

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

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incidence and epidemiology

Endometrial cancer is the sixth most common malignancy among females worldwide with an estimated incidence of about 288 000 new cases in the year 2008. In developed countries, endometrial cancer is the fourth most common cancer in women. Every year about 7400 new cases are registered in the UK and 88 068 in the European Union [1].

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: obesity (body mass index >30 increases risk from three- to four-fold) long-lasting endogenous or exogenous hyperestrogenism (polycystic ovary, tamoxifen therapy, anovulation, nulliparity) hypertension, diabetes mellitus.

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 pre-menopausal and peri-menopausal women.

diagnosis

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

The question of what is the best diagnostic strategy in patients with post-menopausal bleeding still remains controversial [2]. In the past, dilatation and curettage (D&C) was the principal

method of investigation. Several publications have reported that the accuracy of D & C is limited, citing false-negative rates as high as 10%. There is a trend toward minimally invasive exams using endometrial biopsy, vaginal ultrasound scan and hysteroscopy. 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 suggests 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 [3]. Timmerman et al. found a lower diagnostic accuracy for ultrasonography than was reported previously: a sensitivity of 95% and 98% with a specificity of 47% and 35%, respectively, at a cut-off ≤ 4 mm and cut-off ≤ 3 mm. The conclusion was that the use of ultrasonography remains justified, but with the recommendation to use cut-off level of ≤ 3 mm. Saline infusion sonography can be used to distinguish between focal and diffuse pathology. Hysteroscopy with biopsy should be used as the final step, if needed, in the diagnostic pathway of women with post-menopausal bleeding. It is highly accurate and clinically useful in diagnosing endometrial cancer. Its high accuracy relates to diagnosing rather than excluding cancer [4].

histopathological characteristics

Two main clinicopathological types of endometrial carcinoma have been recognised, corresponding to estrogen-dependent endometrioid (Type 1) and estrogen-independent non-endometrioid carcinomas (Type 2). Endometrioid adenocarcinomas represent 80% of 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. Genetic anomalies include 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

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squamous differentiation. Serous carcinomas are considered the prototype of Type 2. Similar to serous carcinomas of the ovary and Fallopian tube, they are characterised by p53 mutations and chromosomal instability and may be associated 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 represent a rare and heterogeneous group of tumours with intermediate features between Type 1 and Type 2. High-grade endometrial carcinomas, including grade 3 endometrioid, serous and clear-cell adenocarcinomas, all have poor prognosis, but may present and respond to adjuvant therapy differently. Unlike typical (or ‘prototypical’) tumours, several cases still remain morphologically ambiguous, indeterminate or hybrid adenocarcinomas, requiring immunohistochemistry (ER, PR, p53, p16, PTEN) and eventually mutational analysis to allow for a correct interpretation.

staging and risk assessment

Endometrial cancer is generally staged according to the International Federation of Gynecology and Obstetrics (FIGO) system [5]. In May 2009, a new staging system was published, but the existing literature and evidence are based mainly on the old classification published in 1988 (Tables 1 and 2).

The preoperative evaluation includes: chest X-ray, clinical and gynaecological examination, transvaginal ultrasound, blood counts and liver and renal function profiles. Abdominal computed tomography (CT) scan is indicated for investigating the presence of extrapelvic disease. Dynamic contrast-enhanced magnetic resonance imaging (MRI) is the best tool to assess the cervical involvement [6, 7]. In a few studies, MRI has been shown to accurately evaluate depth of myometrial invasion. A prospective collaborative trial, comparing MRI and ultrasonography (US), reported that the accuracy of US is comparable to that provided by MRI [8]. The most important limitation of US is the operator dependency with reported accuracies varying between 77% and 91%. [¹⁸F]2-Fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET)/CT could be useful to detect distant metastases accurately.

Table 1. Staging of endometrial cancer (FIGO: 1988). Reprinted from [28], with permission. Copyright 1990 Lippincott Williams & Wilkins.

Stage I	Confined to the uterus
I A	Tumour limited to the endometrium
I B	Invasion to less than half of the myometrium
I C	Invasion to more than half of the myometrium
Stage II	Extension to the uterine cervix
II A	Endocervical glandular involvement only
II B	Cervical stromal invasion
Stage III	Extension beyond the uterus
III A	Tumour invades serosa and/or adnexa, and/or positive peritoneal cytology
III B	Vaginal involvement
III C	Metastasis to pelvic or para-aortic lymph nodes
Stage IV	Invasion in neighbouring organs or distant metastasis
IV A	Tumour invasion of the bladder and/or bowel mucosa
IV B	Distant metastases including intra-abdominal or inguinal lymph nodes

Table 2. Staging of endometrial cancer (FIGO: 2009). Reprinted from [5], with permission from Elsevier B.V.

Stage I	Tumour confined to the corpus uteri
I A	NO or less than half myometrial invasion
I B	Invasion equal to or more than half of the myometrium
Stage II	Tumour invades cervical stroma, but does not extend beyond the uterus
Stage III	Local and/or regional spread of the tumour
III A	Tumour invades the serosa of the corpus uteri and/or adnexae
III B	Vaginal and/or parametrial involvement
III C	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
Stage IV	Tumour invades bladder and/or bowel mucosa, and/or distant metastases
IV A	Tumour invasion of bladder and/or bowel mucosa
IV B	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

Multiple factors have been identified for 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 tumour diameter >2 cm.

In this regard, stage I can be subdivided into three risk categories (reprinted from [5] with permission from Elsevier B.V.):

- 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

surgical treatment

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 has been widely accepted by many authors. A recent publication of the Gynecologic Oncology Group (GOG) LAP2 study has shown similar operative outcomes in the minimally invasive surgery and in the laparotomy 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. A potential enhancement to laparoscopy has been provided by the robotic approach with a high ‘benefit’ in obese women. Since 2002, the use of robotic assisted laparoscopy has advanced rapidly, particularly in the United States. The largest published series of robotic surgery was reported in 2011 by Paley et al. [9]. The major complication rate was significantly less with robotic surgery (20% versus 6.4%) compared with laparotomy, particularly related to wound complications and infections.

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].

Lymphadenectomy could be 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].

Randomised trials have failed to show a survival or relapse free survival benefit in stage I endometrial cancer (I, A) and the role of systematic pelvic lymphadenectomy is an issue of current debate. In an Italian study, 514 patients with stage I endometrial cancer were randomised to receive lymphadenectomy or not (excluding stage IA-IB G1 and non-endometrioid histotype). In this study, systematic lymphadenectomy did not improve disease-free or overall survival [10]. In the ASTEC trial, 1408 women with malignancies confined to the uterus were randomised. In this trial, there was no evidence of a benefit on overall survival or recurrence-free survival when pelvic lymphadenectomy was carried out [11]. The authors concluded that routine systematic pelvic lymphadenectomy cannot be recommended in women with stage I endometrial cancer, unless enrolled in clinical trials. However, the design of these studies has not addressed the most important impact of lymphadenectomy in the high-risk population in order to identify patients who can safely avoid or benefit from adjuvant treatment

A large retrospective study published in 2010, comparing systematic pelvic lymphadenectomy versus systematic pelvic and para-aortic lymphadenectomy (SEPAL study), has suggested that overall survival was significantly longer in patients undergoing pelvic and para-aortic lymphadenectomy [12]. The SEPAL study suggests that high-risk patients may benefit from aggressive surgery.

Sentinel lymph node identification in endometrial cancer has been described, with interesting preliminary results, which deserve further investigation in properly designed clinical studies.

Further randomised trials will be focused on investigating the role of lymphadenectomy for patients with high-risk endometrial cancer to direct subsequent treatment and the role of sentinel node biopsy.

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 recommended to guide surgical staging and adjuvant therapy.

surgical treatment in stage III-IV endometrial cancer

Maximal surgical debulking is indicated in patients with a good performance status and resectable tumour [III, B]. For distant

metastatic disease, palliative surgery could be considered in patients with a good performance status.

When surgery is not feasible due to medical contraindications (5%–10% of patients), or because of irresectable disease, external radiation therapy with or without intracavitary brachytherapy to the uterus and vagina is suitable for individual clinical use [IV, B] (Table 3).

adjuvant treatment

radiotherapy

In 2009, a randomised trial compared vaginal brachytherapy versus observation in stage IA G1–2 endometrial cancer with a similar overall recurrence rate, survival and late toxic effect in the two groups. The optimal adjuvant treatment (Table 4) of intermediate risk endometrial cancer is still to be defined. External beam radiation has been shown to reduce the rate of locoregional recurrence in intermediate risk endometrial cancer. However, three large randomised studies (PORTEC-1 [13], GOG 99 [14] and ASTEC MRC-NCIC CTG EN.5 [15]) failed to demonstrate that radiation improves overall or disease-specific survival. A randomised clinical trial (PORTEC-2) comparing vaginal brachytherapy and external beam radiation in intermediate risk patients showed that the two radiation therapies were equally effective but that the quality of life was better in the vaginal brachytherapy arm [16].

adjuvant treatment

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

Maggi et al. conducted a randomised 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 [17], a result which is also related to the insufficient sample size. A Japanese multicentre randomised 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 [18]. 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 randomised clinical trials (NSGO-EC-9501/EORTC-55991 and MaNGO ILIAD-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 results of the two studies were pooled for analysis [19]. The combined modality treatment was associated with 36% reduction in the risk of relapse

Table 3. Surgical treatment

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

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, 95% CI 0.35–0.88; $P = 0.01$) and favoured the use of adjuvant chemotherapy in addition to radiotherapy.

The on-going 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 the adjuvant treatment of endometrial cancer [I, A].

Locoregional recurrence

The standard treatment of vaginal recurrence is radiation therapy (external beam plus vaginal brachytherapy) with high rates of local control, complete response (CR) and a 5-year survival of 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 of 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 randomised to whole abdominal radiation or to doxorubicin–cisplatin chemotherapy; there was a significant improvement in both PFS (50% versus 38%; $P = 0.07$) and overall survival (55% versus 42%; $P = 0.004$) in favour of chemotherapy [20].

treatment of metastatic disease and relapse

Systemic treatment of 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 used. The main predictors of response in the treatment of metastatic disease are well-differentiated tumours, 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 [21].

In non-randomised 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. The GOG has completed accrual to a non-inferiority randomised phase III study evaluating carboplatin/paclitaxel versus cisplatin/doxorubicin/paclitaxel in patients with stage III, IV or recurrent endometrial cancer (GOG 209), and published results should be available soon. Preliminary results showed that the two drug regimen was as good as the three drug regimen in terms of activity against the cancer and overall survival whereas it was less toxic.

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%. Preliminary data for several molecularly targeted agents for endometrial cancer are emerging. The PI3K/Akt/mTOR pathway is frequently up-regulated in women with endometrial cancer because of loss of the tumour suppressor gene PTEN. Inhibitors of the mammalian target of rapamycin (mTOR) have shown promising early results. The mTOR inhibitor temsirolimus was associated with a 24% response rate in chemotherapy naïve patients. In patients with previous treatment, a 4% response rate with disease stabilization in 46% has been reported [22]. A recent phase II clinical trial demonstrates that single-agent ridaforolimus has anti-tumour activity in women with advanced endometrial cancer, most of whom had received two prior chemotherapy regimens [23]. The study met its primary end point, as 29% of patients achieved a clinical benefit, defined as an objective response or prolonged stable disease of 16 weeks or more. Ridaforolimus also showed an acceptable toxic effect profile. Unfortunately, predictive factors have not yet been identified to select patients most likely to benefit from mTOR inhibitor therapy.

serous carcinoma and clear-cell carcinoma

Serous and clear-cell carcinoma require complete staging with total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy, appendectomy

Table 4. Adjuvant treatment

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

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] [24]. 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 serous or clear-cell uterine cancer. Historically serous endometrial carcinomas have not been considered to be hormone responsive.

prognosis

Endometrial cancer is generally associated with a favourable prognosis. In the EURO CARE-4 study, age-adjusted 5-year relative survival estimates reached 76% in 1995–1999 and 78% in 2000–2002 in Europe. Survival for patients treated in 2000–2002 was highest generally in Northern Europe (especially in Sweden) and lowest in Eastern Europe (Czech Republic and Poland) [25].

A key factor leading to this good prognosis 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 tumours 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 tumour 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 [26].

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 [27]. On the contrary, another study suggests that the 2009 FIGO system does not improve prognosis predictability over the 1988 system.

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

personalised medicine

In this disease setting, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

follow-up and long-term implications

Most recurrences will occur within the first 3 years after treatment. The suggested frequency of follow-up is every 3–4 months with physical and gynaecological examination for the first 2 years, and then with a 6 month interval until 5 years. Further investigations can be carried out if clinically indicated. PET/CT has been shown to be more sensitive and specific than CT alone for the assessment of suspected recurrent endometrial cancer. The utility of PAP smears for detection of local recurrences has not been demonstrated.

note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 5. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

Dr N. Colombo has reported consultancy/honoraria from GlaxoSmithKline, Merck Serono, Roche, Amgen, PharmaMar, Clovis. The other authors have declared no potential conflicts of interest.

Table 5. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America–United States Public Health Service Grading System^a)

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

^aDykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.

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