) | Prof. Dr. med. Petra Feyer, Berlin Prof. Dr. med. Gerlinde Egerer, Heidelberg (till 10/2015) | Dr. med. Christiane Niehues, Berlin (02–10/2016) Dr. med. Timm Dauelsberg, Nordrach |

Table 1 Steering committee.

Table 2 Participating professional societies and organizations.
### Table 2 Participating professional societies and organizations (Continued)

| Participating professional societies and organizations                                                                 | Mandate holder                                                                 | Deputy                        |
|------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------|
| BLFG (Federal Association of Senior Physicians in Gynecology and Obstetrics [Bundesarbeitsgemeinschaft Leitender Ärzten und Ärzte in der Frauenheilkunde und Geburtshilfe]) | Prof. Dr. med. Michael Friedrich, Krefeld                                      |                               |
| BNGO (Professional Association of Gynecological Oncologists in Private Practice in Germany [Berufsverband Niedergelassener Gynäkologischer Onkologen in Deutschland]) | Dr. med. Christoph Uleer, Hildesheim                                          |                               |
| BVF (Professional Association of Gynecologists [Berufsverband der Frauenärzte])                                        | Dr. med. Wolfgang Cremer, Hamburg                                              |                               |
| BVDST (Federal Association of German Radiotherapists [Bundesverband Deutscher Strahlentherapeuten])                   | Prof. Dr. med. Franz-Josef Prött, Wiesbaden                                    | Prof. Dr. med. Peter Niehoff, Offenbach |
| BV Pathologie (Federal Association of German Pathologists [Bundesverband Deutscher Pathologen])                      | Prof. Dr. med. Lars-Christian Horn, Leipzig                                     | Prof. Dr. med. Doris Mayr, Munich |
| DEGRO (German Society for Radiation Oncology [Deutsche Gesellschaft für Radioonkologie])                         | Prof. Dr. med. Dirk Vordermark, Halle                                         |                               |
| DEGUM (German Society for Ultrasound in Medicine [Deutsche Gesellschaft für Ultraschall in der Medizin])             | Prof. Dr. med. Heinrich Prömpeler, Freiburg                                    | Prof. Dr. med. Dieter Grab, Munich |
| DGAV (German Society for General and Visceral Surgery [Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie])   | Prof. Dr. med. Jan Langrehr, Berlin                                            |                               |
| DGCH (German Society of Surgery [Deutsche Gesellschaft für Chirurgie])                                               | Prof. Dr. med. Steffen Leinung, Grimma († 25.11.2016)                           |                               |
| DGE (German Society of Endocrinology [Deutsche Gesellschaft für Endokrinologie])                                   | Prof. Dr. med. Matthias W. Beckmann, Erlangen                                  |                               |
| DGGG (German Society of Gynecology and Obstetrics [Deutsche Gesellschaft für Gynäkologie und Geburtshilfe])           | Prof. Dr. med. Rainer Kimmig, Essen                                           |                               |
| DCHO (German Society of Hematology and Medical Oncology [Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie]) | PD Dr. med. Anne Letch, Berlin                                                 | Dr. med. Volker Hagen, Dortmund |
| DGN (German Society of Nuclear Medicine [Deutsche Gesellschaft für Nuklearmedizin])                                | Prof. Dr. med. Michael J. Reinhardt, Oldenburg                                 | Prof. Dr. med. Michael Kreißl, Magdeburg |
| DGP (German Society of Palliative Medicine [Deutsche Gesellschaft für Palliativmedizin])                           | Prof. Dr. med. Bernd Alt-Eppin, Göttingen                                      |                               |
| DGP (German Society of Pathology [Deutsche Gesellschaft für Pathologie])                                          | Prof. Dr. med. Lars-Christian Horn, Leipzig                                    | Prof. Dr. med. Doris Mayr, Munich |
| DMG (German Menopause Society [Deutsche Menopause Gesellschaft])                                                   | Prof. Dr. med. Ludwig Kiesel, Münster                                          | Dr. med. Ralf Witteler, Münster |
| DRG (German Roentgen Society [Deutsche Röntgengesellschaft])                                                      | Prof. Dr. med. Jan Menke, Göttingen                                           |                               |
| FSH (Self-help Group for Women after Cancer [Frauenselfhilfe nach Krebs])                                          | Marion Gebhardt, Forchheim                                                    | Annemarie Schorsch, Bad Soden |
| GFH (German Society of Human Genetics [Deutsche Gesellschaft für Humangenetik])                                   | Dr. med. Verena Steinke-Lange, Munich                                         | Dr. med. Nils Rahner, Düsseldorf (einmalig 04/2016) |
| KOK (Working Group of the DKG: Conference of Oncological Nursing and Pediatric Nursing [Arbeitsgemeinschaft der DKG: Konferenz Onkologische Kranken- und Kinderkranzpflege]) | Kerstin Paradies, Hamburg                                                     |                               |
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process) after they had disclosed and excluded any conflicts of interest [1]. The guideline was compiled with the direct participation of two patient representatives. Physicians of the Competence Oncology Center of the National Association of Statutory Health Insurance Funds (Kompetenz Zentrum Onkologie des GKV-Spitzenverbandes) and the Medical Service of German Health Funds (MDK-Gemeinschaft) were involved in an advisory capacity during the formulation of specific aspects of this S3-guideline which were relevant for social medicine. They did not participate in the voting on individual recommendations and are not responsible for the contents of this guideline.

### Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| ACR          | American College of Radiology |
| AEG          | atypical endometrial hyperplasia |
| AG           | working group (Arbeitsgruppe) |
| AWMF         | Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.) |
| ÄZQ          | Medical Center for Quality in Medicine (Ärztliches Zentrum für Qualität in der Medizin) |
| BMI          | body mass index |
| CEB          | Basel Institute for Clinical Epidemiology & Biostatistics of the University of Basel |
| CEBM         | Centre for Evidence-Based Medicine (Oxford, UK) |
| CS           | Cowden syndrome |
| CT           | computed tomography |
| DELBI        | German Guideline Assessment Instrument |
| DELPHI       | multistage survey method |
| DKG          | German Cancer Society (Deutsche Krebsgesellschaft e.V.) |
| DKH          | German Cancer Aid (Deutsche Krebshilfe e.V.) |
| EC           | expert consensus |
| FIGO         | International Federation of Gynecology and Obstetrics |
| GoR          | grade of recommendation |
| HCS          | hereditary cancer syndrome |
| HNPPC        | hereditary non-polyposis colorectal cancer |
| HT/HRT       | hormone therapy in perimenopause and post-menopause (hormone replacement therapy) |
| IKNL         | Integral Kankerzentrum Nederland |
| LoE          | level of evidence |
| LS           | Lynch syndrome |
| MMR          | mismatch repair |
| MMMT         | malignant Müllerian mixed tumor/malignant mesodermal mixed tumor: carcinosarcoma |
| MRI          | magnetic resonance imaging |
| OL           | Oncology Guidelines Program |
| PCOS         | polycystic ovarian syndrome |
| PET-CT       | positron emission tomography + computed tomography |
| PHTS         | PTEN hamartoma tumor syndrome |
| PMB          | postmenopausal bleeding |
| SEE-FIM      | section and extensively examine the FIMbriated end of the fallopian tube |
| ST           | statement |
| UICC         | Union internationale contre le cancer |
| WHO          | World Health Organization |

### II Guideline Application

#### Purpose and objectives

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

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

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

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

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

III Methodology of the Guideline

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

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

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

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

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

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

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

#### 1 Epidemiology and risk factors, prevention of endometrial cancer

##### 1.1 Epidemiology and risk factors

##### 1.1.1 Age

| No. | Recommendation | GoR | LoE | Sources |
|-----|----------------|-----|-----|---------|
| 3.1 | The risk of developing endometrial cancer increases with age. | ST | 1 | [5] |

##### 1.1.2 Hormone therapy (HRT) without a progestogen for endometrial protection

| No. | Recommendation | GoR | LoE | Sources |
|-----|----------------|-----|-----|---------|
| 3.2 | Hormone therapy with estrogens alone, without gestagen protection, is a risk factor for the development of endometrial cancer in women who have not undergone hysterectomy. The effect depends on the duration of administration. | ST | 2 | [6–11] |

##### 1.1.3 Hormone therapy with a progestogen for endometrial protection

##### 1.1.3.1 Continuous combined estrogen-progestogen therapy

| No. | Recommendation | GoR | LoE | Sources |
|-----|----------------|-----|-----|---------|
| 3.3 | A reduction in the risk of endometrial cancer was observed for women who received continuous combined hormone therapy with conjugated equine estrogens and medroxyprogesterone acetate as the progestogen over an average period of 5.6 years. | ST | 2 | [12] |

| 3.3.1 | Continuous combined hormone therapy administered for < 5 years may be considered safe with regard to the risk of developing endometrial cancer. | ST | 2 | 6, 7, 9, 10, 12, 13, 14 |

##### 1.1.3.2 Long-term administration of continuous combined HRT

| No. | Recommendation | GoR | LoE | Sources |
|-----|----------------|-----|-----|---------|
| 3.4 | An increased risk of developing endometrial cancer was observed following the long-term administration of continuous combined hormone therapy > 6 years or > 10 years. | ST | 3 | [9, 10] |

#### 1.1.3.3 Sequential combined estrogen/progestogen therapy

| No. | Recommendation | GoR | LoE | Sources |
|-----|----------------|-----|-----|---------|
| 3.5 | The administration of progesterone or dydrogesterone in the context of continuous combined hormone therapy may increase the risk of developing endometrial cancer. | ST | 3 | [13] |

| 3.6 | Sequential combined hormone therapy may increase the risk of developing endometrial cancer. The effect depends on the duration, type and dosage of the administered progestogen. | ST | 3 | [6, 7, 9–11, 14] |

| 3.7 | Sequential combined hormone therapy administered for < 5 years which includes the administration of a synthetic progestogen for at least 12–14 days per month may be considered safe with respect to the risk of developing endometrial cancer. | ST | 3 | [6, 7, 11] |

#### 1.1.4 Tibolone

| No. | Recommendation | GoR | LoE | Sources |
|-----|----------------|-----|-----|---------|
| 3.8 | An increased risk of developing endometrial cancer has been observed for tibolone. | ST | 3 | [6, 11, 15] |

#### 1.1.5 Tamoxifen

| No. | Recommendation | GoR | LoE | Sources |
|-----|----------------|-----|-----|---------|
| 3.9 | Therapy with tamoxifen is a risk factor for developing endometrial cancer. The effect is dependent on the duration of administration. | ST | 1 | [17–20] |

#### 1.1.6 Oral contraceptives

| No. | Recommendation | GoR | LoE | Sources |
|-----|----------------|-----|-----|---------|
| 3.10 | Oral contraceptives reduce the risk for the development of endometrial carcinoma. The strength of the effect is dependent on the duration of intake. | ST | 2 | [21, 22] |
1.1.7 Ovarian stimulation therapy

No. | Recommendation | GoR | LoE | Sources |
--- | --- | --- | --- | --- |
3.11 | Ovarian stimulation therapy increases the risk of endometrial cancer compared to population-based controls, but not compared with infertile women. | ST | 4 | [23, 24] |

1.1.8 Other biological risk factors

No. | Recommendation | GoR | LoE | Sources |
--- | --- | --- | --- | --- |
3.12 | Late age at menarche and late age at the birth of the last child are associated with a reduced risk of developing endometrial cancer; late onset of menopause is associated with an increased risk of developing endometrial cancer. | ST | 3 | [25 – 27] |
3.13 | Diabetes mellitus, disturbance of glucose tolerance, metabolic syndrome and polycystic ovary syndrome (PCOS) increase the risk of developing endometrial cancer. | ST | 3 | [28 – 42] |
3.14 | An increased body mass index (BMI) increases the risk of developing endometrial cancer. | ST | 3 | [43 – 48] |
3.15 | A positive family history of endometrial cancer and/or colon cancer is associated with a higher risk of developing endometrial cancer. | ST | 3 | [49] |

1.1.9 Risk-reducing factors

No. | Recommendation | GoR | LoE | Sources |
--- | --- | --- | --- | --- |
3.16 | Physical activity is associated with a reduced risk of developing endometrial cancer. | ST | 3 | [50 – 54] |
3.17 | The use of intrauterine devices (IUDs; copper spirals or therapeutic levonorgestrel spirals) is associated with a reduced risk of developing endometrial cancer. | ST | 3 | [55, 56] |

2 Screening and Diagnosis of Endometrial Cancer

2.1 Screening/diagnosis of asymptomatic women

2.1.1 Asymptomatic women with no increased risk

No. | Recommendation | GoR | LoE | Sources |
--- | --- | --- | --- | --- |
4.1 | The available data do not show that screening using transvaginal ultrasound in asymptomatic women with no increased risk of endometrial cancer reduces endometrial cancer-specific mortality. | EC | |
4.2 | Transvaginal ultrasonography must not be carried out for purposes of early detection of endometrial cancer in asymptomatic women who are not at increased risk for endometrial carcinoma. | EC | |

2.1.2 Asymptomatic women with an increased risk

No. | Recommendation | GoR | LoE | Sources |
--- | --- | --- | --- | --- |
4.3 | The available data do not show that transvaginal ultrasound screening in asymptomatic women who have an increased risk of developing endometrial cancer (e.g., women with Lynch syndrome, obesity, diabetes mellitus, hormone therapy, metabolic syndrome, PCOS) reduces endometrial cancer-specific mortality. | EC | |
4.4 | The available data do not show that screening of asymptomatic women who have an increased risk of developing endometrial cancer (e.g., women with Lynch syndrome, obesity, diabetes mellitus, hormone therapy, metabolic syndrome, PCOS) using endometrial biopsy, pipelle sampling, Tao brush cytology, tumor marker sampling, fractional curettage or hysteroscopy reduces endometrial cancer-specific mortality. | ST | 4 | [57, 58] |
4.5 | Transvaginal ultrasound examinations must not be carried out for early detection of endometrial carcinoma in asymptomatic women who are at increased risk for endometrial carcinoma (such as those with Lynch syndrome, obesity, diabetes mellitus, hormone therapy, metabolic syndrome, PCOS). | EC | |
### 2.1.3 Asymptomatic women and tamoxifen therapy

| No. | Recommendation                                                                                                                                                                                                 | GoR | LoE | Sources       |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|---------------|
| 4.6 | Asymptomatic patients receiving tamoxifen therapy must not be examined by transvaginal ultrasound to screen for endometrial cancer.                                                                        | A   | 3   | [59–63]       |

### 2.2 Investigations for abnormal premenopausal uterine bleeding

| No. | Recommendation                                                                                                                                                                                                 | GoR | LoE | Sources       |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|---------------|
| 4.7 | The risk of premenopausal women with abnormal uterine bleeding developing endometrial cancer or atypical endometrial hyperplasia is below 1.5%.                                                           | ST  | 2   | [64]          |

| No. | Recommendation                                                                                                                                                                                                 | GoR | LoE | Sources       |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|---------------|
| 4.8 | In women with premenopausal abnormal uterine bleeding who do not have any risk factors (suspicious cytology, obesity, Lynch syndrome, diabetes, polyps, etc.), an attempt at conservative treatment should initially be made, provided that the bleeding is not hemodynamically relevant. If conservative therapy fails, hysteroscopy/curettage should be carried out. | EC  |     |               |
| 4.9 | Hysteroscopy combined with fractional curettage is the gold standard for obtaining a reliable diagnosis of endometrial cancer.                                                                               | ST  | 3   | [65–67]       |
2.3 Procedures for postmenopausal bleeding (PMB)

No. Recommendation GoR LoE Sources
4.10 In a number of small series of symptomatic patients, diagnostic procedures such as pipelle sampling and Tao brush cytology offered positive and negative predictive values for diagnosing endometrial cancer which were comparable to those obtained with curettage plus hysteroscopy. However, larger comparative studies are still lacking. ST 3 [68]
4.10.1 These diagnostic procedures are not at present comprehensively available on a quality-assured basis throughout Germany. EC

No. Recommendation GoR LoE Sources
4.11 When a woman presents with PMB for the first time and her endometrial thickness is ≤ 3 mm, then she should undergo sono graphic and clinical examination after three months. B 1 [69]
4.12 Histological investigations must be carried out if the clinical symptoms persist or reoccur or if there is an increase in endometrial thickness. EC
2.4 Diagnostic imaging procedures
2.4.1 General remarks on imaging procedures

2.4.2 Basic diagnostic imaging procedures
2.4.2.1 Chest X-ray

The IKNL and ACR guidelines recommend taking chest X-rays in 2 different views when making a primary diagnosis of endometrial cancer [71, 72]. It is a basic investigative procedure which primarily aims to assess the patient’s cardiopulmonary status preoperatively and to detect and evaluate any rare pulmonary metastases. Preoperative chest radiographs show initial findings which can be used during potential follow-up examinations.

Although pulmonary metastases are rare at the first manifestation of endometrial cancer, they lead to FIGO stage IV. In a retrospective multicenter study, Amkreutz et al. [73] reported that pulmonary metastases of endometrial cancer were detected in the chest radiographs of 1.3% (7 of 541) patients. All affected patients had high-risk subtypes of endometrial cancer (serous, clear-cell or poorly differentiated endometrioid), and the incidence of pulmonary metastases was 4.1% for these subtypes. No pulmonary metastases were detected in the chest radiographs of patients with low-risk endometrial cancer subtypes. 243 patients did not undergo thoracic imaging as a primary diagnostic procedure. The authors concluded that thoracic imaging was not required to detect metastasis in patients with low-risk subtypes of endometrial cancer. According to the study by Amkreutz et al. [73], around 4% of patients with high-risk subtypes had pulmonary metastasis, and the detection of metastases could be therapeutically relevant for these patients.

2.4.2.2 Abdominal ultrasound

Abdominal ultrasound is part of the basic workup, particularly to assess the internal organs including any possible preexisting urinary transport disorder. Evaluating the lesser pelvis and the retroperitoneum is difficult because of the superimposition of intestinal gases. This guideline concurs with the ACR guideline [72] which considers transabdominal ultrasound to be an unsuitable method for staging endometrial cancer.

2.4.2.3 Transvaginal ultrasound

2.4.3 Tomography as a diagnostic workup method to determine local spread

No. Recommendation GoR LoE Sources
4.14 After obtaining histological confirmation of primary endometrial cancer, transvaginal ultrasound should be carried out to evaluate the extent of myometrial infiltration and cervical infiltration. B 3 [70]

4.15 Preoperative imaging using transvaginal ultrasound is done to document findings and plan the surgical procedure, even if definitive loco-regional staging is only possible following histological examination after surgery. EC

2.4.4 Imaging procedures for distant metastasis

No. Recommendation GoR LoE Sources
4.19 If there is a reasonable suspicion of distant metastases, tomography (and bone scintigraphy if necessary) should be carried out to evaluate distant metastasis and plan treatment. B 3 [71, 72, 76]
2.5 Pathology

2.5.1 Morphology of endometrial cancer

Table 5 The dualistic model of endometrial cancer.

|                      | Type I endometrial cancer | Type II endometrial cancer |
|----------------------|---------------------------|---------------------------|
| Estrogen-associated  | yes                       | no                        |
| Endometrium          | usually hyperplastic      | usually atrophic; SEIC    |
| Receptor positivity  | usually positive          | usually negative or weakly positive |
|                      | Age 55–65 years           | 65–75 years               |
| Prognosis            | depends on the stage, usually favorable | depends on the stage, usually poor |
| Stage                | usually FIGO stage I      | usually FIGO stage II–IV |
| Histological subtype | endometrioid + variants; mucinous | serous, clear-cell |
| Molecular alterations| PTEN inactivation          | p53 mutations             |
|                      | microsatellite instability | E-cadherin inactivation    |
|                      | β-catenin mutations        | PIK3CA alterations        |
| Molecular types      | POLE ultramutated          | copy number high          |
| (TCGA)               | microsatellite instability | (serous-like)             |

Table 6 2014 WHO classification of endometrial hyperplasia compared to earlier classifications [78].

| Dallenbach-Hellweg classification | 1994/2003 WHO classification | 2014 WHO classification |
|-----------------------------------|------------------------------|-------------------------|
| Glandular cystic hyperplasia      | Simple hyperplasia without atypia | Endometrial hyperplasia without atypia |
| Grade 1 adenomatous hyperplasia   |                              |                         |
| Grade 2                           | Complex hyperplasia without atypia |                         |
| Grade 3                           | Simple atypical endometrial hyperplasia | Atypical endometrial hyperplasia/EIN* |
| Complex atypical endometrial hyperplasia |                         |                         |

* EIN = endometrial intraepithelial neoplasia

Table 7 Histopathological classification of endometrial cancer [78, 79].

- Endometrioid adenocarcinoma
- Endometrioid adenocarcinoma variants
  - secretory variant
  - ciliated cell variant
  - villoglandular variant
  - variant with squamous differentiation
- Mucinous adenocarcinoma
- Serous adenocarcinoma
- Clear-cell adenocarcinoma
- Mixed carcinoma
- Undifferentiated carcinoma
  - monomorphic type
  - dedifferentiated type
- Neuroendocrine tumors
  - well differentiated neuroendocrine tumor (carcinoid)
  - poorly differentiated small-cell neuroendocrine carcinoma
  - poorly differentiated large-cell neuroendocrine carcinoma
- Other carcinomas

Carcinosarcomas of the endometrium used to be discussed in the S2K-guideline “Sarcomas of the Uterus”, Version 1.0, 2015, AWMF Registry Number: 015/074, http://www.awmf.org/leitlinien/detail/ll/015-074.html; they are now described in the S3-guideline “Diagnosis, Therapy and Follow-up of Patients with Endometrial Cancer” [80].

2.5.2 Staging of endometrial cancer

Table 5 The dualistic model of endometrial cancer.

No. | Recommendation | GoR | LoE  | Sources |
----|----------------|-----|------|---------|
4.20| The terminology and morphological workup of endometrial hyperplasia must be based on the most current version of the WHO classification. | EC  |     |         |
### 2.5.3 Frozen section analysis for endometrial cancer, malignant Müllerian mixed tumors and AEH

| No. | Recommendation | GoR | LoE | Sources |
|-----|----------------|-----|-----|---------|
| 4.23 | Intraoperative histological examination may be carried out if there is a suspicion of stage pT1b and/or pT2 disease. | EC | | |
| 4.24 | If the surgeon is of the opinion that frozen section analysis is needed to assess the depth of myometrial infiltration and/or infiltration of the endocervical stroma of the endometrial cancer, then these two parameters must be assessed macroscopically and microscopically. | EC | | |
| 4.25 | Frozen section analysis must not be carried out for the purpose of grading or to determine the histological tumor type. | EC | | |
| 4.26 | The fallopian tubes and ovaries must be assessed macroscopically during intraoperative frozen section analysis; findings suspicious for metastasis must be examined histologically. | EC | | |

### 2.5.4 Tissue workup

| No. | Recommendation | GoR | LoE | Sources |
|-----|----------------|-----|-----|---------|
| 4.27 | Tissue samples obtained by (fractional) curettage or endometrial biopsy must be completely embedded. | EC | | |
| 4.28 | The report on the findings of (fractional) curettage or endometrial biopsy must provide information on the evidence for and type of endometrial hyperplasia. If a carcinoma is detected, its histological tumor type must be defined based on the current WHO classification. If there is evidence of tumor tissue in the cervical part of the fractional curettage specimen, every effort must be made to find evidence of or exclude endocervical stroma infiltration. | EC | | |
| 4.29 | The morphological workup of hysterectomy specimens must be carried out in such a way that all therapeutically and prognostically relevant parameters can be determined. The diagnostic workup must be based on the currently valid WHO classification of tumor types and the current TNM classification for staging. | EC | | |

### 2.5.5 Workup and diagnosis of omentectomy specimens in endometrial cancer

| No. | Recommendation | GoR | LoE | Sources |
|-----|----------------|-----|-----|---------|
| 4.32 | The ovaries of patients with endometrial cancer should be completely embedded and must include the hilum of the ovary. The workup of the fallopian tubes should be guided by the SEE-FIM protocol. | EC | | |
2.5.6 Workup and diagnosis of lymphadenectomy specimens in endometrial cancer

| No. | Recommendation | GoR | LoE | Sources |
|-----|----------------|-----|-----|---------|
| 4.34 | All resected lymph nodes in lymphadenectomy specimens obtained during surgery of a patient with endometrial cancer must be completely embedded and examined histologically. | EC | |

| No. | Recommendation | GoR | LoE | Sources |
|-----|----------------|-----|-----|---------|
| 4.35 | Lymph nodes with a maximum extent of up to approx. 0.3 cm should be embedded in their entirety and larger lymph nodes should be either halved along their longitudinal axis or sliced into sections and also completely embedded. | EC | |

| No. | Recommendation | GoR | LoE | Sources |
|-----|----------------|-----|-----|---------|
| 4.36 | Isolated tumor cells are defined as the detection of individual tumor cells or tumor cell complexes with a maximum diameter of < 0.2 mm. Micrometastases are defined as the histological confirmation of tumor cells in lymph nodes with diameters of ≥ 0.2 mm but not bigger than 0.2 cm. | EC | |

2.5.7 Sentinel lymph nodes (investigated in the context of clinical studies)

| No. | Recommendation | GoR | LoE | Sources |
|-----|----------------|-----|-----|---------|
| 4.37 | The report on the findings of lymphadenectomy specimens obtained from patients with endometrial cancer must include the following information:  
- Information about the number of affected lymph nodes compared to the number of resected lymph nodes mapped to the location where the respective lymph node was resected (pelvic, para-aortal),  
- Information about the diameter of the largest lymph node metastasis in mm/cm,  
- Information about the absence/evidence of any extracapsular spread of lymph node metastasis,  
- Information about any evidence of isolated tumor cells in the lymph node as well as any evidence of lymph node invasion in perinodal fatty tissue and/or the lymph node capsule. | EC | |

2.5.8 Morphological prognostic factors

A detailed discussion of morphological prognostic factors is available (in German) in the long version of the guideline [80].

A risk stratification for endometrial cancer based morphological factors developed in consensus by the European Society for Medical Oncology (ESMO), the European Society for Radiotherapy & Oncology (ESTRO) and the European Society of Gynaecological Oncology (ESGO) is summarized in Table 8 [81, 82].
### Table 8 Risk stratification of endometrial cancer according to the European Society for Medical Oncology (ESMO), the European Society for Radiotherapy & Oncology (ESTRO) and the European Society of Gynaecological Oncology (ESGO) [81, 82].

| Risk group       | Characteristics                                                                                                                                 |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Low risk         | endometrioid endometrial cancer, G1, G2, < 50% myometrial infiltration, L0                                                                     |
| Low-intermediate risk | endometrioid endometrial cancer, G1, G2, ≥ 50% myometrial infiltration, L0                                                                    |
| High-intermediate risk | endometrioid endometrial cancer, G3, < 50% myometrial infiltration, L0 or L1, endometrioid endometrial cancer, G1, G2, L1, ≤/= 50% myometrial infiltration |
| High risk        | endometrioid endometrial cancer, G3, ≥ 50% myometrial infiltration, L0 or L1, FIGO/TNM stage II/T2, endometrioid endometrial cancer, FIGO/TNM stage III/T3, R0, non-endometrioid endometrial cancer (serous/clear-cell, undifferentiated, MMMT) |

### Table 9 Tumor risks and mutation detection rates.

| Inheritance       | Lynch syndrome (LS)       | Cowden syndrome (CS)       |
|-------------------|---------------------------|---------------------------|
|                    | autosomal-dominant        | autosomal-dominant        |
| Causative genes   | MLH1, MSH2, MSH6, PMS2, EPCAM | PTEN                      |
| Frequency in the general population | 1:300–500                 | 1 : 200 000? [93]         |
| Frequency in unselected patient cohorts with endometrial cancer | 2–4%                      | < 0.5%                    |
| Frequency in patients with endometrial cancer < 50 years | 9–10%                     |                           |
| Endometrial cancer of the lower uterine segment | 14–29% [91]              |                           |
| Spectrum of mutations in LS-associated endometrial cancer | PMS2: 5%, MLH1: 16%, MSH2: 26%, MSH6: 53% |                           |
| Lifetime risk of endometrial cancer up to the 70th year of life (general population around 2.6%) [107] | Overall: 16–54%, MLH1: 18–54%, MSH2: 21–30%, MSH6: 16–49%, PMS2: 12–15% [83, 86, 94–97] | Overall: 19–28%[98, 99] |
| Average patient age at onset of LS-/CS-associated endometrial cancer (years) | Overall: 50 years MLH1: 44 (29–54), MSH2: 50 (36–66) MSH6: 55 (26–69), PMS2: 57 (44–69) [84, 87–89, 100] | 48–53 [101, 102] |
| Metachronous cancer after a diagnosis of endometrial cancer | 10 years: 25%, 15 years: 50%, 20 years: > 50% [84, 85, 87, 103] |                           |
| Endometrioid type | 57–85%                    | 84% [102]                 |
| Other common tumors/tumor spectrum | colorectal cancer, duodenal cancer, gastric cancer, ovarian cancer, brain tumors, urothelial carcinoma | thyroid cancer, breast cancer, renal cancer, brain tumors, skin tumors |
### 3.2 Risk determination

| No. | Recommendation                                                                                                                                                                                                 | GoR | LoE | Sources  |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|----------|
| 10.2 | An important tool for assessing a genetically caused increased risk of endometrial carcinoma is a medically obtained patient history and family history, taking specific clinical criteria into account (in Lynch syndrome: Amsterdam I/II criteria, revised Bethesda criteria). | EC  |     |          |

### 3.3 Procedure on suspicion of a hereditary form of endometrial cancer

| No. | Recommendation                                                                                                                                                                                                 | GoR | LoE | Sources  |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|----------|
| 10.3 | If there is a suspicion that the patient has a hereditary form of endometrial cancer, the patient should be referred to a certified gynecological cancer center.                                                  | EC  |     |          |

### 3.4 Psychosocial care

| No. | Recommendation                                                                                                                                                                                                 | GoR | LoE | Sources  |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|----------|
| 10.4 | Persons who have already developed disease, carriers, and people at risk for monogenic hereditary disease and an increased risk of developing endometrial cancer and other malignancies should be made aware of their options and the benefit of psychosocial counselling and care. | EC  |     |          |

### 3.5 Clarifying clinically suspicious findings

| No. | Recommendation                                                                                                                                                                                                 | GoR | LoE | Sources  |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|----------|
| 10.5 | If at least one criterion of the revised Bethesda criteria has been met, the (molecular) pathology of the tumor tissue must be investigated further for changes typical for Lynch syndrome. This includes investigating the immunohistochemical expression of DNA mismatch repair proteins, microsatellite analysis and possibly the methylation of MLH1 promoters. | A   | 3   | [84, 87–89, 100] |

| No. | Recommendation                                                                                                                                                                                                 | GoR | LoE | Sources  |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|----------|
| 10.6 | A (molecular-)pathological examination for Lynch syndrome in tumor tissue should be carried out in patients under the age of 60 in whom an endometrial carcinoma is diagnosed.                                      | B   | 3   | [84, 87–89, 100, 104] |

| No. | Recommendation                                                                                                                                                                                                 | GoR | LoE | Sources  |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|----------|
| 10.6.1 | It is still a matter of controversy whether these examinations of tumor material require medical information and counseling to be provided and consent to be given in accordance with the requirements of the law on genetic diagnosis. Until an authoritative interpretation of the gene diagnosis law relative to Lynch syndrome screening in endometrial carcinoma tumor material becomes available, the appropriate information and consent in accordance with the genetic diagnosis law should be ensured before the above molecular-pathological analyses of tumor material are carried out. | EC  |     |          |

| No. | Recommendation                                                                                                                                                                                                 | GoR | LoE | Sources  |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|----------|
| 10.7 | In patients from families in which the Amsterdam criteria are met, but whose tumor tissue does not show the abnormalities typical of Lynch syndrome, Lymph syndrome is not excluded. For further assessment and additional diagnosis if appropriate, genetic counseling should therefore be carried out. | EC  |     |          |
### 3.6 Search for germline mutations

| No. | Recommendation                                                                 | GoR | LoE   | Sources                                      |
|-----|--------------------------------------------------------------------------------|-----|-------|----------------------------------------------|
| 10.8| If a patient has abnormal molecular pathology findings suspicious for Lynch syndrome, the patient must be offered the option of searching for germline mutations in the probably affected MMR gene(s). | A   | 3     | [84, 87–89, 100]                            |
| 10.8.1| If the clinical criteria for another hereditary tumor syndrome with a higher risk of developing endometrial cancer have been met, the search for mutations in the probably affected genes must be carried out directly. | EC  |       |                                              |

#### Fig. 3 Diagnostic workup of tumor samples to investigate for Lynch syndrome [80], [rerif]

- Patient is informed in accordance with the German Genetic Diagnostics Act
- Immunohistochemical examination of MMR proteins (MLH1, MSH2, MSH6, PSH2) in the endometrial cancer tissue
- MLH1 and PSH2 deficiency
  - Methylation analysis
  - Methylation of the MLH1 promoter?
    - No
    - Yes
- Other pattern of deficiencies
  - No deficiency
  - Microsatellite analysis
    - Highly instable (MSI-H)?
    - No
  - Yes
- Interpretation: no indication of Lynch syndrome
- Interpretation: indication of Lynch syndrome in the tumor
- Genetic counselling and diagnostic workup of molecular genetics

### 3.7 Procedure when evidence of mutations is absent or uncertain

| No. | Recommendation                                                                 | GoR | LoE | Sources |
|-----|--------------------------------------------------------------------------------|-----|-----|---------|
| 10.9| If molecular genetic testing was unable to clearly identify a pathogenic germline mutation, this does not mean that the patient has no hereditary tumor syndrome. | EC  |     |         |

### 3.8 Primary prevention for high-risk groups

| No. | Recommendation                                                                 | GoR | LoE | Sources |
|-----|--------------------------------------------------------------------------------|-----|-----|---------|
| 10.10| Due to the lack of any data for these special risk groups, no separate recommendations can be given regarding the benefits of dietary measures or chemoprevention for primary prevention in these groups compared to the normal population. | EC  |     |         |
3.9 Procedure for persons at risk for Lynch or Cowden syndrome

3.10 Endometrial cancer screening in patients with Lynch or Cowden syndrome

3.11 Syndrome-specific screening procedures for patients or high-risk carriers of Lynch or Cowden syndrome

Conflict of Interest
For conflict of interests see guideline report: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Endometriumkarzinom/LL_Endometriumkarzinom_Leitlinienreport_1.0.pdf, last accessed on 13.08.2018.

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