DOI: 10.1002/ijgo.12612

FIGO CANCER REPORT 2018

WILEY International Journal of Gynecology & Obstetrics FIGO

Cancer of the corpus uteri

Frédéric Amant[1,2,3,*] | Mansoor Raza Mirza[4] | Martin Koskas[5] | Carien L. Creutzberg[6]

[1]Division of Gynecologic Oncology, University Hospitals Gasthuisberg, Leuven, Belgium

[2]Center for Gynecologic Oncology Amsterdam, Netherlands Cancer Institute, Amsterdam, Netherlands

[3]Center for Gynecologic Oncology Amsterdam, Amsterdam University Medical Centers, Amsterdam, Netherlands

[4]Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

[5]Division of Gynecologic Oncology, Bichat University Hospital, Paris, France

[6]Department of Radiation Oncology, Leiden University Medical Center, Leiden, Netherlands

*Correspondence
Frédéric Amant, Center for Gynecologic Oncology Amsterdam, Amsterdam University Medical Centers, Amsterdam, Netherlands.
Email: frederic.amant@uzleuven.be

Abstract

Endometrial cancer is the most common gynecological malignancy in high-income countries. Although the overall prognosis is relatively good, high-grade endometrial cancers have a tendency to recur. Recurrence needs to be prevented since the prognosis for recurrent endometrial cancer is dismal. Treatment tailored to tumor biology is the optimal strategy to balance treatment efficacy against toxicity. Standard treatment consists of hysterectomy and bilateral salpingo-oophorectomy. Lymphadenectomy (with ongoing studies of sentinel node biopsy) enables identification of lymph node positive patients who need adjuvant treatment, including radiotherapy and chemotherapy. Adjuvant radiotherapy is used for Stage I–II patients with high-risk factors and Stage III lymph node negative patients. In advanced disease, a combination of surgery to no residual disease and chemotherapy results in the best outcome. Surgery for recurrent disease is only advocated in patients with a good performance status with a relatively long disease-free interval.

KEYWORDS

Chemotherapy; Corpus uteri; Endometrial cancer; FIGO Cancer Report; Gynecologic cancer; Radiotherapy; Surgery

1 | STAGING

1.1 | Anatomy

1.1.1 | Primary site

The upper two-thirds of the uterus located above the internal orifice of the uterus is termed the corpus. The fallopian tubes enter at the upper lateral corners of an inverse pear-shaped body. The portion of the muscular organ that is above a line joining the tubouterine orifices is referred to as the fundus.

Cancer of the corpus uteri is usually referred to as endometrial cancer, which arises from the epithelial lining of the uterine cavity. Its first local extension concerns the myometrium. Cancers arising in the stromal and muscle tissues of the myometrium are called uterine sarcomas and are not discussed in this overview (readers are directed to the chapter on uterine sarcomas in this Supplement by Mbatani et al.[1]).

1.1.2 | Nodal stations

The lymphatic system of the corpus uteri is formed by three main lymphatic trunks: utero-ovarian (infundibulopelvic), parametrial, and presacral. They collectively drain into the hypogastric (also known as internal iliac), external iliac, common iliac, presacral, and para-aortic nodes. Direct metastases to the para-aortic lymph nodes are uncommon. This is surprising given that a direct route of lymphatic spread from the corpus uteri to the para-aortic nodes through the infundibulopelvic ligament has been suggested from anatomical and sentinel lymph node studies.

1.1.3 | Metastatic sites

The vagina, ovaries, and lungs are the most common metastatic sites.

1.2 | Rules for classification

Surgical staging of endometrial cancer replaced clinical staging by the FIGO Committee on Gynecologic Oncology in 1988 and again revised

in 2009. Rules for classification include histologic verification of grading and extent of the tumor.

1.3 | Histopathology

1.3.1 | Histopathologic types (according to WHO/International Society of Gynecological Pathology classification)

All tumors are to be microscopically verified.

The histopathologic types of endometrial carcinomas are[2]:

1. Endometrioid carcinoma: adenocarcinoma; adenocarcinoma-variants (with squamous differentiation; secretory variant; villoglandular variant; and ciliated cell variant).
2. Mucinous adenocarcinoma.
3. Serous adenocarcinoma.
4. Clear cell adenocarcinoma.
5. Undifferentiated carcinoma.
6. Neuroendocrine tumors.
7. Mixed carcinoma (carcinoma composed of more than one type, with at least 10% of each component).

Apart from the classification of endometrial carcinoma, carcinoma of the endometrium comprises mixed epithelial and mesenchymal tumors including:

1. Adenomyoma
2. Atypical polypoid adenomyoma
3. Adenofibroma
4. Adenosarcoma
5. Carcinosarcoma: currently carcinosarcomas, in which both epithelial and mesenchymal components are malignant and aggressive tumors, are considered metaplastic carcinomas, and are treated as aggressive carcinomas.

Endometrial cancers have traditionally been classified in one of the following two categories:

1. Types 1 (grade 1 and 2 endometrioid carcinoma) are the most common endometrial cancers. They may arise from complex atypical hyperplasia and are linked to excess of estrogen stimulation. As they are usually diagnosed at early stages, they present a relatively good prognosis.
2. Types 2 are the least common endometrial tumors. They include grade 3 endometrioid tumors as well as tumors of nonendometrioid histology, and develop from atrophic endometrium. Type 2 tumors are less hormone sensitive. Since they are diagnosed in later stages, they are generally more aggressive and have a poorer prognosis than Type 1 endometrial cancer.

However, the Cancer Genome Atlas studies have identified four molecular subgroups characterized, respectively, by POLE mutation, mismatch repair deficiency, TP53 mutation, and a copy number low group without a specific driver mutation, each with a distinct prognosis.[3,4]

1.3.2 | Histopathologic grades (G)

1. GX: Grade cannot be assessed.
2. G1: Well differentiated.
3. G2: Moderately differentiated.
4. G3: Poorly or undifferentiated.

Degree of differentiation of the adenocarcinoma is another basis for classification carcinoma of the corpus, which are grouped as follows:

1. G1: less than 5% of a nonsquamous or nonmorular solid growth pattern.
2. G2: 6%–50% of a nonsquamous or nonmorular solid growth pattern.
3. G3: greater than 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. However, this should not be done too easily as grade 2 will then lose its discriminative power.[5]

Most authors consider serous and clear cell carcinomas high grade by definition.

Grading of adenocarcinomas with squamous differentiation is allocated according to the nuclear grade of the glandular component.

1.4 | FIGO staging classification

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

1.4.1 | Regional lymph nodes (N)

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

1.4.2 | Distant metastasis (M)

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

TABLE 1 Cancer of the corpus uteri.

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

[a]Either G1, G2, or G3.
[b]Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.
[c]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.[a]

	Union for International Cancer Control (UICC)		
FIGO Stage	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

[a]Carcinosarcomas should be staged as carcinoma.

1.4.3 | Rules related to staging

During staging, distance from tumor to serosa should be measured. Other features should also be reported in the pathologic report of the hysterectomy specimen. For instance, the presence of lymphovascular space invasion (LVSI) should also be indicated, as patients with LVSI-positive tumors have a significantly worse prognosis, especially if extensive LVSI is found.[6] The distinction made using LVSI status could be more relevant than the distinction between Stages IA and IB for predicting survival in Stage I endometrial cancer.[7]

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.

Clinical staging, as designated by FIGO in 1971, applies to a small percentage of corpus cancers that are primarily treated with radiation therapy. In those instances, the designation of that staging system should be noted.

2 | INTRODUCTION

2.1 | Incidence

Endometrial cancer represents the sixth most common malignant disorder worldwide. An estimated 320 000 new cases are diagnosed with this malignancy annually. High-income countries have a greater incidence of endometrial cancer (5.9%) compared with low-resource countries (4.0%), although specific mortality is higher in the latter. The 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.[8] This might be attributable to high rates of obesity and physical inactivity—two major risk factors in high-income countries. Specifically, elevated estrogen levels are known to be the most likely cause of the increased risk of endometrial cancer for postmenopausal obese women.[9] Conversely, physical activity and long-term use of continuous combined estrogen–progestin therapy are associated with a reduced risk of endometrial cancer.[10,11] Interestingly, obesity is associated with earlier age at diagnosis, and with endometrioid-type endometrial cancers. Similar associations were not observed with nonendometrioid cancers, consistent with different pathways of tumorigenesis.[12]

North America and Europe have the highest incidence of endometrial cancer, where it is the most frequent cancer of the female genital tract and the fourth most common site in women after breast, lung, and colorectal cancer.[13]

In Europe, it represents the eighth most common cancer death in women, with a reported 23 700 women dying in 2012.[7] In North America, it is the sixth most frequent cause of death, with approximately 55 000 new cases and 11 000 estimated new deaths each year.[3]

The two major factors that contribute to an increase in the incidence of endometrial cancer in high-income countries are increased prevalence of obesity and extended life expectancy. Other determinants—such as the widespread decrease in use of estrogen plus progestin menopausal hormone therapy—have also been proposed as the cause of the increased incidence rates for endometrial cancer in North America.[14]

Mortality rates for endometrial cancer showed a decrease in most European Union member states among women born before 1940.

Improved cancer treatment and access to health care have been suggested as contributing to this decrease in cancer mortality.[8]

2.2 | Pathophysiology

Endometrial cancer research has gained some momentum in recent years and insights obtained from those studies have significant implications in the clinic. Endometrioid adenocarcinoma progresses through a premalignant phase of intraepithelial endometrial neoplasia in a large proportion of cases.[15] Other histologic types such as serous and clear cell carcinoma arise as a result of a sequence of genetic mutations. Mutations in the tumor suppressor p53 have been shown to play a pivotal role in serous endometrial cancer.[16]

2.3 | Diagnosis

The utility of population screening for endometrial cancer remains to be fully substantiated.[17] Transvaginal ultrasound (TVS) is a possible screening test, as it is reasonably sensitive and specific. Screening is only recommended for high-risk groups, such as those with Lynch type 2 syndrome with a wish for fertility preservation, before the decision for prophylactic hysterectomy is made at a later age.[18] In these cases, endometrial surveillance is performed by aspiration biopsy and transvaginal ultrasonography starting from the age of 35 years (annually until hysterectomy). Prophylactic surgery (hysterectomy and bilateral salpingo-oophorectomy), preferably using a minimally invasive approach, should be discussed at the age of 40 as an option for Lynch type 2 syndrome mutation carriers to prevent endometrial and ovarian cancer.[19]

After physical examination, endometrial cancer is usually suspected with ultrasound—an effective first test with a high negative predictive value when the endometrial thickness is less than 5 mm.[20] Specifically, combination of transvaginal ultrasound with endometrial biopsies obtained by curettage has been shown to have a negative predictive value of 96%.[20] 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 patients with diagnostic uncertainty, hysteroscopy may be performed, and with flexible instruments can also be done without recourse to general anesthesia. However, the prognostic role of cells that are transtubally flushed during hysteroscopy remains uncertain. Anesthesia might be necessary in cases of cervical stenosis or if patient tolerance does not permit an office procedure. Individuals whose pelvic examination is unsatisfactory may also be evaluated with transvaginal or abdominal ultrasound to rule out concomitant adnexal pathology.

After a histopathologic diagnosis of endometrial adenocarcinoma, other factors need to be assessed. These include the local extent of the tumor, evidence of metastatic disease, as well as perioperative risk.

The pathology report from endometrial sampling should indicate at least the tumor type and grade of the lesion. Overall there is only moderate agreement on tumor grade between preoperative endometrial sampling and final diagnosis, with the lowest agreement for grade 2 carcinomas. Agreement between hysteroscopic biopsy and final diagnosis is higher than for dilatation and curettage; however, it is not significantly higher than for office endometrial biopsy.[21]

Full biochemistry (renal and liver function tests), and blood count also represent routine tests in the diagnosis of corpus uterine cancers. A chest X-ray is often performed as it is a universally available, low-cost examination and the consequences of detecting lung metastases, although rare in early stage disease, are significant. Serum CA125 may be of value in advanced disease for follow-up. Evaluation for metastasis is useful particularly in patients with abnormal liver function tests, and clinical findings such as parametrial or vaginal tumor extension. In high-risk patients, CT-based imaging of the chest, abdomen, and pelvis or PET-CT may help determine the surgical approach. Cystoscopy and/or proctoscopy may be helpful if direct extension to the bladder or rectum is suspected.

3 | PROGNOSTIC TUMOR CHARACTERISTICS FOR HIGH-RISK DISEASE

Its early presentation following postmenopausal bleeding results in a generally good prognosis, but it should be treated using evidence-based protocols, and where appropriate, by expert multidisciplinary teams. Four main histopathologic criteria are recommended to determine high-risk disease:

1. Tumor grade 3 (poorly differentiated).
2. Lymphovascular space invasion.
3. Nonendometrioid histology (serous, clear cell, undifferentiated, small cell, anaplastic, etc.).
4. Cervical stromal involvement.

MRI scanning and intraoperative frozen section represent the most accurate means of assessing both the depth of myometrial invasion and cervical involvement.[22–24] Although CT and MRI are equivalent in terms of evaluating nodal metastases, neither is suitable to replace surgical lymph node assessment, which provides histological confirmation.[25,26] PET-CT is the best imaging method to evaluate lymph node and distant metastases, and could be considered in high-risk or advanced stage disease. The role of PET-MRI is currently being investigated.

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

4 | SURGICAL STAGING PROCEDURE FOR ENDOMETRIAL CANCER

Staging of endometrial cancer was changed from clinical to surgical in 1988, by the FIGO Gynecologic Oncology Committee. This recommendation has led to considerable debate and effort to define surgical staging procedures that can be implemented internationally. A generally recommended protocol includes opening of the abdomen with a

vertical midline 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. These procedures should be followed by careful palpation for suspicious or enlarged nodes in the aortic and pelvic areas. However, laparoscopic procedures have increasingly been introduced as standard, especially for early stage disease, as these have been proven safe and reduce acute treatment-related complications.[27,28] The recommended standard surgical procedure is an extra-fascial total hysterectomy with bilateral salpingo-oophorectomy. Adnexal removal is recommended even if the tubes and ovaries appear normal, as they may contain micrometastases. In premenopausal women with low-grade early stage disease, ovarian preservation could be considered.[29,30] Vaginal cuff removal is not advised, nor is there any benefit from excising parametrial tissue in the usual case. Where obvious cervical stromal involvement is demonstrated preoperatively, a modified radical hysterectomy has been historically performed. However, there is consensus (ESMO-ESGO-ESTRO) that simple hysterectomy with free margins together with pelvic and para-aortic lymphadenectomy may be sufficient.[31]

The safety of endoscopic surgery for the treatment of endometrial cancer has also been the subject of considerable debate. Recent studies have demonstrated that laparoscopic removal of the uterus and adnexae appears to be safe. For instance, not many differences have been reported in terms of major complications between abdominal hysterectomy and laparoscopically assisted vaginal hysterectomy (LAVH) or total laparoscopic hysterectomy (TLH). Additionally, laparoscopic interventions are associated with significant decreased risk of major surgical adverse events, shorter hospital stays, less pain, and faster recoveries.[32–34] Owing to the demonstrated oncological safety of the laparoscopic approach,[28,35] hysterectomy and bilateral salpingo-oophorectomy by this route is recommended in those patients with no contraindications to laparoscopy (e.g. large-volume uterus). The endoscopic route also appears safe in high-risk endometrial cancer.[36] This approach can be accompanied by a laparoscopic lymphadenectomy, if surgical staging is to be undertaken. Robotic surgery for morbidly obese patients represents a valuable option for experienced surgeons. In these instances, surgical management using robotics is safe and presents fewer perioperative complications compared with open surgery.[37] Furthermore, retrospective studies have suggested equivalent oncologic outcomes compared with traditional laparoscopic surgery.[38,39]

The utility of lymphadenectomy of the pelvic and para-aortic areas is disputed, albeit it is currently mandated through the staging system. Currently, it is advised that complete lymphadenectomy is reserved for cases with high-risk features. In contrast, selective node sampling has been deemed dubious as a routine approach. Since many individuals with endometrial cancer are obese or elderly, with concomitant medical problems, 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, which might be followed by removal of any enlarged or suspicious nodes. Documentation of positive nodes identifies a high-risk population and helps to tailor adjuvant treatment. Nodal resection also allows identification of node negative patients, potentially reducing the need for external beam radiotherapy.[19]

Several parameters advocate for aortic node sampling. These 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?

Full surgical staging is not required for low-risk tumors, defined as well-differentiated tumors with less than 50% myometrial invasion, with positive nodes in less than 5% of cases. Women with these tumors can be safely operated on by a general gynecologist. Patients at greater risk of extrauterine disease who may require lymphadenectomy should, in contrast, be operated on by gynecological oncologists. Care provided by gynecologic oncologists has been associated with better survival in high-risk cancers[40] and results in efficient use of healthcare resources and minimization of the potential morbidity associated with adjuvant radiation.[41]

A thorough preoperative assessment, with particular attention to the pathology and to radiological features has been defined as the most effective strategy for the triaging of these patients. Triaging for lymphadenectomy is also possible during surgery. Intraoperative assessment mainly involves assessment of myometrial invasion.[22,24,39] Grading on frozen section is possible, though suboptimal compared with preoperative grading.[24]

Concerning sentinel lymph node biopsy, several key surgical points should be respected[42]:

1. Expertise of the surgeon and attention to technical detail.
2. Superficial and deep cervical injection of dye.
3. Complete evaluation of the peritoneal cavity (sentinel lymph node mapping is for clinical Stage I, apparent uterine-confined disease).
4. Sentinel lymph node dissection begins with evaluation of the retroperitoneal spaces and identification of the sentinel drainage pathways that emanate from the parametria, followed by excision of the most proximal lymph nodes in the sentinel pathway.
5. Any suspicious lymph nodes should be removed regardless of sentinel lymph node mapping and frozen section analysis may influence the decision to perform para-aortic lymphadenectomy in some cases.
6. Performance of hemipelvic side-specific lymphadenectomy for mapping failure has been shown to reduce false-negative staging.
7. Enhanced pathology evaluation of sentinel lymph nodes with serial sectioning and immunohistochemistry stains increases the detection of low-volume metastasis.

6 | WHEN SHOULD SURGERY BE PERFORMED?

The effect of waiting time for surgical staging on survival outcome for endometrial cancer is controversial. It has been suggested that a longer waiting time for surgical staging was associated with worse survival outcomes in uterine cancer[43] and the delay between diagnosis and surgery should not exceed 6 weeks.[44] However, when focusing on type 1 endometrial cancer only, the waiting time for surgical staging was not associated with decreased survival outcome, presumably owing to its indolent growth and resulting excellent prognosis.[45]

7 | IS LYMPHADENECTOMY THERAPEUTIC?

Lymphadenectomy is required for accurate staging, yet its therapeutic benefits remain controversial. Historically, one case–control study suggested that lymphadenectomy may be beneficial therapeutically[46] and another showed it improved prognosis even in node-positive women.[47] Another retrospective study suggested that complete lymphadenectomy increases survival in patients with grade 3 tumors.[48] In contrast, two major trials of large-scale cohorts have shown that pelvic lymphadenectomy offers no therapeutic benefits compared with no lymphadenectomy.[49,50] These studies, however, have been criticized for several limiting factors. First, limited effort with respect to the extent of dissection and lymph node evaluation was made. Second, a high proportion of low-risk patients in these studies might have skewed the results. Finally, no direct decision on adjuvant therapy based on lymphadenectomy was designed as part of the protocols. At present, lymphadenectomy is primarily used for staging and should be considered in women with high-risk factors.[51] An international trial of the role of lymphadenectomy to direct adjuvant therapy for high-risk endometrial cancer (STATEC) has recently started. The ongoing ENGOT-EN2-DGCG trial (NCT01244789) aims to shed light into this issue by comparing survival in patients with Stage I grade 3 endometrioid endometrial cancer, Stage I and II type 2 endometrial cancer, or Stage II endometrioid endometrial cancer and without metastatic node after randomization for adjuvant chemotherapy.

In a retrospective study, para-aortic lymphadenectomy resulted in an improved outcome in intermediate and high-risk patients when compared with pelvic lymphadenectomy alone.[52] A limiting factor of this study was that adjuvant therapy was not comparable in the two groups. In patients who underwent both pelvic and para-aortic lymphadenectomy, 77% received chemotherapy as opposed to only 45% in the pelvic lymphadenectomy group. This uncertainty is the reason why addition of para-aortic lymphadenectomy is recommended if pelvic lymphadenectomy is being done, and explains different approaches among different centers.

Sentinel lymph node mapping has been introduced into the surgical staging of endometrial cancer with the goal to reduce morbidity associated with comprehensive lymphadenectomy and to obtain prognostic information from lymph node status. A recent meta-analysis reported overall detection rates higher than 80%, with 50% bilateral pelvic node detection rate and 17% para-aortic detection rate.[53] Use of indocyanine green increases the bilateral detection rate compared with blue dye. Additionally, cervical injection increases the bilateral sentinel lymph node detection rate but decreases the para-aortic detection rate compared with alternative injection techniques. The sensitivity of sentinel lymph node mapping to detect metastases is higher than 90%, reaching almost 100% in a meta-analysis.[53] Randomized studies have suggested that sentinel lymph node mapping can safely replace lymphadenectomy in the staging of endometrial cancer.[54,55]

Apart from the historical distinction between type 1 and 2 endometrial cancer, various approaches (genomic and immunochemistry) have been conducted to better predict prognosis and subsequently adapt therapy. The Cancer Genome Atlas Research Network identified four groups of endometrial carcinomas based on genomic features.[4] Similarly, many immunohistochemical markers have been studied to differentiate between low- and high-risk endometrial carcinomas. Several studies have tried to develop more applicable variants of the TCGA classification by using immunohistochemical markers and DNA sequencing techniques that can be done on formalin-fixed, paraffin embedded tissues.[56,57] L1 cell adhesion molecule (L1CAM) was introduced as a promising biomarker for identification of patients with poor outcome, which has been confirmed in subsequent studies.[58–60] Markers of the p53 pathway,[16] hormone receptor expression,[61] and microsatellite instability,[62] are several of the other relevant biomarkers to predict prognosis of endometrial cancer. Various approaches combining genomic characterization and biomarkers expression provide promising results to tailor adjuvant therapy.[63–65]

8 | ADJUVANT TREATMENT

At present, the indication for adjuvant radiation therapy is based on the presence of risk factors. Low-risk disease (Stage I, grade 1 or 2 with no or superficial myometrial invasion) does not require adjuvant radiation therapy. This was demonstrated in a Danish cohort study of low-risk women, in which surgery alone resulted in a 96% 5-year survival.[66] A seminal Norwegian trial,[67] which included 621 women treated after surgery with vaginal brachytherapy, indicated that overall survival was not improved by additional external beam radiation therapy (EBRT). This study, however, showed that adjuvant radiotherapy reduced the risk of pelvic recurrence. Three other large randomized trials (PORTEC-1 trial,[68] the US GOG#99 trial,[69] and the UK MRC ASTEC trial[70]) studying the benefits of pelvic radiation therapy as adjuvant therapy to surgery have supported its indication only for high-risk patients. The main finding from these trials is the significant reduction in the rates of vaginal and pelvic recurrence after EBRT, but without added survival benefit. In contrast, EBRT added to the risk of long-term morbidity. The patients without lymphadenectomy analyzed in the PORTEC and ASTEC trials presented similar recurrence and survival rates to those with documented node-negative disease in

the GOG#99 trial. Additionally, PORTEC-1 illustrated 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.[71]

Other trials have investigated the value of radiation as an adjuvant therapy in high-risk patients. The PORTEC-2 trial compared the adjuvant value of two radiation approaches, EBRT and vaginal brachytherapy, in 427 women with high/intermediate risk factors. The patients were randomized to EBRT or vaginal brachytherapy.[72] This trial showed that vaginal brachytherapy had excellent vaginal control rates (<2% at 5 years for both EBRT and vaginal brachytherapy groups), with minimal adverse 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.[73] Since this seminal trial, vaginal brachytherapy has replaced EBRT as standard adjuvant treatment for patients with high/intermediate risk factors.

However, in low-risk patients, adjuvant radiation therapy does not lead to a better survival. In a Danish study, omission of any EBRT or vaginal brachytherapy for high/intermediate risk disease led to an increase in recurrence rates (22% for intermediate risk disease, of which 15% locoregional) without affecting survival rates.[74] A patient preference study showed that patient's preferences are biased toward a treatment preventing relapse.[75] However, even treating all women with high/intermediate risk factors (grade 1–2 with deep invasion) is still overtreatment. The currently ongoing PORTEC-4a trial investigates the use of combined clinicopathologic, immunohistochemical, and molecular markers to determine the use of adjuvant vaginal brachytherapy or observation, keeping EBRT only for those with high-risk factors.

Since adjuvant radiotherapy alone and adjuvant chemotherapy alone have shown similar impact on overall or relapse-free survival in patients operated on for endometrial cancer,[76,77] several studies have investigated the effect of sequential combination of chemotherapy and radiotherapy. A meta-analysis pooling the results of two randomized trials (NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE-III) investigating the therapeutic value of combining adjuvant platinum-based chemotherapy with EBRT in patients with risk factors (grade 3 or deep invasion or adverse histologies) found 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).

Three other large randomized trials (GOG#249, GOG#258, PORTEC-3) are currently underway to support and expand on those findings. The randomized GOG-249 trial, which recruited 601 patients with Stage I–II endometrial cancer with high/intermediate or high-risk factors, compared vaginal brachytherapy plus three cycles of carboplatin-paclitaxel chemotherapy with pelvic EBRT alone; results showed no differences in relapse-free survival between the arms, while there was better pelvic control in the pelvic EBRT arm and more acute toxicity in the chemotherapy arm. From this trial, the authors concluded that for Stage I–II endometrial cancer with (high) risk features, pelvic EBRT is still the standard of care.[78] About 50% of the trial population had grade 1–2 disease with a baseline 5-year survival of 86%–91% and for these patients, vaginal brachytherapy alone might be preferable.

In the PORTEC-3 trial, patients with high-risk Stage I–II (32% grade 3 and 29% serous or clear cell cancer) or with Stage III (45%) endometrial cancer were randomly allocated to pelvic EBRT alone or EBRT with two concurrent cycles of cisplatin in weeks 1 and 4 of EBRT, followed by four cycles of carboplatin and paclitaxel. At a median follow-up of 60.2 months, there was no significant difference in overall survival between the arms, but a significant difference in failure-free survival, with women in the combined chemoradiotherapy arm having 7% higher failure-free survival (76% vs 69%; *P*=0.022).[79] Women with Stage III disease had the highest absolute benefit of chemoradiotherapy, with 5-year failure-free survival of 69% versus 58% for radiotherapy alone (*P*=0.03). The large majority of recurrences were at distant sites (22% vs 28%) and pelvic recurrence was rare. In view of the toxicity of chemoradiotherapy with significantly more grade 3–4 adverse events during and after treatment and a persisting higher rate of grade 2 sensory neuropathy at longer term, it can be concluded that the combined schedule cannot be recommended as a new standard of care for Stage I–II disease, but women with Stage III endometrial cancer should be counseled about the failure-free survival benefit.

In the randomized GOG-258 trial for Stage III and Stage IV (residual disease <2 cm allowed), 813 patients were randomized to receive either chemoradiotherapy as used in PORTEC-3 or six cycles of carboplatin and paclitaxel without radiotherapy.[80] Addition of radiation therapy to chemotherapy did not improve overall or progression-free survival, but the rate of pelvic (7% vs 3%; HR 0.36) and para-aortic nodal relapse (21% vs 10%; HR 0.43) was significantly higher in the chemotherapy alone arm. In the ongoing ENGOT-EN2-DGCG-trial, patients with node-negative endometrial cancer with high-risk features are randomized to adjuvant chemotherapy (six cycles of carboplatin-paclitaxel) or observation, with or without brachytherapy in both arms. This trial could provide some answers to the questions regarding optimal use and optimal schedules of adjuvant therapy for women with high-risk endometrial cancer.

In summary, adjuvant radiation therapy is discouraged in low-risk patients and indicated in high-risk patients. Specifically, patients with grade 1–2 tumors and no more than 50% myometrial invasion, or for those with only a single risk factor, adjuvant radiotherapy is not recommended. For patients with high/intermediate risk factors (at least two 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 Stage I–II disease (grade 3 and deep invasion and/or LVSI, unfavorable histologies, unfavorable molecular factors), pelvic EBRT remains the standard of care. Overall, the need for EBRT decreases when surgical staging identifies node-negative disease.[19] Surgical staging also allows clinicians to identify node-positive (Stage III) disease that benefits from adjuvant therapy. For women with Stage III endometrial cancer, the combination of adjuvant chemotherapy and radiation therapy seems most effective to maximize recurrence-free survival. Ongoing and new studies with more individual assessment of molecular features will investigate their role in directing adjuvant treatment.

9 | PROGESTOGEN THERAPY

Although the use of progesterone therapy has been widely recognized in the past, a meta-analysis of six randomized trials totalizing 3339 women has shown no survival benefit for adjuvant progestogen therapy in endometrial cancer.[81] A subsequently published randomized trial of 1012 women also failed to demonstrate any survival benefit.[82] However, hormonal therapy can provide prolonged remission of metastatic disease in women with grade 1 and/or ER/PR receptor-positive disease. Where possible, ER/PR should be determined on a biopsy of the recurrent tumor because the hormone receptor status may change over time.[83]

10 | STAGE II

10.1 | Occult Stage II disease

Therapeutic management of patients with clinically occult Stage II disease is similar to that of patients with Stage I disease.

10.2 | Clinical overt Stage II disease

In these cases, radical hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy, and selective aortic node dissection have been historically used as primary treatment. However, it is important to note that this strategy has been poorly supported by the medical literature. Results of one of the few retrospective studies could not find any survival benefit from radical hysterectomy for patients with suspected gross cervical involvement in comparison with simple or modified radical hysterectomy.[31,84] Surgical treatment in patients with suspected gross cervical involvement is currently under evaluation, as radical hysterectomy increases the risk of adverse events. 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.[85,86] Adjuvant radiotherapy is usually reserved for patients with involved nodes or other adverse factors and/or close or involved surgical margins.

However, neoadjuvant therapy followed by a less extensive simple hysterectomy can represent an alternative. If surgery is not considered feasible because of tumor extension and/or in medically inoperable patients, full pelvic radiotherapy and intracavitary brachytherapy, as in cervical cancer, may be employed either preoperatively or definitively with high disease control and survival rates.[87,88]

11 | STAGE III

Most patients with Stage III endometrial cancer are managed by complete surgical resection of all pelvic and/or nodal disease, followed by postoperative EBRT and/or chemotherapy.

As primary tumors of both the ovary and the endometrium may be present in patients with presumed Stage III disease with adnexal involvement, full surgical staging and expert pathologic examination of the specimen is recommended in these cases.

Adjuvant treatment is indicated for women with Stage III disease as detailed in Section 8 above.

Patients with clinical Stage III endometrial carcinoma in which surgical resection is not possible are treated primarily by pelvic irradiation, with or without chemotherapy.[89] Once therapy has been completed, exploratory laparotomy should be considered for those patients whose disease now appears to be resectable.

12 | STAGE IV

Optimal management in women with Stage IV endometrial cancer includes cytoreductive surgery, which is associated with superior overall survival outcome.[90] In advanced disease, neoadjuvant chemotherapy is also an option, particularly if postoperative morbidity is considered likely and/or ascites is present.[91] After surgery, platinum-based chemotherapy should be considered, based on the trials cited above. 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.

As neoadjuvant chemotherapy is the treatment of choice in advanced-stage disease, as well as in relapsed disease, several studies have investigated the optimal combinations of chemotherapeutic agents that represent the most effective neoadjuvant therapy for Stage IV endometrial cancer patients. As the combinations of doxorubicin, cisplatin, and paclitaxel (TAP)[92] and carboplatin and paclitaxel have been shown to be most effective, these have been the most studied. The former, however, is much more toxic and resulted in treatment-related deaths. A comparative trial of the GOG, randomizing to either TAP or carboplatin-paclitaxel chemotherapy has shown both schedules to have similar efficacy, while carboplatin-paclitaxel was preferred for lower morbidity; full results have not yet been published.[93]

Two randomized trials have compared doxorubicin monotherapy versus doxorubicin–cisplatin doublet.[94,95] Superiority of the combination chemotherapy in terms of progression-free and overall survival, with manageable toxicity, was confirmed in both studies. Doxorubicin–cisplatin doublet versus doxorubicin–cisplatin–paclitaxel triplet was tested in a phase III randomized trial.[92] The triplet regimen resulted in a significantly superior progression-free survival, although this regimen proved to be too toxic, with treatment-related deaths despite the use of growth factors.

The carboplatin–paclitaxel doublet has been tested in several phase II studies in advanced-stage or relapsed disease, demonstrating a response rate of 65%–75% and progression-free survival of about 14 months.[96–98] The interim results of the GOG-0209 trial, a noninferiority trial comparing the combination of doxorubicin, cisplatin, and paclitaxel (TAP) and G-CSF versus carboplatin and paclitaxel, show that the carboplatin and paclitaxel doublet is not inferior to TAP.[98] The better tolerability profile of carboplatin–paclitaxel has led to the

recommendation of the use of carboplatin and paclitaxel as the standard for adjuvant treatment in Stage III and IV disease.

Pelvic radiotherapy in Stage IV disease is sometimes considered to provide local tumor control. Similarly, it has also been suggested that patients with vaginal bleeding or pain from a local tumor mass, or with leg edema due to lymph node involvement, should be treated with pelvic radiotherapy. Palliation of brain or bone metastases can be effectively obtained with short courses (1–5 fractions) of radiotherapy.

13 | SPECIAL CONSIDERATIONS

13.1 | Diagnosis post hysterectomy

Several therapeutic management problems have been reported to arise from post hysterectomy diagnosis. This is particularly true in cases where the adnexae have not been removed, which most often arises following vaginal hysterectomy for pelvic organ 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 may be candidates for additional surgery to remove the adnexae, or adjuvant EBRT. 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

The most common reasons for endometrial carcinoma to be deemed medically inoperable are morbid obesity and severe cardiopulmonary disease. In such cases, uterine brachytherapy is advised and has been shown to achieve cure rates in excess of 70%. In the presence of prognostic factors suggesting a high risk of involved nodes it can be combined with EBRT.[88] Primary radiation therapy for medically inoperable patients with clinical Stage I and II endometrial adenocarcinoma provides disease control, with fewer than 16% of surviving patients experiencing recurrence.[99]

For patients with a well-differentiated lesion, contraindications to general anesthesia, and who are unsuitable for radiotherapy, high-dose progestins may be used. Trials using intrauterine hormone releasing devices instead of oral progestins are underway. In patients with contraindications to high-dose progestins, the uterine hormone releasing device can be considered.

13.3 | Diagnosis in young women

Since endometrial carcinoma is uncommon in women the age of 35 years, diagnosis during the reproductive years should be made with caution, 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 a granulosa cell tumor, polycystic ovaries, or obesity. Fertility preservation is only recommended in grade 1 endometrioid endometrial cancer not invading the myometrium (as determined by MRI).[19] Progestins such as megestrol acetate (160–320 mg/d) or medroxyprogesterone acetate (400–600 mg/d) may be appropriate in these situations. The safety of such an approach has been reported in several studies, for grade 1 endometrial adenocarcinoma and atypical hyperplasia.[100] Few studies reported the safety of fertility-sparing management of grade 2 endometrial cancer.[101] However, a recent large retrospective analysis reported an increased risk associated with uterine preservation in patients with grade 2 and 3 endometrial adenocarcinoma and suggested such management should be limited in time.[29] Equivocal lesions should be examined by an experienced pathologist. In cases of complete response, conception must be encouraged and referral to a fertility clinic is recommended. Although the literature describes successful outcomes, fatal recurrences of endometrial cancer after a conservative approach have been reported; as such, the patient must be informed about the nonstandard treatment. Hysterectomy should be recommended once childbearing is complete.

Ovarian preservation, in patients with grade 1 intramucosal endometrial adenocarcinoma, might represent a beneficial therapeutic option, as this management was not associated with an increase in cancer-related mortality in the largest sample available.[30]

14 | FOLLOW-UP

The objectives of follow-up care for treated endometrial cancer patients are to provide reassurance, diagnose early recurrence, and collect data. The clinical and cost-effectiveness of follow-up implementation has been addressed internationally in one prospective[102] and several retrospective studies.[103–105] Overall, these studies found that about 75% of recurrences in endometrial cancer patients are symptomatic and 25% asymptomatic. Neither recurrence-free nor overall survival was 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. Another important finding of those studies was that the use of routine follow-up Pap smears and chest X-rays is not cost-effective. Given the high salvage rate following radiotherapy, it has been suggested that nonirradiated patients are a group that would benefit from regular follow-up to detect early vaginal recurrence.[106]

Two systematic reviews[107,108] documented evidence for the utility of follow-up examinations, and concluded that follow-up should be practical and directed by symptoms and pelvic examination. These studies also recommend reduction in the frequency of follow-up visits for low-risk patients. Given the low risk of recurrence, vaginal cytology can be omitted, resulting in reduced healthcare costs.[109] It appears that visual inspection is sufficient, since positive cytology is merely diagnosed in cases of symptomatic recurrence.[104,110,111]

More recently, studies of minimal follow-up (nurse led, telephone based) after the first year have been done and results are awaited.[112,113] First results suggest good patient acceptability once prompt access to evaluation in case of symptoms is ensured.

Follow-up care should also include patient counseling as these patients are at risk of second cancers following their primary

endometrial cancer. For instance, the estimated incidence rate of Lynch syndrome in an unselected endometrial cancer population is 3%–6%.[114] Routine pathologic screening of mismatch repair deficiencies in the endometrial cancer specimen, similar to colorectal cancer, has been advocated and is increasingly being introduced in practice.[115] However, in most women with mismatch repair deficiency this is caused by MLH1 promoter hypermethylation and a test of this before referring a patient to a clinical geneticist is recommended. Survivors of endometrial cancer have a three-fold increased risk of second cancer when compared with a matched population. This risk increase seems mainly related to lifestyle factors and genetic susceptibility.[116] These women should be counseled on exercise and weight loss programs.

15 | RECURRENCE

The therapeutic management for localized recurrences includes surgery, radiation therapy, or a combination of both. The choice of these strategies depends on the primary therapy. Screening for distant metastases should be performed before deciding on curative treatment. If primary therapy consisted of surgery alone, radiotherapy represents an effective salvage strategy in cases of vaginal or central pelvic recurrence. In these cases, a combination of EBRT and brachytherapy, preferably image guided, is usually required. Large recurrences should be evaluated for excision, followed by radiotherapy. Alternatively, chemotherapy may be considered to decrease the volume of the recurrence and hence improve the chances of complete surgical resection. Additional chemotherapy with radiotherapy is being evaluated in an ongoing GOG trial. Extended surgery may be justified, especially in patients who have had prior radiation therapy. However, radical surgery within irradiated fields (especially in the case of sidewall recurrence) frequently results in significant morbidity, such as treatment-resistant pain and fistula formation. The results of pelvic exenteration in properly selected cases (central recurrences without signs of distant spread) are similar to those obtained in cervical cancer. Overall, survival rates in well-selected patients are in the order of 50%.

Nonlocalized recurrent tumors are usually treated with progestin therapy: medroxyprogesterone acetate 50–100 mg three times a day or megestrol acetate 80 mg 2–3 times a day. Treatment is continued as long as the disease is stable or in remission. Maximum clinical response may only be observed three or more months after therapy initiation. 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.[96,117] Several ongoing trials are currently investigating the clinical applicability of targeted therapies in patients with nonlocalized recurrent tumors

16 | RECOMMENDATIONS FOR PRACTICE

1. A definitive tissue diagnosis must be obtained preoperatively. This will result in better selection of the surgical approach, and help to differentiate tumors at low- and high-risk of lymph node metastasis. Imaging might be used to determine depth of myometrial invasion, cervical involvement, and lymph node enlargement. **Level of Evidence C**
2. Although lymphadenectomy in clinical Stage I endometrial cancer decreases recurrence, it has no impact on overall or relapse-free survival. **Level of Evidence A**. In the clinic, lymphadenectomy should be performed for staging only in high-risk cases. There is little evidence to support a therapeutic benefit, but it may be used to select women with positive nodes for adjuvant therapy and reduce the need for EBRT in node-negative patients. **Level of Evidence C**
3. In patients with Stage I endometrial cancer with low-, intermediate-, or high/intermediate risk features, adjuvant radiotherapy has no impact on survival, but significantly reduces the rate of pelvic recurrence. **Level of Evidence A**. In high-risk patients, vaginal brachytherapy effectively reduces the risk of vaginal relapse. **Level of Evidence A**. EBRT should be considered in patients with presumed Stage I–II disease with strong adverse factors, positive nodes, or advanced stage disease to ensure pelvic control. **Level of Evidence A**
4. The addition of adjuvant chemotherapy to radiotherapy in patients with high-risk disease improves progression-free survival, but an overall survival benefit is unproven. **Level of Evidence A**
5. Adjuvant chemotherapy for patients with early stage, high-risk disease should only be considered for those with serous cancers and after individual patient counseling (no proven benefit in overall survival), and preferably be done within clinical trials.
6. Chemotherapy is a more effective strategy compared with whole abdominal radiation in patients with Stage IV disease and abdominal disease with residual nodules less than 2 cm diameter. **Level of Evidence A**
7. Targeted therapy in endometrial cancer should be further developed and only considered within clinical trials.
8. The use of adjuvant hormonal therapy (progestogen) has not been properly substantiated. **Level of Evidence A**
9. High-risk and advanced stage endometrial cancer patients should be managed where possible by a gynecological oncologist, working within a multidisciplinary team. **Level of Evidence A**
10. Patients with endometrial cancer are frequently old and frail, and this should be taken into consideration when prescribing adjuvant therapy. Professional consensus

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

ACKNOWLEDGMENTS

This chapter updates the information published in the FIGO Cancer Report 2015 (Amant F, Mirza MR, Koskas M, Creutzberg CL. Cancer of the corpus uteri. *Int J Gynecol Obstet*. 2015;131(Suppl.2):S96–104).

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

1. Mbatani N, Olawaiye A, Prat J. Uterine sarcomas. *Int J Gynecol Obstet*. 2018;143(Suppl.2):51–58.
2. Kurman RJ, Carcangiu ML, Herrington S, Young RH. *Tumours of the Female Reproductive Organs*. WHO classification of tumours. Lyon: IARC Press; 2014.
3. Piulats JM, Guerra E, Gil-Martin M, et al. Molecular approaches for classifying endometrial carcinoma. *Gynecol Oncol*. 2017;145:200–207.
4. Cancer Genome Atlas Research N, Kandoth C, Schultz N, et al. Integrated genomic characterization of endometrial carcinoma. *Nature*. 2013;497:67–73.
5. Scholten AN, Smit VT, Beerman H, van Putten WL, Creutzberg CL. Prognostic significance and interobserver variability of histologic grading systems for endometrial carcinoma. *Cancer*. 2004;100:764–772.
6. Winer I, Ahmed QF, Mert I, et al. Significance of lymphovascular space invasion in uterine serous carcinoma: What matters more; extent or presence? *Int J Gynecol Pathol*. 2015;34:47–56.
7. Aristizabal P, Graesslin O, Barranger E, et al. A suggested modification to FIGO stage I endometrial cancer. *Gynecol Oncol*. 2014;133:192–196.
8. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65:87–108.
9. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: A systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371:569–578.
10. Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. *Eur J Cancer*. 2010;46:2593–2604.
11. Cust AE. Physical activity and gynecologic cancer prevention. *Recent Results Cancer Res*. 2011;186:159–185.
12. Nevadunsky NS, Van Arsdale A, Strickler HD, et al. Obesity and age at diagnosis of endometrial cancer. *Obstet Gynecol*. 2014;124(2 Pt 1):300–306.
13. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68:7–30.
14. Wartko P, Sherman ME, Yang HP, Felix AS, Brinton LA, Trabert B. Recent changes in endometrial cancer trends among menopausal-age U.S. women. *Cancer Epidemiol*. 2013;37:374–377.
15. Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. *Cancer*. 1985;56:403–412.
16. Edmondson RJ, Crosbie EJ, Nickkho-Amiry M, et al. Markers of the p53 pathway further refine molecular profiling in high-risk endometrial cancer: A TransPORTEC initiative. *Gynecol Oncol*. 2017;146:327–333.
17. Jacobs I, Gentry-Maharaj A, Burnell M, et al. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: A case-control study within the UKCTOCS cohort. *Lancet Oncol*. 2011;12:38–48.
18. Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2009: A review of current American Cancer Society guidelines and issues in cancer screening. *CA Cancer J Clin*. 2009;59:27–41.
19. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27:16–41.
20. Karlsson B, Granberg S, Wikland M, et al. Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding–a Nordic multicenter study. *Am J Obstet Gynecol*. 1995;172:1488–1494.
21. Visser NCM, Reijnen C, Massuger L, Nagtegaal ID, Bulten J, Pijnenborg JMA. Accuracy of endometrial sampling in endometrial carcinoma: A systematic review and meta-analysis. *Obstet Gynecol*. 2017;130:803–813.
22. Ugaki H, Kimura T, Miyatake T, et al. Intraoperative frozen section assessment of myometrial invasion and histology of endometrial cancer using the revised FIGO staging system. *Int J Gynecol Cancer*. 2011;21:1180–1184.
23. Cade TJ, Quinn MA, McNally OM, Neesham D, Pyman J, Dobrotwir A. Predictive value of magnetic resonance imaging in assessing myometrial invasion in endometrial cancer: Is radiological staging sufficient for planning conservative treatment? *Int J Gynecol Cancer*. 2010;20:1166–1169.
24. Ozturk E, Dikensoy E, Balat O, Ugur MG, Aydin A. Intraoperative frozen section is essential for assessment of myometrial invasion but not for histologic grade confirmation in endometrial cancer: A ten-year experience. *Arch Gynecol Obstet*. 2012;285:1415–1419.
25. DelMaschio A, Vanzulli A, Sironi S, et al. Estimating the depth of myometrial involvement by endometrial carcinoma: Efficacy of transvaginal sonography vs MR imaging. *AJR Am J Roentgenol*. 1993;160:533–538.
26. Epstein E, Blomqvist L. Imaging in endometrial cancer. *Best Pract Res Clin Obstet Gynaecol*. 2014;28:721–739.
27. Janda M, Gebski V, Davies LC, et al. Effect of total laparoscopic hysterectomy vs total abdominal hysterectomy on disease-free survival among women with Stage I endometrial cancer: A randomized clinical trial. *JAMA*. 2017;317:1224–1233.
28. Walker JL, Piedmonte MR, Spirtos NM, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 Study. *J Clin Oncol*. 2012;30:695–700.
29. Gonthier C, Trefoux-Bourdet A, Koskas M. Impact of conservative managements in young women with Grade 2 or 3 endometrial adenocarcinoma confined to the endometrium. *Int J Gynecol Cancer*. 2017;27:493–499.
30. Koskas M, Bendifallah S, Luton D, Darai E, Rouzier R. Safety of uterine and/or ovarian preservation in young women with grade 1 intramucous endometrial adenocarcinoma: A comparison of survival according to the extent of surgery. *Fertil Steril*. 2012;98:1229–1235.
31. Phelippeau J, Koskas M. Impact of radical hysterectomy on survival in patients with Stage 2 Type1 endometrial carcinoma: A matched cohort study. *Ann Surg Oncol*. 2016;23:4361–4367.
32. Walker JL, Piedmonte MR, Spirtos NM, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. *J Clin Oncol*. 2009;27:5331–5336.
33. Mourits MJ, Bijen CB, Arts HJ, et al. Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: A randomised trial. *Lancet Oncol*. 2010;11:763–771.
34. Obermair A, Janda M, Baker J, et al. Improved surgical safety after laparoscopic compared to open surgery for apparent early stage endometrial cancer: Results from a randomised controlled trial. *Eur J Cancer*. 2012;48:1147–1153.
35. Galaal K, Bryant A, Fisher AD, Al-Khaduri M, Kew F, Lopes AD. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. *Cochrane Database Syst Rev*. 2012;(9):CD006655.
36. Koskas M, Jozwiak M, Fournier M, et al. Long-term oncological safety of minimally invasive surgery in high-risk endometrial cancer. *Eur J Cancer*. 2016;65:185–191.
37. Bernardini MQ, Gien LT, Tipping H, Murphy J, Rosen BP. Surgical outcome of robotic surgery in morbidly obese patient with endometrial cancer compared to laparotomy. *Int J Gynecol Cancer*. 2012;22:76–81.

38. Cardenas-Goicoechea J, Shepherd A, Momeni M, et al. Survival analysis of robotic versus traditional laparoscopic surgical staging for endometrial cancer. *Am J Obstet Gynecol*. 2014;210:160.e161–160.e111.
39. Wright JD, Burke WM, Wilde ET, et al. Comparative effectiveness of robotic versus laparoscopic hysterectomy for endometrial cancer. *J Clin Oncol*. 2012;30:783–791.
40. Chan JK, Sherman AE, Kapp DS, et al. Influence of gynecologic oncologists on the survival of patients with endometrial cancer. *J Clin Oncol*. 2011;29:832–838.
41. Roland PY, Kelly FJ, Kulwicki CY, Blitzer P, Curcio M, Orr JW Jr. The benefits of a gynecologic oncologist: A pattern of care study for endometrial cancer treatment. *Gynecol Oncol*. 2004;93:125–130.
42. Holloway RW, Abu-Rustum NR, Backes FJ, et al. Sentinel lymph node mapping and staging in endometrial cancer: A Society of Gynecologic Oncology literature review with consensus recommendations. *Gynecol Oncol*. 2017;146:405–415.
43. Elit LM, O'Leary EM, Pond GR, Seow HY. Impact of wait times on survival for women with uterine cancer. *J Clin Oncol*. 2014;32:27–33.
44. Strohl AE, Feinglass JM, Shahabi S, Simon MA. Surgical wait time: A new health indicator in women with endometrial cancer. *Gynecol Oncol*. 2016;141:511–515.
45. Matsuo K, Opper NR, Ciccone MA, et al. Time interval between endometrial biopsy and surgical staging for type I endometrial cancer: Association between tumor characteristics and survival outcome. *Obstet Gynecol*. 2015;125:424–433.
46. Kilgore LC, Partridge EE, Alvarez RD, et al. Adenocarcinoma of the endometrium: Survival comparisons of patients with and without pelvic node sampling. *Gynecol Oncol*. 1995;56:29–33.
47. Larson DM, Broste SK, Krawisz BR. Surgery without radiotherapy for primary treatment of endometrial cancer. *Obstet Gynecol*. 1998;91:355–359.
48. Cragun JM, Havrilesky LJ, Calingaert B, et al. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. *J Clin Oncol*. 2005;23:3668–3675.
49. Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): A randomised study. *Lancet*. 2009;373:125–136.
50. Benedetti Panici P, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: Randomized clinical trial. *J Natl Cancer Inst*. 2008;100:1707–1716.
51. Aalders JG, Thomas G. Endometrial cancer–revisiting the importance of pelvic and para aortic lymph nodes. *Gynecol Oncol*. 2007;104:222–231.
52. Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): A retrospective cohort analysis. *Lancet*. 2010;375:1165–1172.
53. Bodurtha Smith AJ, Fader AN, Tanner EJ. Sentinel lymph node assessment in endometrial cancer: A systematic review and meta-analysis. *Am J Obstet Gynecol*. 2017;216:459–476.e410.
54. Rossi EC, Kowalski LD, Scalici J, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): A multicentre, prospective, cohort study. *Lancet Oncol*. 2017;18:384–392.
55. Soliman PT, Westin SN, Dioun S, et al. A prospective validation study of sentinel lymph node mapping for high-risk endometrial cancer. *Gynecol Oncol*. 2017;146:234–239.
56. Talhouk A, McConechy MK, Leung S, et al. A clinically applicable molecular-based classification for endometrial cancers. *Br J Cancer*. 2015;113:299–310.
57. Talhouk A, McConechy MK, Leung S, et al. Confirmation of ProMisE: A simple, genomics-based clinical classifier for endometrial cancer. *Cancer*. 2017;123:802–813.
58. Zeimet AG, Reimer D, Huszar M, et al. L1CAM in early-stage type I endometrial cancer: Results of a large multicenter evaluation. *J Natl Cancer Inst*. 2013;105:1142–1150.
59. van der Putten LJ, Visser NC, van de Vijver K, et al. L1CAM expression in endometrial carcinomas: An ENITEC collaboration study. *Br J Cancer*. 2016;115:716–724.
60. Bosse T, Nout RA, Stelloo E, et al. L1 cell adhesion molecule is a strong predictor for distant recurrence and overall survival in early stage endometrial cancer: Pooled PORTEC trial results. *Eur J Cancer*. 2014;50:2602–2610.
61. Trovik J, Wik E, Werner HM, et al. Hormone receptor loss in endometrial carcinoma curettage predicts lymph node metastasis and poor outcome in prospective multicentre trial. *Eur J Cancer*. 2013;49:3431–3441.
62. Zighelboim I, Goodfellow PJ, Gao F, et al. Microsatellite instability and epigenetic inactivation of MLH1 and outcome of patients with endometrial carcinomas of the endometrioid type. *J Clin Oncol*. 2007;25:2042–2048.
63. Stelloo E, Bosse T, Nout RA, et al. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. *Mod Pathol*. 2015;28:836–844.
64. van der Putten LJM, Visser NCM, van de Vijver K, et al. Added value of estrogen receptor, progesterone receptor, and L1 cell adhesion molecule expression to histology-based endometrial carcinoma recurrence prediction models: An ENITEC collaboration study. *Int J Gynecol Cancer*. 2018;28:514–523.
65. Kommoss S, McConechy MK, Kommoss F, et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. *Ann Oncol*. 2018;29:1180–1188.
66. Poulsen HK, Jacobsen M, Bertelsen K, et al. Adjuvant radiation therapy is not necessary in the management of endometrial carcinoma stage I, low risk cases. *Int J Gynecol Cancer*. 1996;6:38–43.
67. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: Clinical and histopathologic study of 540 patients. *Obstet Gynecol*. 1980;56:419–427.
68. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: Multicentre randomised trial. PORTEC Study Group. Post operative radiation therapy in endometrial carcinoma. *Lancet*. 2000;355:1404–1411.
69. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: A Gynecologic Oncology Group study. *Gynecol Oncol*. 2004;92:744–751.
70. Blake P, Swart AM, Orton J, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): Pooled trial results, systematic review, and meta-analysis. *Lancet*. 2009;373:137–146.
71. Creutzberg CL, van Putten WL, Koper PC, et al. Survival after relapse in patients with endometrial cancer: Results from a randomized trial. *Gynecol Oncol*. 2003;89:201–209.
72. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): An open-label, non-inferiority, randomised trial. *Lancet*. 2010;375:816–823.
73. Nout RA, Putter H, Jurgenliemk-Schulz IM, et al. Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: First results of the randomized PORTEC-2 trial. *J Clin Oncol*. 2009;27:3547–3556.
74. Ortoft G, Hansen ES, Bertelsen K. Omitting adjuvant radiotherapy in endometrial cancer increases the rate of locoregional recurrences but has no effect on long-term survival: The Danish Endometrial Cancer Study. *Int J Gynecol Cancer*. 2013;23:1429–1437.

75. Kunneman M, Pieterse AH, Stiggelbout AM, et al. Treatment preferences and involvement in treatment decision making of patients with endometrial cancer and clinicians. *Br J Cancer*. 2014;111:674–679.
76. Susumu N, Sagae S, Udagawa Y, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: A Japanese Gynecologic Oncology Group study. *Gynecol Oncol*. 2008;108:226–233.
77. Maggi R, Lissoni A, Spina F, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: Results of a randomised trial. *Br J Cancer*. 2006;95:266–271.
78. Randall M, Filiaci V, McMeekin D, et al. A Phase 3 trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy in patients with high-risk, early-stage endometrial cancer: A Gynecology Oncology Group Study. *Int J Rad Oncol Biol Phys*. 2017;99:1313.
79. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): Final results of an international, open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2018;19:295–309.
80. Matei D, Filiaci VL, Randall M, Steinhoff M, DiSilvestro P, Moxley KM. A randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel vs. carboplatin and paclitaxel for optimally debulked, advanced endometrial carcinoma. *J Clin Oncol*. 2017;35:5505.
81. Martin-Hirsch PL, Lilford RJ, Jarvis GJ. Adjuvant progestagen therapy for the treatment of endometrial cancer: Review and meta-analyses of published randomised controlled trials. *Eur J Obstet Gynecol Reprod Biol*. 1996;65:201–207.
82. COSA-NZ-UK Endometrial Cancer Study Groups. Adjuvant medroxyprogesterone acetate in high-risk endometrial cancer. *Int J Gynecol Cancer*. 1998;8: 387–391.
83. Vandenput I, Trovik J, Leunen K, et al. Evolution in endometrial cancer: Evidence from an immunohistochemical study. *Int J Gynecol Cancer*. 2011;21:316–322.
84. Takano M, Ochi H, Takei Y, et al. Surgery for endometrial cancers with suspected cervical involvement: Is radical hysterectomy needed (a GOTIC study)? *Br J Cancer*. 2013;109:1760–1765.
85. Sartori E, Gadducci A, Landoni F, et al. Clinical behavior of 203 stage II endometrial cancer cases: The impact of primary surgical approach and of adjuvant radiation therapy. *Int J Gynecol Cancer*. 2001;11:430–437.
86. Mariani A, Webb MJ, Keeney GL, Calori G, Podratz KC. Role of wide/radical hysterectomy and pelvic lymph node dissection in endometrial cancer with cervical involvement. *Gynecol Oncol*. 2001;83:72–80.
87. Lee MH, Aquino-Parsons C, Hoskins PJ, Lim P, Kwon JS. Preoperative radiotherapy for inoperable stage II endometrial cancer: Insights into improving treatment and outcomes. *J Obstet Gynaecol Can*. 2013;35:635–639.
88. van der Steen-Banasik E, Christiaens M, Shash E, et al. Systemic review: Radiation therapy alone in medical non-operable endometrial carcinoma. *Eur J Cancer*. 2016;65:172–181.
89. Vargo JA, Boisen MM, Comerci JT, et al. Neoadjuvant radiotherapy with or without chemotherapy followed by extrafascial hysterectomy for locally advanced endometrial cancer clinically extending to the cervix or parametria. *Gynecol Oncol*. 2014;135:190–195.
90. Barlin JN, Puri I, Bristow RE. Cytoreductive surgery for advanced or recurrent endometrial cancer: A meta-analysis. *Gynecol Oncol*. 2010;118:14–18.
91. Vandenput I, Van Calster B, Capoen A, et al. Neoadjuvant chemotherapy followed by interval debulking surgery in patients with serous endometrial cancer with transperitoneal spread (stage IV): A new preferred treatment? *Br J Cancer*. 2009;101:244–249.
92. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: A Gynecologic Oncology Group Study. *J Clin Oncol*. 2004;22:2159–2166.
93. Miller D, Filiaci V, Fleming G, et al. Late-breaking Abstract 1: Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. *Gynecol Oncol*. 2012;125:771.
94. van Wijk FH, Aapro MS, Bolis G, et al. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: Definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer Group. *Ann Oncol*. 2003;14:441–448.
95. Thigpen JT, Brady MF, Homesley HD, et al. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: A gynecologic oncology group study. *J Clin Oncol*. 2004;22:3902–3908.
96. Akram T, Maseelall P, Fanning J. Carboplatin and paclitaxel for the treatment of advanced or recurrent endometrial cancer. *Am J Obstet Gynecol*. 2005;192:1365–1367.
97. Hoskins PJ, Swenerton KD, Pike JA, et al. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: A phase II study. *J Clin Oncol*. 2001;19:4048–4053.
98. Sorbe B, Andersson H, Boman K, Rosenberg P, Kalling M. Treatment of primary advanced and recurrent endometrial carcinoma with a combination of carboplatin and paclitaxel-long-term follow-up. *Int J Gynecol Cancer*. 2008;18:803–808.
99. Podzielinski I, Randall ME, Breheny PJ, et al. Primary radiation therapy for medically inoperable patients with clinical stage I and II endometrial carcinoma. *Gynecol Oncol*. 2012;124:36–41.
100. Koskas M, Uzan J, Luton D, Rouzier R, Darai E. Prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma: Systematic review and meta-analysis. *Fertil Steril*. 2014;101:785–794.e783.
101. Hwang JY, Kim DH, Bae HS, et al. Combined oral medroxyprogesterone/levonorgestrel-intrauterine system treatment for women with Grade 2 Stage IA endometrial cancer. *Int J Gynecol Cancer*. 2017;27:738–742.
102. Allsop JR, Preston J, Crocker S. Is there any value in the long-term follow up of women treated for endometrial cancer? *Br J Obstet Gynaecol*. 1997;104:122.
103. Salvesen HB, Akslen LA, Iversen T, Iversen OE. Recurrence of endometrial carcinoma and the value of routine follow up. *Br J Obstet Gynaecol*. 1997;104:1302–1307.
104. Agboola OO, Grunfeld E, Coyle D, Perry GA. Costs and benefits of routine follow-up after curative treatment for endometrial cancer. *CMAJ*. 1997;157:879–886.
105. Shumsky AG, Stuart GC, Brasher PM, Nation JG, Robertson DI, Sangkarat S. An evaluation of routine follow-up of patients treated for endometrial carcinoma. *Gynecol Oncol*. 1994;55:229–233.
106. Ackerman I, Malone S, Thomas G, Franssen E, Balogh J, Dembo A. Endometrial carcinoma–relative effectiveness of adjuvant irradiation vs therapy reserved for relapse. *Gynecol Oncol*. 1996;60:177–183.
107. Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T. Follow-up after primary therapy for endometrial cancer: A systematic review. *Gynecol Oncol*. 2006;101:520–529.
108. Kew FM, Roberts AP, Cruickshank DJ. The role of routine follow-up after gynecological malignancy. *Int J Gynecol Cancer*. 2005;15:413–419.
109. Salani R, Nagel CI, Drennen E, Bristow RE. Recurrence patterns and surveillance for patients with early stage endometrial cancer. *Gynecol Oncol*. 2011;123:205–207.
110. Sartori E, Pasinetti B, Carrara L, Gambino A, Odicino F, Pecorelli S. Pattern of failure and value of follow-up procedures in endometrial and cervical cancer patients. *Gynecol Oncol*. 2007;107(1 Suppl.1):S241–S247.

111. Berchuck A, Anspach C, Evans AC, et al. Postsurgical surveillance of patients with FIGO stage I/II endometrial adenocarcinoma. *Gynecol Oncol*. 1995;59:20–24.
112. Nordin AJ. Mode of detection of recurrent gynecological malignancy: Does routine follow-up delay diagnosis and treatment? *Int J Gynecol Cancer*. 2006;16:1746–1748.
113. Leeson SC, Beaver K, Ezendam NPM, et al. The future for follow-up of gynaecological cancer in Europe. Summary of available data and overview of ongoing trials. *Eur J Obstet Gynecol Reprod Biol*. 2017;210:376–380.
114. Hampel H, Frankel W, Panescu J, et al. Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. *Can Res*. 2006;66:7810–7817.
115. Moline J, Eng C. Equality in lynch syndrome screening: Why should we hold patients with endometrial cancer to a different standard? *J Clin Oncol*. 2014;32:2277.
116. Wiltink LM, Nout RA, Fiocco M, et al. No increased risk of second cancer after radiotherapy in patients treated for rectal or endometrial cancer in the randomized TME, PORTEC-1, and PORTEC-2 trials. *J Clin Oncol*. 2015;33:1640–1646.
117. Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: A Gynecologic Oncology Group Study. *J Clin Oncol*. 2006;24:36–44.