clinical recommendations

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Endometrial carcinoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

The crude incidence of endometrial carcinoma in the European Union is 16 cases/100 000 women/year (range 13–24). The mortality is 4–5 cases/100 000/year. The lifetime risk of developing endometrial carcinoma is ~1.7–2%, and age-standardized incidence rates continue to rise in most developed countries.

diagnosis

The diagnosis of endometrial carcinoma requires histopathological confirmation. This diagnosis is made according to the WHO pathological classification. About 80% of endometrial carcinomas are of endometrioid type. Serous (5–10%), clear cell (1–5%), mucinous, mixed, squamous cell, transitional cell and undifferentiated carcinomas are other established subtypes. Endometrial carcinosarcoma is now considered a special, poor-prognosis subtype of endometrial carcinoma.

staging and risk assessment

Endometrial carcinoma is a surgically staged disease. The minimal procedure should include the acquisition of peritoneal fluid or washings, a thorough exploration of the abdominal cavity and pelvic and para-aortic nodal areas, and a total hysterectomy with bilateral salpingo-oophorectomy. In high-risk cases retroperitoneal lymph node dissection and omentectomy (for serous carcinomas) are often recommended, though the effect of these procedures on survival is debated [III, B].

The most widely used staging system is the one endorsed by the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) as given in Table 1.

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degree of differentiation:

Cases of endometrial carcinoma should be graded according to their degree of histological differentiation, as follows:

G1, a non-squamous, non-morula solid growth pattern comprises ≤5% of the tumor;
G2, a non-squamous, non-morula solid growth pattern comprises 5–50% of the tumor;
G3, a non-squamous, non-morula solid growth pattern comprises >50% of the tumor.

- Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade 1 or 2 tumor by one.
- Before surgery, patients should have a chest X-ray, clinical and gynecological examination including transvaginal ultrasound, blood counts, liver and renal function profiles. A CT scan of the abdomen and retroperitoneal nodes may be helpful in determining extra-uterine spread. Contrast-enhanced dynamic MRI is the best way to assess the uterine and locoregional pelvic extension of the disease [I, A]. There is, however, no fully reliable method to assess an individual patient's risk category either pre- or intra-operatively (frozen section). The preoperative histological diagnosis (type and grade) based on any type of endometrial sampling is changed at final histological evaluation in up to 25% of cases.
- Established, independent prognostic factors are FIGO surgical stage, histological grade, depth of myometrial invasion, histological type, tumor diameter, lymph–vascular space involvement, endocervical stromal invasion and patient age.
- About 75% of patients present with stage I disease and can be subdivided into three risk categories with regard to disease relapse and survival:

(i) low risk

- stage Ia/Ib, grade 1 or 2, endometrioid histology

(ii) intermediate risk

- stage Ic, grade 1 or 2, endometrioid histology
- stage Ia/Ib, grade 3, endometrioid histology

(iii) high risk

- stage Ic, grade 3, endometrioid histology
- stage Ia or Ib or Ic, serous, clear cell, small cell or undifferentiated histology.

Table 1. Staging of endometrial cancer as endorsed by the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO)

Stage I	Confined to the uterus
Ia	Tumor limited to the endometrium
Ib	Invasion to less than half of the myometrium
Ic	Invasion to more than half of the myometrium
Stage II	Extension to the uterine cervix
IIa	Endocervical glandular involvement only
IIb	Cervical stromal invasion
Stage III	Extension beyond the uterus
IIIa	Tumor invades serosa and/or adnexa, and/or positive peritoneal cytology
IIIb	Vaginal involvement
IIIc	Metastasis to pelvic or para-aortic lymph nodes
Stage IV	Invasion in neighboring organs or distant metastases
IVa	Tumor invasion of the bladder and/or bowel mucosa
IVb	Distant metastases including intra-abdominal or inguinal lymph nodes

treatment plan

The type of surgery and postoperative therapy depends on the stage and other clinicopathological risk factors.

stage I

(i) low-risk group: no adjuvant therapy.

(ii) intermediate-risk group: adjuvant pelvic radiotherapy significantly reduces the risk of pelvic/vaginal relapses, but has no impact on overall survival (OS) [I, A]. Within the intermediate-risk group, in patients aged ≥60 years, with deeply invasive G1 or G2 or superficially invasive G3 tumors, the loco-regional relapse rate is >15%, and adjuvant radiotherapy is recommended [II, B].

(iii) high-risk group: pelvic radiotherapy is recommended in order to increase loco-regional control. Adjuvant, platinum-based chemotherapy gives a significantly improved OS and progression-free survival (PFS) compared with adjuvant radiotherapy [I, A].

stage II

- Stage IIa: treated as stage I.
- Stage IIb: extended radical hysterectomy, bilateral salpingo-oophorectomy and lymph node dissection. Patients who had an extrafascial hysterectomy, or who have high-risk disease (according to definitions given for stage I) are recommended to have adjuvant pelvic (with or without intravaginal) radiotherapy.
- The adjuvant administration of progestational agents in low-stage endometrial cancer does not increase survival and is not recommended [I, A].

stages III and IV

- Maximal surgical cytoreduction is considered in patients with good performance status [III, B].
- Patients with stage III disease solely on the basis of positive peritoneal cyology are treated as patients with stage I or II disease, based on the other clinicopathological data.
- Pelvic control is increased with pelvic radiotherapy.
- Cisplatin, carboplatin, anthracyclines and paclitaxel have single-agent objective response rates.
- The combination of doxorubicin with cisplatin and paclitaxel (with bone marrow support) significantly improves PFS and OS compared with cisplatin and doxorubicin, but at the cost of higher toxicity, making it less attractive in this patient population [I, A].
- Cisplatin and doxorubicin significantly improved PFS and OS in patients with low residual stage III and IV disease compared with whole abdominal radiation therapy with pelvic boost [I, A].
- Because of toxicity considerations, an alternative option may be the combination of carboplatin and paclitaxel [III, B].
- Dosages, number of chemotherapy courses and response evaluation as recommended for advanced-stage ovarian cancer.
- Progestational agents, e.g. medroxyprogesterone acetate 200 mg daily, are active in steroid receptor-positive tumors (mostly G1 and G2 lesions) [III, B].

follow-up

Most recurrences will occur within the first 3 years after treatment, and 3- to 4-montly evaluations with history, physical and gynecological examination are usually recommended. Follow-up intervals of 6 months are recommended during the fourth and fifth years, and annually thereafter. No impact on survival of a routine follow-up strategy has been demonstrated. However, since a significant number of relapses occur isolated in the vagina or pelvis, early detection and possibly curative treatment of these should be the main focus of follow-up. Routine technical examinations such as PAP smears or imaging studies are of unproven benefit.

note

Levels of evidence [I–V] and grades of recommendations [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified clinical practice by the experts and the ESMO faculty.

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