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## FIGO CANCER REPORT 2012

### Cancer of the corpus uteri

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#### 1. Staging

##### 1.1. Anatomy

###### 1.1.1. Primary site

The upper two-thirds of the uterus above the level of the internal cervical os is called the corpus. The fallopian tubes enter at the upper lateral corners of a pear-shaped body. The portion of the muscular organ that is above a line joining the tubo-uterine orifices is often referred to as the fundus.

###### 1.1.2. Nodal stations

The major lymphatic trunks are the utero-ovarian (infundibulo-pelvic), parametrial, and presacral, which drain into the hypogastric, external iliac, common iliac, presacral, and para-aortic nodes.

###### 1.1.3. Metastatic sites

The vagina and lungs are the common metastatic sites.

##### 1.2. Rules for classification

The FIGO Committee on Gynecologic Oncology, following its meeting in 1988, recommended that endometrial cancer be surgically staged. There should be histologic verification of grading and extent of the tumor.

##### 1.3. Histopathology

###### 1.3.1. Histopathologic types (according to World Health Organization/International Society of Gynecological Pathology classification)

All tumors are to be microscopically verified.

The histopathologic types are:

- Endometrioid carcinoma: adenocarcinoma; adenoacanthoma (adenocarcinoma with squamous metaplasia); and adenosquamous carcinoma (mixed adenocarcinoma and squamous cell carcinoma).
- Mucinous adenocarcinoma.
- Serous adenocarcinoma.
- Clear cell adenocarcinoma.
- Undifferentiated carcinoma.
- Mixed carcinoma (carcinoma composed of more than 1 type, with at least 10% of each component).

###### 1.3.2. Histopathologic grades (G)

- GX: Grade cannot be assessed.
- G1: Well differentiated.
- G2: Moderately differentiated.
- G3: Poorly or undifferentiated.

Cases of carcinoma of the corpus should be grouped with regard to the degree of differentiation of the adenocarcinoma as follows:

- G1: <5% of a nonsquamous or nonmorular solid growth pattern.
- G2: 6%–50% of a nonsquamous or nonmorular solid growth pattern.
- G3: >50% of a nonsquamous or nonmorular solid growth pattern.

###### 1.3.3. Pathologic grading notes

Notable nuclear atypia (pleomorphism and prominent nucleoli), inappropriate for the architectural grade, raises the grade of a Grade 1 or Grade 2 tumor by 1.

In serous and clear cell adenocarcinomas, nuclear grading takes precedent. Most authors consider serous and clear cell carcinomas high grade by definition.

Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

##### 1.4. FIGO staging classification

The current FIGO staging classification for cancer of the corpus uteri is given in Table 1. Comparison of the stage groupings with the TNM classification is given in Table 2.

**Table 1**  
Cancer of the corpus uteri.

FIGO Stage	
I <sup>a</sup>	Tumor confined to the corpus uteri
IA <sup>a</sup>	No or less than half myometrial invasion
IB <sup>a</sup>	Invasion equal to or more than half of the myometrium
II <sup>a</sup>	Tumor invades cervical stroma, but does not extend beyond the uterus <sup>b</sup>
III <sup>a</sup>	Local and/or regional spread of the tumor
IIIA <sup>a</sup>	Tumor invades the serosa of the corpus uteri and/or adnexae <sup>c</sup>
IIIB <sup>a</sup>	Vaginal involvement and/or parametrial involvement <sup>c</sup>
IIIC <sup>a</sup>	Metastases to pelvic and/or para-aortic lymph nodes <sup>c</sup>
	IIIC1 <sup>a</sup> : Positive pelvic nodes
	IIIC2 <sup>a</sup> : Positive para-aortic nodes with or without positive pelvic lymph nodes
IV <sup>a</sup>	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA <sup>a</sup>	Tumor invasion of bladder and/or bowel mucosa
IVB <sup>a</sup>	Distant metastasis, including intra-abdominal metastases and/or inguinal nodes)

<sup>a</sup> Either G1, G2, or G3.

<sup>b</sup> Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.

<sup>c</sup> Positive cytology has to be reported separately without changing the stage.

**Table 2**Cancer of the corpus uteri: FIGO staging compared with the TNM classification.<sup>a</sup>

FIGO Stage	Union for International Cancer Control (UICC)		
	T (tumor)	N (lymph nodes)	M (metastasis)
I	T1	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
III	T3	N0–N1	M0
IIIA	T3a	N0	M0
IIIB	T3b	N0	M0
IIIC1	T1–T3	N1	M0
IIIC2	T1–T3	N1	M0
IVA	T4	Any N	M0
IVB	Any T	Any N	M1

<sup>a</sup> Carcinosarcomas should be staged as carcinoma.

#### 1.4.1. Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be assessed.
- N0: No regional lymph node metastasis.
- N1: Regional lymph node metastasis to pelvic lymph nodes.
- N2: Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes.

#### 1.4.2. Distant metastasis (M)

- MX: Distant metastasis cannot be assessed.
- M0: No distant metastasis.
- M1: Distant metastasis (includes metastasis to inguinal lymph nodes or intraperitoneal disease).

#### 1.4.3. Rules related to staging

Corpus cancer is surgically staged, therefore procedures previously used for determination of stage are no longer applicable (e.g. the findings of fractional curettage to differentiate between Stage I and Stage II).

There may be a small number of patients with corpus cancer who will be treated primarily with radiation therapy. In these cases, the clinical staging adopted by FIGO in 1971 would still apply, but designation of that staging system would be noted.

Ideally, distance from tumor to serosa should be measured.

As a minimum, any enlarged or suspicious lymph nodes should be removed in all patients. For high-risk patients (grade 3, deep myometrial invasion, cervical extension, serous or clear cell histology), complete pelvic lymphadenectomy and resection of any enlarged para-aortic nodes is recommended.

## 2. Introduction

Worldwide, endometrial cancer is the sixth most common malignant disorder with approximately 290 000 new cases annually. The incidence is higher in high-income countries (5.5%) compared with low-income countries (4.2%), although specific mortality is higher in the latter. Cumulative risk of endometrial cancer up to the age of 75 years has been estimated as 1.6% for high-income regions and 0.7% for low-income countries [1]. This difference has been associated with an epidemic of obesity and physical inactivity, two important risk factors, in high-income countries. Moreover, endometrial cancer patients with obesity also tend to have a poorer outcome [2]. On the other hand, physical activity and long-term use of continuous combined estrogen–progestin therapy is associated with a reduced risk of endometrial cancer [2–4].

In North America and Europe, endometrial cancer is the most frequent cancer of the female genital tract and the fourth most common site after breast, lung, and colorectal cancer [1]. The incidence is rising as life expectancy increases [5]. Furthermore, an estimated 22 000 European women died of endometrial cancer in 2008, which is the eighth most common cause of death from cancer in women. In North America, it is the sixth most frequent cause of death, with approximately 44 000 new cases and 8000 estimated new deaths each year [1].

Endometrioid adenocarcinoma progresses through a premalignant phase of intraepithelial endometrial neoplasia in a large proportion of cases [6]. Other forms such as serous and clear cell carcinoma arise as a result of a sequence of genetic mutations. In serous endometrial cancer, the mutant p53 plays a pivotal role [7]. Endometrial cancer research has gained some momentum in recent years and now provides better information for clinical practice. Its early presentation following postmenopausal bleeding results in a generally good prognosis, but it should be treated by evidence-based protocols, and where appropriate, by expert multidisciplinary teams.

The role of population screening for endometrial cancer remains low [8], although certain high-risk groups such as those with Lynch type 2 syndrome can undergo endometrial surveillance by biopsy, or transvaginal ultrasonography if post menopausal. Following presentation, ultrasound is an effective first test with a high negative predictive value when the endometrial thickness is less than 5 mm. In one of the largest studies undertaken, there was a negative predictive value of 96% among 1168 women in whom the results of transvaginal ultrasound were correlated with an endometrial biopsy obtained by curettage [9]. When a biopsy is required, this can be obtained usually as an office procedure using a number of disposable instruments developed for this purpose. In certain cases, hysteroscopy may be helpful, and with flexible instruments can also be done without recourse to general anesthesia. However, the biological role of cells that are transtubally flushed during hysteroscopy remains uncertain. If cervical stenosis or patient tolerance does not permit an office procedure, hysteroscopy and curettage under anesthesia may be necessary. Individuals whose pelvic examination is unsatisfactory may also be evaluated with transvaginal or abdominal ultrasound to rule out concomitant adnexal pathology.

Following a histopathologic diagnosis of endometrial adenocarcinoma, the local extent of the tumor, and evidence of metastatic disease should be determined. In addition, the perioperative risk should be assessed.

As a minimum, the pathology report from endometrial sampling should indicate the tumor type and grade of the lesion. A chest X-ray, full biochemistry (renal and liver function tests), and blood count are routine. A serum CA-125 may be of value in advanced disease for follow-up. Evaluation for metastasis is indicated particularly in patients with abnormal liver function tests, and clinical findings such as parametrial or vaginal tumor extension. In high-risk patients, imaging of abdomen and lymph nodes may help determining the surgical approach. In certain situations, cystoscopy and/or proctoscopy may be helpful, if direct extension to bladder or rectum is suspected.

## 3. Prognostic tumor characteristics for high-risk disease

The recommended histopathologic criteria for determining high-risk disease are as follows:

- Tumor grade 3 (poorly differentiated).
- More than 50% of myometrial invasion.
- Lymphovascular space invasion.
- Non-endometrioid histology (serous, clear cell, undifferentiated, small cell, anaplastic, etc).

- Cervical stromal involvement.

The most accurate means of assessing both depth of myometrial invasion and cervical involvement is MRI scanning and intraoperative frozen section [10–12]. CT and MRI are equivalent in terms of evaluating nodal metastases, but neither is good enough to replace surgical lymph node assessment which provides histological confirmation [13–18].

Nonsurgical staging for endometrial cancer, where extrauterine disease exists, is inherently inaccurate, particularly in respect of small nodal involvement, intraperitoneal implants, and adnexal metastasis.

#### 4. Surgical staging procedure for endometrial cancer

In 1988, the FIGO Cancer Committee changed the official FIGO staging from clinical to surgical for endometrial cancer. Since that recommendation, considerable debate has ensued as to what constitutes an internationally acceptable approach. A generally recommended protocol would be that the abdomen should be opened with a vertical midline abdominal incision and peritoneal washings taken immediately from the pelvis and abdomen, followed by careful exploration of the intra-abdominal contents. The omentum, liver, peritoneal cul-de-sac, and adnexal surfaces should be examined and palpated for any possible metastases, followed by careful palpation for suspicious or enlarged nodes in the aortic and pelvic areas. The standard surgical procedure should be an extrafascial total hysterectomy with bilateral salpingo-oophorectomy. Adnexal removal is recommended even if the tubes and ovaries appear normal, as they may contain micrometastases. Vaginal cuff removal is not necessary, nor is there any benefit from excising parametrial tissue in the usual case. If cervical stromal involvement is demonstrated preoperatively, or if unsuspected cervical involvement is noted and can be encompassed by a modified radical hysterectomy, this may be the most appropriate operation in experienced hands.

There has also been considerable debate on the safety of endoscopic surgery for the treatment of endometrial cancer. Recent studies have demonstrated that laparoscopic removal of the uterus and adnexae (in experienced hands) appears to be safe. Whereas there is no difference in terms of major complications between abdominal hysterectomy and laparoscopically assisted vaginal hysterectomy (LAVH) or total laparoscopic hysterectomy (TLH), the laparoscopic approach is associated with a longer operative time, but a shorter hospital stay, less pain, and quicker resumption of daily activities [19,20]. Oncological safety data are lacking, although hysterectomy and bilateral salpingo-oophorectomy can be safely done with laparoscopy in those patients with no contraindications to laparoscopy (e.g. large-volume uterus) [21]. This approach can be accompanied by a laparoscopic lymphadenectomy, if surgical staging is to be undertaken. If unexpected metastases are identified, conversion to an open procedure is necessary. Robotic surgery for the surgical management of the morbidly obese patient is an option only in experienced hands, but randomized trials about safety and survival are lacking.

Although mandated through the staging system, lymphadenectomy of the pelvic and para-aortic areas remains controversial. Selective node sampling is of dubious value as a routine and complete lymphadenectomy should be reserved for cases with high-risk features. Many individuals with endometrial cancer are obese or elderly, with other medical problems, and clinical judgment is required to determine if additional surgery is warranted. Any deeply invasive tumor or radiological suggestion of positive nodes is an indication for retroperitoneal lymph node evaluation, with removal of any enlarged or suspicious nodes. Documentation of positive nodes identifies a high-risk population

and helps to tailor adjuvant treatment, since patients with Stage III disease appear to benefit from chemotherapy [22].

Indications for aortic node sampling would include suspicious aortic or common iliac nodes, grossly positive adnexae, grossly positive pelvic nodes, and high grade tumors showing full thickness myometrial invasion. Patients with clear cell, papillary serous, or carcinosarcoma histologic subtypes are also candidates for aortic node sampling.

#### 5. Who should perform the surgery?

Low-risk tumors will have positive nodes in less than 5% of cases (well differentiated and <1/2 myometrial invasion) and do not require full surgical staging. These women can be safely operated on by a general gynecologist, but those at greater risk of extrauterine disease, who may require lymphadenectomy, should be referred to a gynecological oncologist. This triaging of women can be done most effectively by a thorough preoperative assessment, paying particular attention to the pathology and to radiological features. Triaging for lymphadenectomy is also possible during surgery. Intraoperative assessment mainly involves assessment of myometrial invasion [10,12]. Grading on frozen section is possible, though suboptimal compared with preoperative grading [12].

#### 6. Is lymphadenectomy therapeutic?

Although required for accurate staging, a therapeutic benefit for lymphadenectomy is controversial. Historically, one case-control study suggested that it may be therapeutic [23] and another showed a good prognosis even in node-positive women [24]. Another retrospective study showed a survival benefit of complete lymphadenectomy for patients with grade 3 tumors [25]. In the UK, the MRC ASTEC trial, which randomized 1400 women undergoing surgery for presumed Stage I endometrial cancer to pelvic lymphadenectomy or no lymphadenectomy, showed no therapeutic benefit [26]. An Italian randomized trial of pelvic (and in 30% para-aortic) lymphadenectomy versus no lymphadenectomy in 540 women also did not show any difference in rates of relapse or survival [27]. Both studies have been criticized because the nodal status was not used to direct adjuvant radiation or chemotherapy.

Lymphadenectomy is primarily used for staging and should be considered in women with high-risk factors [28]. Although a direct survival benefit of lymphadenectomy has not been documented, the procedure identifies node-positive patients that may benefit from adjuvant treatment.

In a retrospective study, para-aortic lymphadenectomy resulted in an improved outcome in intermediate and high-risk patients [29].

#### 7. Adjuvant radiotherapy

Histologic findings are used to determine the need for adjuvant radiotherapy, as the majority of patients are at low risk of recurrence, and adjuvant treatment should be tailored to prognostic factors. Low-risk disease (Stage I, grade 1 or 2 with no or superficial myometrial invasion) does not require adjuvant radiotherapy, as demonstrated in a Danish cohort study of low-risk women, with 96% 5-year survival after surgery alone [30]. A seminal Norwegian trial [31], which included 621 women treated after surgery with vaginal brachytherapy, indicated that overall survival was not improved by additional external beam therapy, although it did reduce the risk of pelvic recurrence.

Three large randomized trials of pelvic radiotherapy versus no further treatment after surgery have determined the role of radiotherapy based on risk factors, and have led to reduced indications for adjuvant radiotherapy: the PORTEC trial [32], the US GOG#99 trial [33], and the UK MRC ASTEC trial [34]. All of these

trials reported a significant reduction in the rates of vaginal and pelvic recurrence with external beam radiation therapy (EBRT), but without any survival benefit. EBRT added to the risk of long-term morbidity. PORTEC and ASTEC trials had similar recurrence and survival rates without lymphadenectomy, compared with GOG#99 that included patients with documented node-negative disease. In these trials, so-called high-intermediate risk groups were defined based on age, grade, depth of invasion, and in GOG#99 also lymphovascular space invasion (LVSI). Only women with several of these risk factors had a clinically relevant reduction of the risk of pelvic relapse with radiation therapy, and in view of the absence of any survival benefit, radiation therapy was omitted for those with low to intermediate risk factors. PORTEC-1 showed that most pelvic relapses were located in the vaginal vault (75%), and that salvage rates were high in women who had not had previous radiation therapy [35].

The PORTEC-2 trial randomized 427 women with high-intermediate risk factors to EBRT or vaginal brachytherapy alone [36]. This trial showed that vaginal brachytherapy had excellent vaginal control rates (<2% at 5 years for both EBRT and vaginal brachytherapy groups), with minimal side effects and significantly better quality of life. Quality of life of patients in the brachytherapy group remained the same as those of an age-matched normal population [37,38]. Vaginal brachytherapy has replaced EBRT as standard adjuvant treatment for patients with high-intermediate risk factors.

The seminal NSGO/EORTC trial investigated the use of both EBRT and adjuvant platinum-based chemotherapy compared with EBRT alone for patients with risk factors (grade 3 or deep invasion or adverse histologies). This trial was published in a pooled analysis with the Italian ILIADE trial [39].

While trials comparing adjuvant EBRT alone with adjuvant cisplatin-based chemotherapy alone have not shown any difference in overall or relapse-free survival [40,41], the pooled NSGO/EORTC and ILIADE trial analysis reported a significant 9% improvement in progression-free survival (69% vs 78% at 5 years; Hazard Ratio [HR] 0.63) with the addition of chemotherapy to EBRT, and a trend for a 7% improvement in 5-year overall survival (75% vs 82%; HR 0.69,  $P=0.07$ ).

Ongoing trials are currently investigating the roles of EBRT or chemotherapy alone or combined EBRT and chemotherapy for patients with high-risk or advanced stage disease (GOG#249, GOG#258, PORTEC-3, Danish/EORTC trials).

In summary, whether or not lymphadenectomy has been performed, adjuvant radiotherapy is not indicated for patients with grade 1–2 tumors and no more than 50% myometrial invasion, or for those with only a single risk factor. For patients with high-intermediate risk factors (at least 2 of the factors: age >60 years, deep myometrial invasion, grade 3, serous or clear cell histology, LVSI), vaginal brachytherapy alone is preferable to EBRT, providing excellent vaginal control without impacting on quality of life. In patients with higher-risk disease (3 or more risk factors, Stages II and III), the roles of EBRT and/or chemotherapy are currently being investigated.

## 8. Progestogen therapy

This has been widely prescribed in the past, but a meta-analysis of 6 randomized trials involving a total of 3339 women has shown no survival benefit for adjuvant progestogen therapy in endometrial cancer [42]. A subsequently published randomized trial of 1012 women also failed to demonstrate any survival benefit [43].

## 9. Stage II

Patients with clinically occult Stage II disease are generally managed in a similar fashion to patients with Stage I disease.

Radical hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy, and selective aortic node dissection can be used as primary treatment for clinically overt cervical involvement. Preoperative MRI scanning is advisable to exclude bladder involvement and ensure local resectability. Studies indicate excellent results for this approach, with no benefit from the addition of radiation for patients with negative nodes [44–47]. Adjuvant radiotherapy is usually reserved for patients with involved nodes and/or close or involved surgical margins.

The need for adjuvant radiotherapy has not been studied in a randomized trial, but a SEER study reported improved survival for patients with Stage II endometrial cancer when adjuvant radiotherapy was used after radical and simple hysterectomy [48, 49].

If surgery is not considered feasible because of tumor extension, full pelvic radiotherapy and intracavitary brachytherapy, as in cervical cancer, may be employed.

## 10. Stage III

Most patients with Stage III endometrial cancer are managed by complete surgical resection of all metastatic disease, followed by postoperative EBRT and/or chemotherapy. The randomized GOG#122 trial included patients with Stages III and IV disease and residual tumor up to 2 cm, and compared whole abdominal radiation with intensive adjuvant chemotherapy (8 cycles of doxorubicin and cisplatin). It showed a survival benefit for chemotherapy (42% vs 53% estimated 5-year survival), although event rates were high in both arms [22]. Adjuvant platinum-based chemotherapy (more recently, carboplatin and paclitaxel) is increasingly used to reduce the risk of metastases. Retrospective studies have shown substantial pelvic recurrence rates when EBRT was omitted when using chemotherapy [50,51], and current ongoing trials are investigating the roles of EBRT, chemotherapy, and combinations (GOG#259; PORTEC-3 trials).

Patients with presumed Stage III disease because of adnexal involvement should have full surgical staging and expert pathologic examination of the specimen, as primary tumors of both the ovary and the endometrium may be present. Management should be individualized, and based on the stage of each tumor.

Patients with clinical Stage III endometrial carcinoma that is not felt to be resectable by virtue of vaginal or parametrial extension are best treated primarily by pelvic irradiation. Once therapy has been completed, exploratory laparotomy should be considered for those patients whose disease now appears to be resectable.

## 11. Stage IV

Patients with Stage IV disease based on intraperitoneal spread benefit from cytoreductive surgery only if there is no residual tumor [52]. Neoadjuvant chemotherapy is an option, particularly if ascites is present, and postoperative morbidity is considered likely [53]. After surgery, platinum-based chemotherapy should be considered, based on the GOG#122 trial cited above [22].

Patients with evidence of extra-abdominal metastases are usually managed with systemic platinum-based chemotherapy, or hormonal therapy if grade 1 and/or receptor positive. Combination chemotherapy is the treatment of choice in advanced-stage disease as well as in relapsed disease. The combinations of doxorubicin, paclitaxel, and cisplatin [54] and carboplatin and paclitaxel have been shown to be most effective. The former is much more toxic.

Doxorubicin monotherapy versus doxorubicin–cisplatin doublet has been investigated in 2 randomized trials [55,56]. Both documented superiority of the combination chemotherapy in terms of progression-free (PFS) and overall survival (OS), with manageable toxicity. Doxorubicin–cisplatin doublet versus doxorubicin–cisplatin–paclitaxel triplet was tested in a phase III randomized

trial [54]. The triplet regimen resulted in a significantly superior PFS, though this regimen proved to be too toxic, with treatment-related deaths despite the use of growth factors.

Carboplatin–paclitaxel doublet was tested in several phase II studies in advanced-stage or relapsed disease, demonstrating a response rate of 65%–75% and PFS of about 14 months [57–59]. Efficacy of carboplatin–paclitaxel seems better than doxorubicin–cisplatin, although results of a phase III GOG trial comparing these regimens are still awaited. Moreover, carboplatin–paclitaxel is well tolerated by patients.

Pelvic radiotherapy in Stage IV disease may be used to provide local tumor control and/or to treat symptoms such as vaginal bleeding or pain from a local tumor mass, or leg edema due to lymph node involvement. Palliation of brain or bone metastases can be effectively obtained with short courses (1–5 fractions) of radiotherapy.

## 12. Targeted therapy

While surgery, radiotherapy, and cytotoxic therapy have improved outcomes for patients with endometrial cancer, insights into pathogenesis of cancer have led to the development of drugs targeting molecular pathways vital to cancer cell survival including angiogenesis, DNA repair, and apoptosis. The tumor suppressor gene PTEN (phosphate and tensin homolog detected on chromosome 10) is important for normal cellular function. Mutations in PTEN result in decreased apoptosis and are found in up to 83% of endometrioid carcinomas of the uterus [60]. Decreased transcription due to mutation leads to decreased phosphatidylinositol 3-kinase (PI3K) inhibition, increased activity of Akt, and uncontrolled function of mTOR. Elevated activity of mTOR is seen in a vast majority of endometrial cancers [61,62]. The mammalian target of rapamycin (mTOR) is a kinase that regulates cell growth and apoptosis [63]. Temsirolimus, deforolimus, and everolimus are mTOR inhibitors that have been tested as single agents in phase II studies. They have been found to promote stable disease in 44% of patients with metastatic or recurrent cancer of the endometrium [64,65].

Development of a new blood supply (angiogenesis) is essential to the development and maintenance of any tissue [66,67]. Diffusion of nutrients over small distances is sufficient for cellular function, but in order for tumor growth to exceed 1 mm<sup>3</sup> in volume, new vessels must be recruited [67]. Tumor cells generate angiogenic factors that promote new vessel formation and recruit supporting cells. The vessel density and circulating tumor levels of many proangiogenic proteins such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) are poor prognostic factors for many solid tumors, including endometrial carcinoma [67]. VEGF is one of the best characterized angiogenesis mediators [68,69]. Increased production of VEGF as well as other growth factors is frequently observed in regions of hypoxia or inflammation and in the presence of activated oncogenes or down-regulated tumor suppressor genes [70,71]. Overexpression of VEGF results in increased endothelial cell proliferation, decreased apoptosis, and increased fenestration of endothelial cells [70,72]. VEGF overexpression has been shown to be associated with a poor prognosis in most gynecologic malignancies including endometrial cancer [73]. The role of drugs inhibiting angiogenesis pathways, such as bevacizumab and tyrosine kinase inhibitors, is being studied in endometrial cancer.

## 13. Special considerations

### 13.1. Diagnosis post hysterectomy

Diagnosis of endometrial carcinoma post hysterectomy can present some management problems, particularly if the adnexae have

not been removed. This situation most often arises following vaginal hysterectomy for pelvic prolapse. Recommendations for further postoperative therapy are based on known risk factors for extrauterine disease related to the histologic grade and depth of myometrial invasion. Individuals with grade 3 lesions, deep myometrial invasion, or LVSI are candidates for additional surgery to remove the adnexae, or adjuvant external beam pelvic radiation therapy. Patients with a grade 1 or 2 lesion with minimal myometrial invasion and no LVSI involvement generally require no further therapy.

### 13.2. Medically inoperable patients

Morbid obesity and severe cardiopulmonary disease are the general reasons a patient with endometrial carcinoma may be thought to be medically inoperable. Uterine brachytherapy can achieve cure rates in excess of 70% and may be combined with external beam radiotherapy in the presence of prognostic factors suggesting a high risk of involved nodes.

For patients with a well-differentiated lesion, contraindications to general anesthesia, and who are unsuitable for radiotherapy, high-dose progestins may be used.

### 13.3. Diagnosis in young women

The diagnosis of endometrial carcinoma during the reproductive years should be made with caution, since this malignancy is uncommon in women under 35 years, and grade 1 endometrial carcinoma may be confused with severe atypical hyperplasia. In these women, consideration should be given to an estrogen-related underlying condition such as granulosa cell tumor, polycystic ovaries, or obesity. Progestins may be appropriate in these situations if preservation of fertility is desired. Equivocal lesions should be examined by an experienced pathologist. If carcinoma is confirmed, hysterectomy with adnexal removal remains the treatment of choice. When uncertainty remains regarding the presence of true carcinoma, the ultimate decision rests with the patient, after thorough counseling. Although the literature describes successful outcomes, fatal recurrences of endometrial cancer after a conservative approach have been reported, and hysterectomy and adnexal removal should be recommended after childbearing has been completed.

## 14. Follow-up

The conventional reasons for follow-up of treated cancer patients involve providing reassurance, diagnosing early recurrence, and collecting data. One prospective [74] and several retrospective studies [75–79] internationally have addressed follow-up. Overall, about 75% of recurrences were symptomatic and 25% asymptomatic, and neither recurrence-free nor overall survival were improved in asymptomatic cases compared with those detected at clinical presentation. Most (65%–85%) recurrences were diagnosed within 3 years of primary treatment, and 40% of recurrences were local. The use of routine follow-up Pap smears and chest X-rays is not cost-effective. In nonirradiated patients, a strong case can be made for regular follow-up to detect vaginal recurrence at the earliest opportunity, given the high salvage rate following radiotherapy [80].

Two systematic reviews [81,82] documented evidence for the utility of follow-up examinations, and concluded that follow-up should be practical and directed by symptoms and pelvic examination, and that frequency of follow-up visits may be reduced in low-risk patients. Given the low risk of recurrence, vaginal cytology can be omitted, resulting in reduced healthcare costs [83]. It appears that visual inspection is sufficient, since positive cytology is merely diagnosed in cases of symptomatic recurrence [77,84,85].

## 15. Recurrence

Localized recurrences are managed preferentially by surgery, irradiation, or a combination of the two, depending on the primary therapy. Screening for distant metastases should be performed before deciding on curative treatment. With an increasing number of patients managed by surgery alone, radiotherapy provides an effective salvage treatment in cases of vaginal or central pelvic recurrence. A combination of EBRT and brachytherapy, preferably image-guided, is usually required. Large recurrences should be evaluated for excision, followed by radiotherapy. Additional chemotherapy is being evaluated in an ongoing GOG trial. Extended surgery may be justified, especially in patients who have had prior radiation therapy. The results of pelvic exenteration in properly selected cases are similar to those obtained in cervical cancer.

Patients with non-localized recurrent tumors may be candidates for progestin therapy (medroxyprogesterone acetate 50–100 mg 3 times a day or megestrol acetate 80 mg 2–3 times a day). The progestin therapy is continued as long as the disease is static or in remission. Maximum clinical response may not be apparent for 3 or more months after initiating therapy. Platinum-based chemotherapy (cisplatin and doxorubicin, or carboplatin and paclitaxel) has been recommended for patients with advanced or recurrent disease, not amenable to cure by surgery and/or radiotherapy [22,57]. Targeted therapies are being investigated in several ongoing trials.

## 16. Recommendations for practice

- Preoperatively, a definitive tissue diagnosis must be obtained. This helps to determine the surgical approach, and to differentiate between tumors at low and high risk of lymph node metastasis. Imaging can be useful to determine depth of myometrial invasion, cervical involvement, and lymph node enlargement. **Level of Evidence C**
- Lymphadenectomy in clinical Stage I endometrial cancer has no impact on overall or relapse-free survival. **Level of Evidence A**. Outside clinical trials, lymphadenectomy should be performed for staging only in high-risk cases. There is little evidence to support a therapeutic benefit, but it should be used to select women with positive nodes for adjuvant therapy. **Level of Evidence C**
- Adjuvant radiotherapy for women with Stage I endometrial cancer with low, intermediate, or high-intermediate risk features has no impact on survival, although it reduces the rate of pelvic recurrence. **Level of Evidence A**. Vaginal brachytherapy effectively reduces the risk of vaginal relapse in patients with risk factors. **Level of Evidence A**. External beam radiotherapy should be considered in patients with positive nodes or advanced stage disease to ensure pelvic control. **Level of Evidence B**
- The addition of adjuvant chemotherapy to radiotherapy in patients with high-risk factors improves progression-free survival, but overall survival benefit is unproven. **Level of Evidence A**
- Adjuvant chemotherapy for patients with early stage, high-risk disease should only be considered within clinical trials.
- Chemotherapy is superior to whole abdominal radiation for patients with Stage III disease and abdominal disease with residual nodules less than 2 cm diameter. **Level of Evidence A**
- Targeted therapy in endometrial cancer should only be considered within clinical trials.
- There is no evidence to support the use of adjuvant hormonal therapy (progestogen). **Level of Evidence A**
- Patients with high-risk and advanced stage endometrial cancer should be managed where possible by a gynecological oncologist,

working within a multidisciplinary team. **Professional consensus**

- Patients with endometrial cancer are frequently old and frail, and this should be taken into account when prescribing adjuvant therapy. **Professional consensus**

## Conflict of interest

The authors have no conflicts of interest to declare.

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