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Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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incidence and epidemiology

Endometrial cancer is the most common malignancy of the female genital tract in the world and the seventh most common cause of death from cancer in women in western Europe. Every year ~7406 new cases are registered in the UK, 88 068 in the European Union and 40 102 in North America.

More than 90% of cases occur in women older than 50 years of age, with a median age of 63 years. In the UK, the incidence in older women (aged 60–79) increased by >40% between 1993 and 2007; this was also the case in most European countries. Multiple risk factors have been identified: early onset of menstruation, obesity, nulliparity, late menopause, diabetes mellitus, hypertension, infertility, unopposed estrogen exposure and tamoxifen. In addition, up to 5% of endometrial cancers are associated with Lynch syndrome type II (known as hereditary non-polyposis colorectal carcinoma syndrome); those with this syndrome have a lifetime risk of developing endometrial cancers of 30–60%. There is increasing evidence that the use of combined oral contraceptives decreases the risk of endometrial neoplasia, reducing its incidence in premenopausal and perimenopausal women.

diagnosis

Most cases of endometrial cancer are diagnosed in early stages because of abnormal uterine bleeding as the presenting symptom in 90% of the cases.

The best diagnostic strategy in patients with postmenopausal bleeding still remains controversial. In the past, the principal method of investigation was dilatation and curettage (D&C). Now endometrial biopsy and hysteroscopy have almost completely replaced D&C. The Pipelle or the Vabra devices used for endometrial sampling are very sensitive techniques for the detection of endometrial carcinoma (99.6 and 97.1%). A recent study concludes that the first step in the diagnostic pathway should be the measurement of endometrial thickness, using a cut-off point of 3 or 4 mm, followed by endometrial sampling. Saline infusion sonography can be used to distinguish between focal and diffuse pathology. Hysteroscopy should be used as the final step in the diagnostic pathway of women with postmenopausal bleeding.

histopathological characteristics

Two main types of endometrial carcinoma have been recognized on the basis of clinical, pathological and molecular features. Type I or endometrioid adenocarcinomas represent 80% of endometrial carcinomas and serous carcinomas are the prototype of type II carcinomas. Endometrial carcinomas, at least in well-differentiated form, are composed of glands that resemble those of the normal endometrium and can be associated with or preceded by endometrial hyperplasia. In the most widely accepted grading systems, the rate of solid to glandular component (<5% for grade 1 and >50% for grade 3) defines three architectural grades. Serous carcinomas are all high-grade carcinomas. They have several features in common with serous carcinomas of the ovary and Fallopian tube, including the association with a form of intraepithelial serous carcinoma, referred to as 'endometrial intraepithelial carcinoma' (EIC), a lesion which is thought to be the precursor lesion. Clear cell carcinomas are rare, comprising ~1% of endometrial adenocarcinomas. Endometrioid adenocarcinomas frequently show microsatellite instability and mutations of the PTEN, PIK3CA, K-Ras and β-catenin genes. Microsatellite instability is typically found in patients with hereditary non-polyposis colon cancer. The β-catenin gene is more frequently mutated in carcinomas with squamous differentiation. Serous carcinomas are characterized by p53 mutations and chromosomal instability. Clear cell carcinomas have absent reactivity for estrogen and progesterone receptors and low immunoreactivity for p53.

staging and risk assessment

Endometrial cancer is generally staged according to the International Federation of Gynecology and Obstetrics (FIGO)

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system. Since 1988, the FIGO system has recommended surgical staging with systematic pelvic and para-aortic lymphadenectomy. In May 2009, a new FIGO staging system was published, but the existing literature and evidence are based on the old classification (Tables 1 and 2).

The preoperative evaluation includes: chest X-ray, clinical and gynecological examination, transvaginal ultrasound, blood counts, and liver and renal function profiles. Abdominal computed tomography (CT) scan is indicated for investigating extrapelvic disease. Dynamic contrast-enhanced magnetic resonance imaging (MRI) is the best tool to assess the cervical involvement. [^{18}F]Fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT could be useful to detect distant metastases accurately.

Multiple factors have been identified for relative high risk of recurrence in apparent early-stage disease: histological subtype, grade 3 histology, myometrial invasion ≥50%, lymphovascular space invasion (LVSI), lymph node metastases and tumor diameter >2 cm.

In this regard, stage I can be subdivided into three risk categories:

Low risk:	stage IA (G1 and G2) with endometrioid type
Intermediate risk:	stage IA G3 with endometrioid type stage IB (G1 and G2) with endometrioid type
High risk:	stage IB G3 with endometrioid type all stages with non-endometrioid type

Table 1. Staging of endometrial cancer (FIGO, 1988)

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
II	Extension to the uterine cervix
IIa	Endocervical glandular involvement only
IIb	Cervical stromal invasion
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
IV	Invasion in neighboring organs or distant metastasis
IVa	Tumor invasion of the bladder and/or bowel mucosa
IVb	Distant metastases including intra-abdominal or inguinal lymph nodes

surgical treatment

The most adequate surgical technique is still currently debated (Table 3), as is the role of lymphadenectomy in terms of overall survival and recurrence rate. The surgical approach for the treatment of endometrial cancer has traditionally been laparotomy. Nevertheless, in the last 15 years, the use of minimally invasive techniques is widely accepted by many authors. A recent publication of the GOG LAP2 study has shown similar operative outcomes in the minimally invasive surgery group. Laparoscopy seems to provide equivalent results in terms of disease-free survival and overall survival compared with laparotomy, with further benefit: shorter hospital stay, less use of pain killers, lower rate of complications and improved quality of life. Moreover, the robotic approach could be a 'benefit' in obese women.

surgical treatment in stage I endometrial cancer

The standard surgical approach for stage I endometrial cancer consists of total hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy [I, A].

Table 2. Staging of endometrial cancer (FIGO, 2009)

Stage	
I	Tumor confined to the corpus uteri
Ia	No or less than half myometrial invasion
Ib	Invasion equal to or more than half of the myometrium
II	Tumor invades cervical stroma, but does not extend beyond the uterus
III	Local and/or regional spread of the tumor
IIIa	Tumor invades the serosa of the corpus uteri and/or adnexae
IIIb	Vaginal and/or parametrial involvement
IIIc	Metastasis to pelvic and/or para-aortic lymph nodes III C1 Positive pelvic nodes III C2 Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVa	Tumor invasion of bladder and/or bowel mucosa
IVb	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

The role of systematic pelvic lymphadenectomy is an issue of current debate. In an Italian study, 514 patients with stage I endometrial cancer were randomized (excluding stage IA–IB G1 and non-endometrioid histotype). In this study, systematic lymphadenectomy did not improve disease-free or overall survival. In the ASTEC trial, women with malignancies confined to the uterus were randomized. In this trial there was no evidence of benefit on overall survival or recurrence-free survival when pelvic lymphadenectomy was performed. The authors concluded that routine systematic pelvic lymphadenectomy cannot be recommended in women with stage I endometrial cancer, unless enrolled in clinical trials.

Lymphadenectomy is highly important in determining a patient's prognosis and in tailoring adjuvant therapies. Hence, many authors suggest a complete surgical staging for intermediate–high risk endometrioid cancer (stage IA G3 and IB) [II, B].

surgical treatment in stage II endometrial cancer

Traditionally, the surgical approach consists of radical hysterectomy with bilateral salpingo-oophorectomy and systematic pelvic lymphadenectomy with or without para-aortic lymphadenectomy. In stage II, lymphadenectomy is essential to guide surgical staging and adjuvant therapy

surgical treatment in stage III–IV endometrial cancer

Maximal surgical debulking is imperative in patients with a good performance status [III, B]. For distant metastatic disease, palliative surgery could be considered in patients with a good performance status after multidisciplinary decision making.

Table 3. Surgical treatment

Stage I	IA G1–G2	Hysterectomy with bilateral salpingo-oophorectomy
	IA G3	Hysterectomy with bilateral salpingo-oophorectomy ± bilateral pelvic/para-aortic lymphadenectomy
	IB G1 G2 G3	Hysterectomy with bilateral salpingo-oophorectomy ± bilateral pelvic/para-aortic lymphadenectomy
Stage II		Hysterectomy with bilateral salpingo-oophorectomy and bilateral pelvic/para-aortic lymphadenectomy
Stage III		Maximal surgical cytoreduction with a good performance status
Stage IV	IVA	Anterior and posterior pelvic exenteration
	IVB	Systemic therapeutical approach with palliative surgery

When surgery is not feasible due to medical contraindications (5–10% of patients), external radiation therapy with or without intracavitary brachytherapy to the uterus and vagina is suitable for individual clinical use [IV, B].

adjuvant treatment (Table 4)

radiotherapy

At present there is great uncertainty regarding what is the optimal adjuvant treatment for localized endometrial cancer. In 2009, a randomized trial compared vaginal brachytherapy vs observation in stage IA G1–2 with a similar overall recurrence rate, survival and late toxicity in the two groups. External beam radiation has been shown to reduce the rate of locoregional recurrence in intermediate-risk endometrial cancer. However, three large randomized studies (PORTEC-1, GOG 99 and ASTEC MRC-NCIC CTG EN.5) failed to demonstrate that radiation improves overall or disease-specific survival. A randomized clinical trial (PORTEC-2) comparing vaginal brachytherapy and external beam radiation in intermediate-risk patients has failed to show any difference in overall survival or progression-free survival (PFS). The quality of life was better in the vaginal brachytherapy arm.

Table 4. Adjuvant treatment

Stage I	IA G1–G2	Observation
	IA G3	Observation or vaginal brachytherapy If negative prognostic factors pelvic radiotherapy and/or adjunctive chemotherapy could be considered
	IB G1 G2	Observation or vaginal brachytherapy If negative prognostic factors pelvic radiotherapy and/or adjunctive chemotherapy could be considered
	IB G3	Pelvic radiotherapy If negative prognostic factors combination of radiation and chemotherapy could be considered
Stage II		Pelvic radiotherapy and-vaginal brachytherapy If grade 1–2 tumor, myometrial invasion <50%, negative LVSI and complete surgical staging: brachytherapy alone If negative prognostic factors: chemotherapy ± radiation
Stage III–IV		Chemotherapy If positive nodes: sequential radiotherapy If metastatic disease: chemotherapy–radiotherapy for palliative treatment

adjuvant chemotherapy

Platinum-based chemotherapy can be considered in stage I G3 with adverse risk factors (patient age, lymphovascular space invasion and high tumor volume) and in patients with stage II–III [II, B].

Maggi *et al.* conducted a randomized trial in 345 high-risk patients comparing five courses of cisplatin, doxorubicin and cyclophosphamide with external pelvic radiation. The authors reported no difference between therapies in terms of PFS or overall survival. A Japanese multicenter randomized trial compared whole-pelvic irradiation with three or more courses of cyclophosphamide, doxorubicin and cisplatin chemotherapy in patients with old stages IC–IIIC endometrioid adenocarcinoma. No difference in overall survival, relapse rate or PFS was observed. In a subgroup analysis, chemotherapy appeared superior to pelvic radiotherapy in patients aged >70 years with outer half myometrial invasion, those with grade 3, those with stage II or those with stage I disease and positive peritoneal cytology.

combined radiotherapy–chemotherapy

Two randomized clinical trials (NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE- III) were undertaken to clarify whether the sequential use of chemotherapy and radiotherapy improved PFS over radiation therapy alone in high-risk endometrial cancer patients (stage I–IIA, IIIC, any histology). The combined modality treatment was associated with 36% reduction in the risk of relapse or death [hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.41–0.99; $P = 0.04$]. Cancer-specific survival was significantly different (HR 0.55, CI 0.35–0.88; $P = 0.01$] and favored the use of adjuvant chemotherapy in addition to radiotherapy.

The ongoing PORTEC 3 study is comparing radiotherapy with the concomitant and sequential use of chemotherapy and radiotherapy in patients with endometrioid stage I grade 3, stage II–III and any stage serous and clear cell carcinomas.

Current evidence does not support the use of progestins in adjuvant treatment of endometrial cancer [I, A].

locoregional recurrence

The standard treatment for vaginal recurrence is radiation therapy (external beam plus vaginal brachytherapy): with high rates of local control, complete response (CR) and 5-year survival is 50%. For central pelvic recurrence the treatment of choice is surgery or radiation therapy, while for regional pelvic recurrences it is radiation therapy, associated if possible with chemotherapy.

advanced disease

There is no agreement on the standard treatment for women with advanced endometrial cancer. Typically, a combination of surgery, radiotherapy and/or chemotherapy is employed.

In the GOG-122 trial, there were 396 patients with stage III and optimally debulked stage IV disease who were randomized to whole abdominal radiation or to doxorubicin–cisplatin chemotherapy; there was a significant improvement in both PFS (50% vs.38%; $P = 0.07$) and overall survival (55% vs.42%; $P = 0.004$) in favor of chemotherapy.

treatment of metastatic disease and relapse

Systemic treatment for metastatic and relapsed disease may consist of endocrine therapy or cytotoxic chemotherapy. Hormonal therapy is recommended for endometrioid histologies only and involves mainly the use of progestational agents; tamoxifen and aromatase inhibitors are also being used. The main predictors of response in the treatment of metastatic disease are well-differentiated tumors, a long disease-free interval and the location and extent of extrapelvic (particularly pulmonary) metastases. The overall response to progestins is ~25%. Single cytotoxic agents have been reported to achieve a response rate up to 40% in chemotherapy-naïve patients with metastatic endometrial cancer. Among those, platinum compounds, anthracyclines and taxanes are most commonly used alone and in combination.

In non-randomized trials, paclitaxel with carboplatin or cisplatin demonstrated a response rate >60% and a possibly prolonged survival compared with historical experience with other non paclitaxel-containing regimens. Based upon these results, many consider that paclitaxel-based combination regimens are preferred for first-line chemotherapy of advanced and recurrent endometrial cancer. Endometrial cancer recurring after first-line chemotherapy is largely a chemoresistant disease. Various agents have been tested in a number of small phase II trials in patients previously exposed to chemotherapy. Only paclitaxel has consistently shown a response rate >20%. In a recently published study, the combination of weekly topotecan and docetaxel had clinical benefit and was well tolerated in heavily pretreated patients.

papillary serous carcinoma and clear cell carcinoma

Papillary serous and clear cell carcinoma require complete staging with total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy, appendicectomy and peritoneal biopsies. They are more aggressive with higher rates of metastatic disease and lower 5-year survival rates [I, A].

There is considerable evidence from retrospective series that platinum-based adjuvant chemotherapy for early (stage I and II) disease improves PFS and overall survival [III, B]. Platinum-based chemotherapy is recommended in patients with stage III or IV [I, A]. The same chemotherapy regimens usually employed for epithelial ovarian cancer can be considered in women with advanced or recurrent papillary serous or clear cell uterine cancer. Historically papillary serous endometrial carcinomas have not be considered to be hormone responsive.

prognosis

In the USA, the overall 5-year survival rate in women with endometrial cancer is 83%.

A key factor leading to this high rate is that most cases are diagnosed at an early stage.

The most important prognostic factors at diagnosis are: stage, grade, depth of invasive disease, LVSI and histological subtype. Endometrial tumors have a 5-year survival of 83%

compared with 62% for clear cell and 53% for papillary carcinomas. LVSI is present in 25% of cases. Five-year overall survival is 64% and 88% with or without LVSI, respectively.

Given the importance of tumor stage for both prognosis and adjuvant treatment it is necessary to compare the performance of the 1988 and 2009 FIGO staging systems. Based on the 2009 system, survival was 89.6% and 77.6% for stage IA and IB. The newly defined stage IIIC substages are prognostically different. Survival for stage IIIC1 was 57% compared with 49% for stage IIIC2.

Two recent studies conclude that the revised FIGO 2009 system is highly prognostic. The reduction in stage I substages, the elimination of cervical glandular involvement and the stratification of women with nodal disease all improved the performance of the staging system. On the contrary, another study suggests that the 2009 FIGO system does not improve predictive ability over the 1988 system.

Regarding the new staging system, future research should be focused on developing individualized risk models in endometrial cancer.

follow-up

Most recurrences will occur within the first 3 years after treatment. Patients should undergo follow-up every 3–4 months with physical and gynecological examination for the first 2 years, and then with a 6 month interval until 5 years. Further investigations can be performed if clinically indicated. The utility of PAP smears for detection of local recurrences has not been demonstrated.

note

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

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