

Interdisciplinary S2k guidelines on the diagnosis and treatment of endometrial carcinoma

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Introduction

The first recommendations for the diagnosis and treatment of endometrial cancer had been published by the Uterus Commission of the Gynecological Oncology Working Group (AGO), affiliated to the German Society for Gynecology and Obstetrics (DGGG) and the German Cancer Society (DKG), in 1999 (S1 guideline). This guideline was updated twice, on the S1-level, most recently in 2006. Between October 2007 and 2008 another update was performed on the S2k level by an interdisciplinary group of experts representative of the users. The methodologic procedure was based on the regulations described in the DKG's working instructions for producing interdisciplinary consensus-based guidelines.

The process of developing consensus-based guidelines (S2 konsensus guidelines) does not provide the systematic preparation of the evidence; instead, a discussion and critical evaluation of the published literature are carried out by the members of the guideline group. During a consensus conference, the participants also have an opportunity to make suggestions for ways of expressing the detailed guideline text in more concrete ways and supplementing it. The basic principles and criteria for the grading of the recommendations are discussed at the start of the consensus procedure. Changes and additions to the guideline on the basis of the voting results during the

nominal group process are carried out by the guideline coordinators. The revised version is sent in written form to all the members of the guideline group for final comments and adoption.

Epidemiology and risk factors

Endometrial cancer is the fourth most frequent cancer among women in Germany. EC is the ninth most frequent cause of cancer death. Type I EC (typically endometrioid EC) is related to exposition to unopposed estrogens. For the more aggressive type II EC (typically serous EC, clear cell EC) only old age and preceding radiotherapy of the uterus have been identified as risk factors.

Early detection and screening

Statements

- General screening cannot be recommended
 - There is no evidence that the mortality can be reduced as a result of screening in high-risk populations
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Screening with endovaginal ultrasonography and subsequent endometrial biopsy may be useful in high-risk groups (obesity, diabetes mellitus, known endometrial hyperplasia, hereditary nonpolyposis colorectal cancer syndrome). Even in these women, however, there is a lack of studies to demonstrate the efficacy of screening. In HNPCC syndrome, prophylactic hysterectomy (+bilateral salpingoophorectomy) may be useful for prevention of EC (+ovarian cancer).

For the Uterus Commission of the Gynecological Oncology Working Group (AGO).

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Diagnosis

Statements

- It is necessary to obtain a histological sample in order to confirm the diagnosis
 - There are no imaging techniques capable of replacing surgical staging in endometrial carcinoma. In patients who are inoperable due to comorbidities, magnetic resonance imaging may be helpful for treatment planning
-

Postmenopausal bleeding and all abnormal bleeding patterns in premenopausal patients with one of the risk factors mentioned above should be examined as follows:

- gynecological examination.
- Transvaginal ultrasonography (suspicious, if endometrial thickness of more than 5 mm in postmenopausal women with bleeding). In postmenopausal women on hormone or SERM therapy and in premenopausal patients measurement of the endometrial thickness alone is not diagnostically useful.
- Hysteroscopy and fractionated curettage.

Clinical/histopathological diagnosis

Statements

- The histological classification of endometrial carcinomas and their precursor lesions is carried out in accordance with the WHO requirements
 - Minimum requirements for reporting histopathological findings in endometrial carcinoma are: tumor type, grading, depth of invasion into the Myometrium, cervical infiltration, lymph-node involvement, R classification, and vascular and lymphatic invasion
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The “term” adenomatous hyperplasia grades I–III should not longer be used.

As both, serous and clear cell EC are associated with a poor prognosis, even at low tumor stages, this diagnosis must be explicitly mentioned, even if there is only focal evidence of it in a type I carcinoma or in an endometrial polyp.

It is only when there is certain evidence of infiltration of the EC into the endocervical glands or endocervical stroma that curettage is capable of leading to a diagnosis of stage T2a or T2b.

The value of intraoperative macroscopic assessment and/or frozen-section of the hysterectomy specimen is uncertain to define the depth of myometrial invasion.

Structures for providing care

Care for patients with preinvasive lesions or EC should be provided in collaboration between registered gynecologists in private practice and specialized centers for gynecological oncology, that work in accordance with the certification criteria of the AGO, the German Society of Gynecology and Obstetrics (DGGG) and the German Cancer Society (DKG).

Patient information

Statements

- Information materials (print or Internet media) that are of high quality and produced with appropriate specialist competence should be provided, in accordance with the quality requirements set out in the Guideline on Gynecological Information. By communicating the risks in a comprehensible way (including details of incidences, rather than relative percentages), these materials should provide patients with support in taking independent decisions for or against medical procedures
 - Information should be communicated to the patient both comprehensively and accurately, observing the following basic principles of patient-centered communication
 - (1) Expression of empathy and active listening
 - (2) Direct and sensitive ways of touching on difficult subjects
 - (3) If possible, avoidance of specialized medical terms, or with explanations of specialist terms being given if necessary
 - (4) Strategies for improving understanding (repetition, summing up of important information, use of graphics, etc.)
 - (5) Encouraging the patient to ask questions
 - (6) Permission and encouragement to express emotions
 - (7) Offering further assistance (e.g., from self-help groups, psycho-oncology, psychological cancer counseling)
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Basic principles of treatment for primary EC

Decision making regarding the appropriate treatment is carried out in an interdisciplinary tumor board involving gynecological oncology, radiotherapy, anesthesiology, pathology and the patient.

Only if there are contraindications for surgical treatment, primary radiotherapy and/or systemic treatment become an option.

Treatment of precursors of EC

Statements

- Hyperplasia of the endometrium without atypia can be treated conservatively
 - Hyperplasia of the Endometrium with atypia is associated with a high risk of malignant change. Conservative treatment should only be attempted if the patient wishes to have a child and a high degree of compliance can be expected
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In patients with atypical endometrial hyperplasia there is a risk of 30% of progression to invasive EC and a risk of 20–40% of invasive EC in the hysterectomy specimen that has been missed by curettage. This risk has to be carefully balanced against the wish for fertility preservation.

Conservative treatment for early EC

Statement

- Conservative therapy can be considered for women with well-differentiated, progesterone receptor-positive endometrioid endometrial carcinoma in clinical stage 1a who strongly wish to have a child
-

Due to the high risk of recurrence after conservative treatment, surgical therapy appropriate to the stage is required if the patient’s wish for children has been fulfilled or abandoned.

Surgical treatment

Statements

- Surgical treatment for endometrial carcinoma should include removal of a cytological sample from the abdominal cavity, hysterectomy, bilateral adnexectomy and pelvic and para-aortic lymphadenectomy up to the renal pedicle
 - In the presence of serous or clear cell carcinoma, multiple peritoneal biopsies should be taken and omentectomy should be carried out
 - In stages pT1a, pT1b and in the presence of G1 or G2, lymphadenectomy is optional
 - In stage pT2b, the parametria should also be resected
 - In advanced stages, resection of the tumor should be as complete as possible, in order to improve the effectiveness of adjuvant systemic and radiotherapeutic measures
-

If a lymphadenectomy has not been performed since stage 1a or 1b and G1 or G2 had been suspected but the

final histology shows a higher stage or grade or high risk histology, the surgical staging should be completed in a second operation, if possible.

Similarly, if a simple hysterectomy has been performed as no EC was suspected, and the pathologist describes an unexpected EC, an adequate surgical staging should be performed in a second operation.

Lymph node removal should not be carried out as a sampling procedure, but definitely as systematic lymphadenectomy, including both, the pelvic and para-aortic nodes up to the renal veins. At least 15 pelvic and 10 para-aortic nodes should be removed.

If there is relevant comorbidity, lymphadenectomy may be omitted. Lack of experience on part of the surgeon with lymphadenectomy in obese patients, or a lack of infrastructure for caring for patients with multiple morbidities cannot be used to justify failure to carry out lymphadenectomy. In these cases, the patient should be referred to a center for gynecological oncology.

Routine frozen-section evaluation of the hysterectomy specimen or pelvic lymph nodes is not recommended generally, as this method is not sufficiently reliable, and complete pelvic and para-aortic lymphadenectomy is optional in patients who are at low risk. Frozen-section evaluation, however, may be useful in relation to specific issues in individual patients.

If carried out by a surgeon familiar with the technique, laparoscopic lymphadenectomy in combination with laparoscopy-assisted vaginal hysterectomy/bilateral salpingo-oophorectomy appears to be as safe as the open abdominal procedures.

Radiotherapy

Statements

- Primary radiotherapy for endometrial carcinoma is indicated if the patient is not operable due to comorbidity
 - In patients with a high risk of local recurrence, adjuvant radiotherapy should be carried out in order to reduce the risk of locoregional recurrence
 - Adjuvant radiotherapy has no effect on the overall survival in stages I and II
 - There are no adequate data on this topic for more advanced stages
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Recent randomized controlled trials and respective metaanalyses have shown that teletherapy of the pelvis significantly reduces the loco-regional recurrence rate in stages I and II EC, but has no beneficial effect on overall survival. The effects of brachytherapy and teletherapy reducing locoregional recurrence in stage I are comparable.

In particular, if a systematic lymphonodectomy has demonstrated a pN0 status in type I EC stages I and II, teletherapy is not indicated.

Systemic therapy

Adjuvant systemic therapy

Statements

- Adjuvant endocrine therapy with gestagens has no therapeutic effect
 - In optimally operated endometrial carcinoma in stages III and IV, chemotherapy is an alternative to radiotherapy
 - In endometrial carcinomas in stages IC G3, II G3, and III, adjuvant chemotherapy may represent an alternative to radiotherapy
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A few randomized controlled trials have demonstrated that adjuvant systemic chemotherapy might be superior to or equivalent with traditional radiotherapy in high risk EC or advanced EC. As the data are not sufficient to recommend a replacement of adjuvant radiotherapy by adjuvant chemotherapy, the latter is classified as possible alternative to radiotherapies in the above mentioned situations.

Palliative systemic therapy

Statements

- If surgery and/or radiotherapy are no longer possible in patients with recurrences or metastases, gestagen treatment is recommended for patients with progesterone receptor-positive carcinomas and asymptomatic metastases
 - If progression occurs during endocrine therapy, in receptor-negative tumors, and when there are symptomatic and life-threatening tumor signs, palliative chemotherapy may be useful
 - The indication for systemic combination chemotherapy regimens needs to be established strictly, in view of their lack of effect or only marginal effect on the overall survival
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Recurrences, metastases

Statements

- Resectable recurrences of endometrial carcinoma should be treated surgically
 - In inoperable patients, radiotherapy should be carried out
 - If neither surgery nor radiotherapy is possible, palliative systemic therapy should be carried out
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Supportive therapy

Statement

- Supportive therapy in accordance with the guidelines is required for prophylaxis against and minimization of treatment-related or tumor-related symptoms
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Apart from general supportive measures (antiemetic treatment, prevention and treatment of granulocytopenia, anemia, etc.) special consideration must be given in EC patients to local side effects (enteritis, proctitis, cystitis, lymphedema, vaginal dryness, vaginal stenosis and disturbed sexual function).

Psycho-oncology

Statements

- Psycho-oncological care for patients with endometrial carcinoma is an integral component of oncological diagnosis, treatment, rehabilitation and follow-up and represents an interdisciplinary task
 - The patients should be informed at an early stage about the availability of inpatient and outpatient psycho-oncological assistance and should receive skilled psycho-oncological care if needed
 - The patient's quality of life must be regularly assessed during treatment, rehabilitation, and follow-up, also in order to assess the potential need for psycho-oncological treatment
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Rehabilitation

Statement

- All patients should be informed and advised in detail by the attending physician regarding the statutory facilities for subsequent treatment, regular therapy, and outpatient rehabilitation
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Follow-up care

Statements

- Aspects requiring attention during the follow-up include: genital atrophy phenomena (dyspareunia), lymphedema in the lower extremities, radiogenic reactions in the ureter, bladder and bowel, and hormonal deficiencies
 - Since a curative approach is possible if a local recurrence is recognized at an early stage, a 3-month follow-up interval should be observed in the first 2–3 years after primary therapy, with speculum examination, vaginal and rectal examination, and ultrasonography if appropriate
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continued

Statements

- More detailed imaging diagnosis is only required in symptomatic patients
- The following points should be addressed in discussion with the patient during the follow-up:
 - (1) Transient and long-term effects of the disease and treatment
 - (2) Assistance available (self-help groups, psychosocial cancer counseling services)
 - (3) Psycho-oncological/psychotherapeutic treatment facilities
 - (4) Sexuality and relationship
 - (5) Quality of life

EC is a very common cancer. Nevertheless evidence regarding optimal diagnosis and treatment of this disease is rather poor as compared to other cancers. High quality clinical trials with sufficient numbers of participants are necessary to define the optimal modalities.

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Appendix

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