Gynecologic Oncology 134 (2014) 385–392

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Endometrial cancer: A review and current management strategies: Part I

SGO Clinical Practice Endometrial Cancer Working Group, William M. Burke [a,b,*], James Orr [c], Mario Leitao [d], Emery Salom [e], Paola Gehrig [f], Alexander B. Olawaiye [g], Molly Brewer [h], Dave Boruta [i], Jeanine Villella [j,k], Tom Herzog [l], Fadi Abu Shahin [m], for the Society of Gynecologic Oncology Clinical Practice Committee

[a] Division of Gynecologic Oncology Valley Hospital, Paramus, NJ, USA
[b] Columbia University Medical Center, New York, NY, USA
[c] Medical Director, Florida Gynecologic Oncology, Fort Meyers, FL, USA
[d] Gynecology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[e] Division of Gynecologic Oncology, Florida International University, Miami, FL, USA
[f] Division of Gynecologic Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[g] Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[h] Division of Gynecologic Oncology, Carole and Ray Neag Comprehensive Cancer Center, University of Connecticut Health Center, Farmington, CT, USA
[i] Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston, MA, USA
[j] Division of Gynecologic Oncology, Winthrop University Hospital, Long Island, NY, USA
[k] Division of Gynecologic Oncology, SUNY Stony Brook School of Medicine, Long Island, NY, USA
[l] Division of Gynecologic Oncology, Columbia University Medical Center, New York, NY, USA
[m] Florida Gynecologic Oncology, Fort Meyers, FL, USA

HIGHLIGHTS

- We present risk factors for endometrial cancer, including genetic predisposition.
- We review the diagnostic and metastatic evaluation of women with endometrial cancer.
- We describe the surgical management of early and advanced endometrial cancer.

ARTICLE INFO

Article history:
Received 28 February 2014
Accepted 20 May 2014
Available online 4 June 2014

Keywords:
Endometrial cancer
Review
Surgery
Diagnosis
Risk factors
Evaluation

ABSTRACT

Endometrial carcinoma is the most common gynecologic malignancy. A thorough understanding of the epidemiology, pathophysiology, and management strategies for this cancer allows the obstetrician–gynecologist to identify women at increased risk, contribute toward risk reduction, and facilitate early diagnosis. The Society of Gynecologic Oncology's Clinical Practice Committee has reviewed the literature and created evidence-based practice recommendations for diagnosis and treatment. This article examines:

- Risk factors, including genetic predisposition
- Diagnostic and metastatic evaluation
- Surgical management of early and advanced cancer, including lymphadenectomy in early cancer.

Contents

* Corresponding author at: One Valley Health Plaza, Paramus, NJ 07652, USA.
E-mail address: wmb7@columbia.edu (W.M. Burke).

http://dx.doi.org/10.1016/j.ygyno.2014.05.018
0090-8258/

The Society of Gynecologic Oncology's ("SGO") Clinical Practice Committee has developed a series of Clinical Documents designed to improve the overall quality of women's cancer care; reduce the use of unnecessary, ineffective, or harmful interventions; and facilitate the optimal treatment of patients, with a goal to maximize the therapeutic benefit and minimize the risk of harm at acceptable cost.

Clinical Documents are intended to be educational devices that provide information to assist health care providers in patient care. This Clinical Document is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical Documents are not intended to supplant the judgment of the health care provider with respect to particular patients or special clinical situations. Clinical decisions in any particular case involve a complex analysis of a patient's condition and available courses of action, with the ultimate determination made by the health care provider based on each individual patient's circumstances. Therefore, clinical considerations may lead a provider to take an appropriate course of action that varies from this Document.

This Clinical Document has met SGO's criteria for an Evidence-based Clinical Document.

In developing Clinical Documents, SGO follows a rigorous process to assure that any conflicts of interest are disclosed and appropriately addressed and that relationships with manufacturers and other third parties do not influence the development process.

More specifically, SGO adheres to the principles adopted by the Council of Medical Specialty Societies ("CMSS") in developing, adopting, and promulgating clinical guidelines and consensus statements. Consistent with CMSS principles, SGO received no funding from any manufacturer to support the development of this Clinical Document nor any other clinical consensus statement or practice guideline developed and published by SGO.

In accordance with CMSS principles, SGO requires that its clinical documents be subject to multiple levels of review, beginning with a review by SGO's full Clinical Practice Committee. After review and approval by the Clinical Practice Committee, Clinical Documents are submitted to the SGO Council, SGO's governing body, which reviewed and approved the Clinical Document for submission to SGO's journal.

In accordance with those principles, each member of the task force that developed the Clinical Document executed a detailed disclosure statement. None of the members of the task force has a financial relationship or other relationship that conflicts with the writing of this document.

Introduction

Endometrial carcinoma is the most common gynecologic malignancy and will be encountered by almost every gynecologist. A thorough understanding of the epidemiology, pathophysiology, and management strategies for endometrial carcinoma allows the obstetrician–gynecologist to identify women at increased risk, contribute toward risk reduction, and facilitate early diagnosis of this cancer. The purpose of this document is to review the risks and benefits of current treatment options and optimize treatment for women with endometrial cancer.

Epidemiology

In the United States, endometrial cancer will be diagnosed in an estimated 52,630 women in 2014, with 8590 succumbing to their disease. Most endometrial cancers are diagnosed at an early stage (75%), and the reported survival rate is 75% [1]. The mean age of diagnosis in the United States is 60 years [2]. Caucasian women have a 2.88% lifetime risk of developing uterine cancer compared with a 1.69% risk for African-American women. African-American women are more likely to have non-endometrioid, high-grade tumors and a more advanced stage of disease at the time of diagnosis compared with Caucasian women who have similar demographics [3].

Clinical presentation

What are the most common symptoms associated with endometrial cancer?

The most common symptoms are abnormal uterine bleeding and vaginal discharge. Patients who have advanced disease may have symptoms similar to those seen with advanced ovarian cancer, such as abdominal or pelvic pain, abdominal distension, early satiety, or change in bowel or bladder function.

Risk factors

What are the most common risk factors associated with developing an endometrial cancer?

Prolonged unopposed estrogen exposure is associated with most type I endometrial cancers. Estrogen replacement therapy prescribed to control menopausal symptoms increases the risk of developing endometrial cancer by 2- to 20-fold, with an increasing risk correlating with the duration of use. Concomitant administration of progestins continuously or intermittently (10 to 15 days/month) significantly reduces this increased risk of cancer [4,5]. Exposure to unopposed endogenous estrogen, as occurs in chronic anovulation (polycystic ovary syndrome), with estrogen-producing tumors, and with excessive peripheral conversion of androgens to estrone in adipose tissue, is also associated with an increased risk for developing endometrial hyperplasia and cancer. Tamoxifen, a selective estrogen receptor modulator, acts as an estrogen antagonist in breast tissues and an agonist in bone and endometrial tissues. Tamoxifen use is associated with a 6- to 8-fold increase in the incidence of endometrial cancer [6].

The obesity epidemic in the United States may have a profound impact on the incidence of endometrial cancer seen this country. The profound increased incidence of endometrial cancer associated with obesity [7] may be explained by higher endogenous estrogen production via aromatization in adipose tissues. Additionally, premenopausal obese women are more likely to suffer from chronic anovulation. Diabetes mellitus is associated with an increased risk for endometrial cancer that may be related to concurrent obesity, although an independent association between diabetes and endometrial cancer has been reported [8]. Hypertension has been epidemiologically associated with an increased risk of endometrial cancer, but whether hypertension represents an independent risk factor or the association is confounded by the presence of medical comorbidities, such as diabetes and obesity, is unclear [9].

Age also represents an important risk factor for developing endometrial cancer. Most women are diagnosed after menopause, with only 15% diagnosed before the age of 50 years and only 5% before 40 years of age [10]. Younger women who develop endometrial cancer are more likely to be obese and nulliparous and have well-differentiated endometrioid histology and lower-stage disease than older women [11].

Reproductive characteristics associated with increased risk of endometrial cancer include nulliparity, infertility, early age of menarche, and late age of menopause [12]. Importantly, the use of combination oral contraceptive pills, depot medroxyprogesterone acetate, and progesterone secreting intra-uterine devices reduces the risk of developing endometrial cancer. Smoking has also been associated with a reduced risk for endometrial cancer, especially in postmenopausal women [13].

Genetic predisposition

Is there a familial risk for developing endometrial cancer?

Women with Lynch syndrome or hereditary nonpolyposis colon cancer (HNPCC) are at an increased risk of developing endometrial, colon, and ovarian cancer. This autosomal dominant syndrome is characterized by a germline mutation in one of the mismatch repair genes: *MLH1*, *MSH2*, *PMS2*, or *MSH6*. The estimated cumulative risk of developing endometrial cancer by age 70 is 54% for *MLH1*, 21% for *MSH2*, and 16% for *MSH6* mutations [14]. This risk of endometrial cancer rises significantly after the age of 40, with a mean age of diagnosis of 46 years. Somatic mutations in the *PTEN* gene are common in sporadic endometrial cancers [15]. A germline *PTEN* mutation can be found in patients with Cowden syndrome, and patients who have this rare autosomal dominant familial syndrome are at increased risk for breast, thyroid, and endometrial cancers [16]. The association between germline mutations in *BRCA* genes and the risk of endometrial cancer remains controversial [17].

Diagnostic evaluation

Who should evaluate a woman with suspicious symptoms for endometrial cancer?

A gynecologist or other medical provider who is familiar with endometrial cancer should evaluate women with symptoms suspicious for the disease. All providers should be capable of completing a thorough history and physical examination, ordering transvaginal ultrasonography, and performing office endometrial sampling based on ultrasonographic findings or the persistence of symptoms despite normal findings on radiographic studies. If a medical provider has not been trained to perform endometrial sampling or is not comfortable performing the procedure, abnormal ultrasonographic findings or persistent symptoms should generate an immediate gynecologic referral.

How should women with symptoms suggestive of endometrial cancer be evaluated?

The standard diagnostic evaluation for endometrial cancer includes pelvic ultrasonography, office endometrial biopsy, or dilatation and curettage (D&C) with or without hysteroscopy. Pelvic ultrasound is not necessary if a patient has undergone a previous endometrial sampling showing an invasive cancer. A review of data from approximately 2900 patients collected from 13 published studies demonstrated that an endometrial thickness cut-off of 5 mm on ultrasonography resulted in a sensitivity of 90% and a specificity of 54% compared to 98% and 35%, respectively, if the cut-off was reduced to 3 mm. In addition, the 3-mm cut-off could reduce the pretest probability of endometrial cancer from 10% to 0.7% in women with negative results. The reviewers concluded that a 3-mm endometrial thickness cut-off on transvaginal ultrasonography might reliably exclude endometrial cancer in women with postmenopausal bleeding [18].

The most common outpatient endometrial sampling device is the Pipelle aspiration catheter. A meta-analysis of studies on the efficacy of several devices indicates that Pipelle has the best performance, with detection rates of 99.6% and 98% for endometrial cancer and endometrial hyperplasia, respectively [19]. All devices analyzed had a high specificity rate of 98%. Biopsy under hysteroscopic guidance remains the gold standard in the diagnostic evaluation for endometrial cancer. Compared to blind D&C, D&C with hysteroscopic guidance has a higher accuracy and superior diagnostic yield [20,21].

If initial investigations yield negative results, what should be done if symptoms persist?

Persistence of symptoms following negative initial assessment results deserves further diagnostic evaluation. The approach should be dictated by the order of investigative evaluation. For example, if the initial assessment involved only pelvic ultrasonography, endometrial sampling should be performed. Similarly, if an office endometrial biopsy has already been performed, hysteroscopy with D&C is required.

Recommendations

- *Outpatient endometrial biopsy with the Pipelle catheter is reliable and accurate for the detection of disease in most cases of endometrial cancer (level of evidence: A).*
- *Hysteroscopic-guided endometrial biopsy remains the gold standard for endometrial cancer diagnosis (level of evidence: A).*

- *Transvaginal ultrasonography is highly sensitive and specific in predicting the presence of endometrial cancer and can be used to triage patients for endometrial biopsy (level of evidence: B).*
- *If symptomatology persists despite negative findings from the previously cited tests, further evaluation is justified because none of these tests have 100% sensitivity (level of evidence: B).*

Metastatic evaluation

Is a metastatic evaluation necessary in women with newly diagnosed endometrial cancers?

Because endometrial cancer is a surgically staged disease, one purpose of surgery is to assess the extent of disease. Preoperative assessment of spread is not typically required, but under special circumstances, preoperative assessment of metastatic disease may be clinically important. These circumstances include when the patient is a poor surgical candidate due to medical comorbidities or when symptoms suggest possible metastasis to unusual sites, such as bone or the central nervous system.

What is the recommended metastatic assessment for newly diagnosed endometrial cancers?

Imaging modalities are the most popular method for evaluating for metastasis because they are noninvasive. These modalities include computed tomography (CT) scan, magnetic resonance imaging (MRI), and integrated positron emission tomography and computed tomography (PET/CT) scan. Identification of metastatic lymph nodes by both CT scan and MRI is based on measurement of node size, with the short-axis diameter greater than 10 mm or 8 mm being the most accepted criterion. Both modalities have a sensitivity ranging from 27% to 66% and a specificity of 73% to 99% [22,23]. The sensitivity, specificity, and positive predictive value of PET/CT scan in detecting lymph node metastasis are 51% to 69%, 90% to 100%, and 43% to 91%, respectively [24,25]. The performance of the PET/CT scan is similar for the detection of distant metastasis, with sensitivity of 100%, specificity of 94%, and positive predictive value of 63% [26]. Despite these data, however, lack of reproducibility, a question of cost-effectiveness, and a lack of proven clinical benefit preclude the recommendation for universal preoperative metastatic evaluation with MRI, CT, or PET/CT in patients with newly diagnosed endometrial cancer. In one recent study, preoperative CT was found to be costly and rarely altered management in patients with uterine neoplasms, particularly among endometrioid carcinomas [27].

Measurement of serum CA125 has also been investigated as a means of preoperative evaluation for metastasis. Studies have shown a correlation between preoperative CA125 concentrations and extrauterine disease, including lymph node metastasis [28]. Other studies, however, have shown either no correlation or a high-false positive rate, raising questions about the usefulness of the test [29]. Selective use of serum CA125 assessment may be helpful in the management of patients who may not be able to undergo comprehensive staging surgery and in those with high-risk endometrial cancer histology, such as papillary serous [30].

Recommendations

- *Routine preoperative assessment of endometrial cancer patients with imaging tests evaluating for metastasis is not necessary (level of evidence: A).*
- *Serum CA125 measurement may be useful in management planning of selected endometrial cancer patients but cannot currently be recommended for routine clinical use (level of evidence: C).*

Approach to endometrial cancer: best practices

What role does a gynecologic oncologist play in the initial management of endometrial cancer?

Treatment with curative intent must encompass all sites of local, regional, or systemic disease. Total hysterectomy involving removal of the tubes and ovaries has been the mainstay of treatment for uterine cancer. However, in 1988, with mounting evidence that extrauterine disease was associated with poor outcomes and that patients with advanced disease required more than just surgical intervention, corpus cancer was converted to a surgically staged disease. Although opinion as to the role of routine lymphadenectomy remains divided, relative consensus has been reached that the information gained by comprehensive surgical staging, including lymphadenectomy, offers prognostic pathologic findings that can be used to individualize additional treatment.

Some patients with early-stage disease do not clearly benefit from comprehensive staging, but no true and reliable preoperative predictive model accurately identifies such individuals. Additionally, intraoperative decisions about the need for comprehensive staging are hindered by the difficulty of ensuring broad institutional reproducibility and reliable intraoperative assessment. Therefore, we offer the following observations:

- Gynecologic oncologists are the only physicians specifically trained to understand all of the nuances associated with preoperative and intraoperative care of patients with endometrial cancer, and their training allows proper decision making on an individual basis once final pathology is available.
- Clinical evidence indicates that uterine cancer should be initially approached with a minimally invasive surgical technique. Gynecologic oncologists are the only subspecialists specifically trained to perform comprehensive staging using minimally invasive approaches.
- Comprehensive staging with a minimally invasive approach confers little increased surgical risk to patients.
- Patient outcomes are improved when high-volume surgeons in high-volume institutions render care, and this outcome model is typically reproduced by standard gynecologic oncology practice.
- Nearly 20% of women believed preoperatively to have early-stage uterine cancer are found to have advanced (stages III–IV) disease [31]. Current literature suggests that management of these women by a gynecologic oncologist results in improved disease-specific survival.

These data suggest that a gynecologic oncologist should be involved in the initial care of every woman seeking treatment for endometrial cancer. Such involvement enhances the preoperative and intraoperative decision process, allows completion of any necessary procedure (comprehensive staging or debulking), facilitates the decision regarding the need for additional therapy, and results in a comprehensive and cost-effective clinical approach.

What is the recommended initial management for early endometrial cancer?

Although most women diagnosed with endometrial cancer present with early-stage disease confined to the uterus, metastatic disease is identified in a significant percentage when comprehensive staging is performed [31]. In 1988, the International Federation of Gynecologists and Obstetricians (FIGO) formally recommended surgical staging as part of the initial treatment for endometrial cancer. Even with revisions of the staging system in 2009, total hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic and para-aortic lymph node dissection continue to be recommended.

What is the preferred surgical approach for staging early endometrial cancer?

Traditionally, surgical staging for endometrial cancer has been accomplished with open laparotomy. Throughout the 1990s, multiple studies demonstrated the feasibility of a laparoscopic approach [32,33]. Subsequent randomized, controlled trials have compared laparotomy with laparoscopy. In Gynecologic Oncology Group Study (GOG) LAP2, 2616 women with endometrial cancer were randomized in 2:1 fashion to undergo comprehensive surgical staging via either laparoscopy or laparotomy [34]. Conversion from laparoscopy to laparotomy

occurred in 25.8% of cases, primarily due to poor exposure. Laparoscopy was associated with fewer moderate-to-severe postoperative adverse events than laparotomy (14% vs 21%; $P < 0.0001$) and similar rates of intraoperative complications. Although operative time was longer for laparoscopy, the incidence of hospitalization of more than 2 days was significantly lower compared to laparotomy (52% vs 94%; $P < 0.0001$). Laparoscopy patients reported higher scores on several quality-of-life measures over the 6-week recovery period compared to laparotomy patients [35]. A meta-analysis of survival data from three randomized trials did not detect a survival difference between surgical approaches [36]. Similarly, the estimated overall 5-year survival reported in GOG LAP2 for laparotomy and laparoscopy were almost identical at 89.8% [37]. Though GOG LAP2 failed to demonstrate the non-inferiority of laparoscopy compared to laparotomy with respect to recurrence, the overall recurrence rates were much less than expected in both arms, 11.4% and 10.2% respectively [37]. Therefore, because the initial results of GOG Lap2 showed that laparoscopic surgical management of uterine cancer is superior for short-term safety and length-of-stay and that the recurrence rates and 5-year overall survival rates are similar in the two treatment arms, laparoscopy should be embraced as the preferred surgical approach for comprehensive surgical staging in women with endometrial cancer.

What is the role of robotic assistance in laparoscopic surgical management of early endometrial cancer?

Laparoscopic surgical technologies are continually evolving. In addition to a prolonged learning curve, laparoscopic surgical staging is often difficult to complete in obese women. In GOG LAP2, conversion from laparoscopy to laparotomy occurred in 17.5% of patients with body mass index (BMI) of 25, 26.5% of patients with BMI of 34 to 35, and 57.1% of patients with BMI greater than 40 [34]. The daVinci Surgical System (Intuitive Surgical, Sunnyvale, CA) is designed to addressing these challenges. The platform provides several unique and beneficial features, including a three-dimensional image of the surgical field, "wristed" instruments with seven degrees of freedom, tremor filtration, and the ability to operate while seated. One drawback to this robotic platform is the lack of haptic feedback. Several case series describing the use of robotic-assisted laparoscopy for endometrial cancer surgical staging have been published [38,39] Robotic-assisted laparoscopy has not been prospectively compared in a randomized trial to conventional laparoscopy for the performance of endometrial cancer surgical staging. Regardless, the existing literature suggests that robotic-assisted laparoscopy has benefits similar to those established for traditional laparoscopy in comparison to laparotomy. Technical proficiency may be attained more easily with robotic assistance than with conventional laparoscopy, thereby facilitating the completion of comprehensive staging in obese patients with endometrial cancer [40]. Cost comparisons between surgical approaches used for the management of endometrial cancer have been published [41]. Although traditional laparoscopy is typically the least expensive surgical approach, robotic-assisted laparoscopy appears to be less costly than laparotomy, especially when societal costs associated with recovery are considered.

What is the risk of port site metastases after laparoscopic or robotic staging for early endometrial cancer?

Port site metastases occurring in women undergoing laparoscopic procedures for gynecologic malignancies has been well documented. However, the rate of port-site tumor implantation after laparoscopic procedures in women with malignant disease is low and almost always occurs in the setting of synchronous, advanced intra-abdominal or distant metastatic disease [42]. More specifically, the rate of port site recurrences in women with early endometrial cancer undergoing minimally invasive surgery has been shown to be less than 1% [43]. The risk of port site metastases should not be used as an argument against offering women with early stage endometrial cancers either a conventional or a robotic approach to their disease.

When is vaginal hysterectomy appropriate in management of early endometrial cancer?

Although a vaginal approach is one of the preferred surgical approaches for hysterectomy in women with benign disease, it precludes the thorough abdominal survey and lymphadenectomy that is recommended in the management of endometrial cancer. For women who are elderly, are obese, or have extensive comorbid conditions, the risks associated with surgical staging via an abdominal or laparoscopic approach may outweigh its potential benefit. Several authors have reported on vaginal hysterectomy for treatment of early endometrial cancer in women at high surgical risk. These studies report similar survival rates in women undergoing vaginal hysterectomy and those in whom the abdominal approach is used [44–46]. Although it should not be considered the standard of care, vaginal hysterectomy may be an appropriate treatment in select patients who are at high risk for surgical morbidity.

Recommendations

- *The initial management of endometrial cancer should include total hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy. Exceptions to this approach should be made only after consultation with a practitioner specializing in the treatment of endometrial cancer, such as a gynecologic oncologist (level of evidence: A).*
- *Laparoscopy should be embraced as the standard surgical approach for comprehensive surgical staging in women with endometrial cancer (level of evidence: A).*
- *Vaginal hysterectomy may be an appropriate treatment in select patients who are at high risk for surgical morbidity (level of evidence: C).*
- *Robotic-assisted laparoscopic staging is feasible and safe in women with endometrial cancer (level of evidence: B).*

Role of lymphadenectomy in early endometrial cancer

Definitive guidelines on the assessment of lymphatic dissemination in endometrial cancer are unclear. Controversy remains over the indications for, the anatomic extent of, and the therapeutic value of lymphadenectomy in the management of the disease.

What is the definition of comprehensive surgical staging?

Comprehensive surgical staging of endometrial cancer involves removing the uterus, cervix, adnexa, pelvic, and para-aortic lymph node tissues and obtaining pelvic washings. Pelvic lymphadenectomy is typically defined as removal of the nodal tissue from the caudal half of the common iliac arteries, the anterior and medial aspect of the cranial half of the external iliac artery and vein, and the caudal half of the obturator fat pad anterior to the obturator nerve. Para-aortic lymph node dissection is defined as removal of nodal tissue over the caudal inferior vena cava from the level of the inferior mesenteric artery to the mid right common iliac artery and removal of the nodal tissue between the aorta and left ureter from the mid inferior mesenteric artery to the mid left common iliac artery.

Adequate nodal dissection requires that lymphatic tissue be demonstrated pathologically from each side (right and left), but no specific nodal counts are required. Thus, some practitioners may choose selective lymph node sampling rather than full dissection. When only sampling is performed, retrospective data suggested that patients who underwent multiple site sampling had improved survival over those who had limited or no sampling performed [47]. The caveat to nodal sampling rather than full dissection is that inspection or palpation of nodes has not been shown to be a sensitive method for detecting positive lymph nodes, with fewer than 10% of patients with lymphadenopathy having grossly involved nodes [31].

Despite the well-defined criteria for surgical staging, surgeons still debate the extent of lymphadenectomy necessary. Particular controversy surrounds whether to perform bilateral complete para-aortic lymph node dissection in all patients. Para-aortic nodes may be positive in the absence of pelvic lymphadenopathy [48,49]. In a large retrospective

trial, 734 treated patients had isolated para-aortic lymphadenopathy identified. The authors reported a 1% to 1.6% rate of isolated para-aortic lymph node involvement in the setting of negative pelvic lymph nodes, a rate that was consistent for both low- and high-grade lesions [49]. Therefore, their current practice is to perform surgical staging with pelvic lymphadenectomy as well as limited inframesenteric para-aortic lymphadenectomy or to offer sentinel node mapping [50,51]. Other data suggest that para-aortic lymph node dissection may be warranted only in those with high-risk pathology. Mariani and associates prospectively examined 281 patients undergoing lymphadenectomy at the time of endometrial cancer staging and found that 22% of patients with high-risk disease had lymph node metastases [48]. Of these, 51% had both pelvic and para-aortic lymphadenopathy, 33% had positive pelvic lymph nodes only, and 16% had isolated para-aortic lymphadenopathy. Because 77% of those with para-aortic lymph node involvement had metastases above the inferior mesenteric artery, they propose systematic pelvic and extended para-aortic lymphadenectomy up to the renal vessels in patients with high-risk disease [48,52]. Conversely, they found that patients with low-grade disease (i.e., grade 1 and 2 endometrioid lesions with, <50% myometrial invasion and tumor size ≤2 cm) had no lymphadenopathy and did not benefit from a systematic lymphadenectomy.

What are the advantages and potential complications of comprehensive staging?

The advantages of comprehensive surgical staging lie in diagnosis, prognosis, and proper triage of patients for adjuvant therapy. FIGO endometrial cancer staging is based on surgical pathology, and comprehensive surgery allows for accurate definition of disease extent. GOG 33 found that 9% of patients who had clinically determined stage I disease had pelvic nodal metastases, 6% had para-aortic lymphadenopathy, 5% had spread to adnexa, and 6% had other extrauterine metastases at the time of surgery [31]. These patients with more advanced stage disease have poorer prognoses, which may not be recognized without comprehensive surgical staging.

Comprehensive surgical staging also allows for proper triage of adjuvant therapy. In addition to defining patients with more advanced stages of endometrial cancer and the need for radiation therapy and/or chemotherapy, patients with stage I disease who should receive further treatment can be identified. GOG 99 defined a high-intermediate risk group of patients with early-stage endometrial cancer who can benefit from additional therapy in terms of progression-free survival and fewer local recurrences [53]. Patients were triaged to pelvic radiation therapy based on age and pathologic factors, including grade (2-3), depth of invasion (outer one-third), and lymphovascular space invasion. In GOG 33, 22% of clinical stage I patients had outer one-third myometrial invasion, 71% had grade 2 or 3 disease, and 15% had lymphovascular space invasion and would have been triaged to adjuvant radiation therapy based on age and the number of risk factors present [31]. Furthermore, those patients without high-intermediate risk factors can be identified and their overtreatment can be avoided, sparing them from potential complications of radiation therapy.

Comprehensive surgical staging includes pelvic and para-aortic lymphadenectomy, which is associated with inherent risks. Potential complications of these procedures include injury to major vessels or nerves, lymphedema, and associated cellulitis. Lymphedema occurs in 5% to 38% of patients undergoing pelvic lymph node dissection and can affect quality of life. Such negative effects can be avoided by limiting the pelvic lymphadenectomy to superior to the circumflex iliac vein, avoiding removal of the circumflex iliac nodes caudal to the external iliac nodes [54,55].

What is the evidence for and against the benefits of surgical staging?

GOG 33 was among the first trials to describe the benefits of surgical staging, with evidence that clinical stage I disease may pathologically include risk factors warranting adjuvant radiation therapy in 15% to 25% of early-stage patients. In addition, another 5% to 9% of patients may be upstaged by extrauterine involvement, significantly affecting prognosis and plans for adjuvant therapy [31]. GOG 99 defined high-intermediate risk factors for recurrence based on surgical pathology in women with stage I cancer. Women with high-intermediate risk factors were randomized to radiation therapy or observation after comprehensive surgery. The incidence of recurrence was 12% in the observation group and 3% in the radiotherapy group, and there was no difference in overall survival [53]. Results of these trials suggest that comprehensive surgical staging can identify women at high risk of recurrence, allowing appropriate triage to additional therapy.

Several observational studies have compared outcomes in patients who had early-stage endometrial cancer with and without systematic lymphadenectomy. Retrospective single-institution studies advocate lymphadenectomy for all grades of tumor [47,56]. A large series using a national database supports lymph node dissection for grade 3 tumors only, with no benefit seen in grade 1 or 2 tumor [57]. This was also found in an observational study that examined patients with intermediate- or high-risk factors for recurrence who underwent surgery with pelvic lymphadenectomy with or without para-aortic lymph node dissection. Those who had a para-aortic lymphadenectomy had a survival benefit compared with those who did not, but this effect was not seen in patients with low-risk cancers [58]. Rather than triaging based on risk factors, other investigators suggest that the benefit of lymphadenectomy depends on the number of lymph nodes removed at the time of surgery [59,60]. However, no randomized trials support the benefit of lymphadenectomy in early-stage endometrial cancer.

Some randomized trials provide some evidence against surgical staging. Pancini and associates randomized 514 women with clinical stage I endometrial cancer to either systematic pelvic lymphadenectomy or no lymph node dissection and found no improvement in disease-free or overall survival between the two groups [61]. This was followed by the ASTEC trial, a large multicenter European trial that randomized 1408 women with clinical stage I endometrial cancer to staging surgery with or without pelvic lymphadenectomy [62]. Though flawed, this trial offers some of the best data available exploring the benefit to comprehensive surgical staging. Women with early-stage disease who had intermediate- or high-risk factors for recurrence were subsequently randomized, independent of lymph node status, to the ASTEC radiotherapy trial. Investigators found no difference in progression-free or overall survival and recommended against routine pelvic lymphadenectomy in presumed early-stage endometrial cancer.

Despite such randomized trials showing no benefit to comprehensive surgical staging, controversy still exists due, in part, to criticisms of the ASTEC trial, which include a high rate of crossover to radiotherapy and selection bias. Patients were secondarily randomized to radiation therapy based on uterine pathology only, leaving some patients with lymphadenopathy untreated by radiotherapy. One benefit of nodal dissection is triage to adjuvant therapy. However, the clinical value of triage to treatment in this trial was obscured because only 50% of the patients with high-risk disease were randomized to adjuvant therapy. Furthermore, 7% to 9% of low-risk patients and 53% to 61% of those with advanced-stage disease excluding lymph node involvement were not randomized to adjuvant therapy, although they did receive some radiotherapy. In addition, the lymphadenectomy vs. no dissection arms were unbalanced in terms of high-risk criteria. The lymphadenectomy arm contained 3% more high-risk histology, 3% more high-grade lesions, 3% more lymphovascular space invasion, and 10% more deep myometrial invasions, despite randomization. This difference may appear small but could have affected the power of the study to detect differences in survival [63]. The ASTEC trial also does not provide information about the usefulness of pelvic lymphadenectomy for guiding adjuvant treatment because patients were secondarily randomized to radiotherapy without factoring in lymph node status. Additionally, the benefit of para-aortic lymph node dissection was not addressed because patients underwent para-aortic node palpation and selective sampling, rather than systemic dissection.

What is the role of sentinel lymph node dissection in endometrial cancer?

Sentinel lymph node assessment, which is standard of care in malignancies such as breast cancer and melanoma, is now being introduced in gynecologic cancers. Pelvic lymphadenectomy can be associated with long-term morbidity such as lymphedema. One study showed that approximately 6% of patients undergoing pelvic lymphadenectomy for endometrial cancer have lymphedema [54]. To decrease this incidence as well as to determine who would benefit from lymph node assessment and improve detection of lymph node metastases, sentinel lymph node assessment has been introduced in endometrial cancer management. Khoury-Collado and colleagues [51] assessed 266 endometrial cancer patients with lymphatic mapping. Sentinel lymph node identification was successful in 223 (84%) of cases, with a 12% incidence of positive lymph nodes and 3% of those having metastasis confirmed by immunohistochemistry. Another study showed that sentinel lymph node assessment upstaged 10% of patients with low-risk and 15% of those with intermediate-risk endometrial cancer [64]. Use of this technique may offer the solution to determining which early-stage endometrial cancer patients will benefit from lymph node assessment.

Recommendations

- *Patients with grade 1–2 endometrioid tumors, less than 50% myometrium invasion, and tumor of 2 cm or less seem to be at low risk for recurrence and may not require a surgical lymphadenectomy (level of evidence: B).*
- *Lymphadenectomy may alter or eliminate the need for adjuvant therapy and its associated morbidity (level of evidence: B).*
- *Sentinel lymph node dissection may reduce the morbidity associated with standard lymphadenectomy and may enhance the therapeutic benefit of surgical staging in early endometrial cancer (level of evidence: I).*

Surgical approach for advanced endometrial cancer

In approximately 10% to 15% of all new cases of endometrial cancer, disease is found outside the uterus. These cases account for more than 50% of all uterine cancer-related deaths, with survival rates as low as 5% to 15% [65]. Due to a paucity of cases, no randomized prospective trials currently provide insight on the best treatment option. Therefore, treatment often consists of radical surgery followed by any combination of radiation, chemotherapy, and novel therapeutic agents.

Is there a role for cytoreductive surgery for advanced stage III/IV endometrial cancer?

The treatment paradigm for advanced FIGO stage III and IV endometrial carcinoma has shifted in the past few decades to a multimodality approach that includes surgery, chemotherapy, and radiation therapy, with cytoreduction being the most crucial aspect. Multiple retrospective studies address the advantages of optimal cytoreductive surgery in patients with stage III and IV endometrial adenocarcinoma. Each study demonstrates a statistically significant progression-free and overall survival advantage when optimal cytoreduction was achieved [66,67].

Is there a role for maximal cytoreductive effort in advanced endometrial cancer?

Support for initial maximal cytoreductive effort is provided by data showing that the extent of residual disease among advanced-stage endometrial cancer appears to have a direct influence on survival. Theories explaining the possible advantages of cytoreduction of large-volume disease include improved performance status, decreased hypermetabolic tumor burden, improved vascular perfusion and drug delivery after resection of devitalized tissue, and decreased tumor volume and concomitant mutation potential that can lead to drug resistance. All cited studies report cytoreduction as an independent prognostic factor for overall survival. For those patients in whom the tumor was determined to be unresectable, the median survival was 2 to 8 months, regardless of further treatment with radiation and/or chemotherapy [66,68]. When patients could undergo optimal cytoreductive surgery, their survival was twice that of those who underwent a suboptimal cytoreduction. Optimally debulked patients also appear to have a survival advantage if surgery results in microscopic or no residual disease. The median survival for patients who had less than 1 cm residual disease was 15 months compared with 40 months among those who had microscopic disease [69]. Median survival for patients with no residual disease was 40 months compared with 19 months for those who had any residual disease [66]. Further, regardless of the amount of preoperative tumor burden, no significant difference in survival rates has been seen between patients with preoperative small (<2 cm) and large-volume (>2 cm) metastatic disease when optimal cytoreduction is achieved [66].

Does surgical management improve outcome in recurrent endometrial cancer?

Multiple studies have addressed the potential benefit of secondary cytoreductive surgery on overall survival in patients with recurrent endometrial cancer. Whether recurrent endometrial cancer is localized to the pelvis or disseminated throughout the abdomen, secondary cytoreduction has been shown to improve both progression-free and overall survival. More specifically, survival seems to be dependent on the type of recurrence (solitary recurrence vs. carcinomatous), the ability to achieve optimal cytoreduction, and the time from original treatment to recurrence [70]. Median overall survival after secondary cytoreductive surgery for recurrent endometrial cancer ranges from 39 to 57 months after surgery [71,72]. In previously irradiated patients with localized recurrence, pelvic exenteration remains the only curative option, although it is associated with significant postoperative morbidity (60% to 80%) and even mortality (10% to 15%). Despite such high postoperative morbidity, the reported 20% to 40% 5-year survival rates makes pelvic exenteration the only curative option and may justify the radicality of the approach [73].

Recommendations

- *Aggressive surgical cytoreduction improves progression-free and overall survival in patients with advanced or recurrent endometrial cancer (level of evidence: C).*
- *Exenteration offers the only curative option in patients with recurrent endometrial cancer who have received previous irradiation (level of evidence: C).*

Conflict of interest statement

Mario M. Leitao, Jr, MD is a consultant for Intuitive Surgical. Thomas J. Herzog is a consultant for Merck, Morphotek, and Genentech. All other authors declare no conflicts of interest.

Acknowledgments

Manuscript editing was funded by the Society of Gynecologic Oncology (SGO).

References

[1] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63(1):11–30.
[2] Jick H, Walker AM, Rothman KJ. The epidemic of endometrial cancer: a commentary. Am J Public Health 1980;70(3):264–7.
[3] Oliver KE, et al. Racial disparities in histopathologic characteristics of uterine cancer are present in older, not younger blacks in an equal-access environment. Gynecol Oncol 2011;123(1):76–81.
[4] Pike MC, et al. Estrogen-progestin replacement therapy and endometrial cancer. J Natl Cancer Inst 1997;89(15):1110–6.
[5] Shapiro S, et al. Risk of localized and widespread endometrial cancer in relation to recent and discontinued use of conjugated estrogens. N Engl J Med 1985;313(16):969–72.
[6] Fisher B, et al. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. J Natl Cancer Inst 1994;86(7):527–37.
[7] Renehan AG, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371(9612):569–78.
[8] Soliman PT, et al. Association between adiponectin, insulin resistance, and endometrial cancer. Cancer 2006;106(11):2376–81.

[9] Soler M, et al. Hypertension and hormone-related neoplasms in women. Hypertension 1999;34(2):320–5.
[10] Gallup DG, Stock RJ. Adenocarcinoma of the endometrium in women 40 years of age or younger. Obstet Gynecol 1984;64(3):417–20.
[11] Soliman PT, et al. Risk factors for young premenopausal women with endometrial cancer. Obstet Gynecol 2005;105(3):575–80.
[12] McPherson CP, et al. Reproductive factors and risk of endometrial cancer. The Iowa Women's Health Study. Am J Epidemiol 1996;143(12):1195–202.
[13] Zhou B, et al. Cigarette smoking and the risk of endometrial cancer: a meta-analysis. Am J Med 2008;121(6):501–8 [e3].
[14] Bonadona V, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 2011;305(22):2304–10.
[15] Zhou XP, et al. Distinct PTEN mutational spectra in hereditary non-polyposis colon cancer syndrome-related endometrial carcinomas compared to sporadic microsatellite unstable tumors. Hum Mol Genet 2002;11(4):445–50.
[16] Eng C. PTEN: one gene, many syndromes. Hum Mutat 2003;22(3):183–98.
[17] Levine DA, et al. Risk of endometrial carcinoma associated with BRCA mutation. Gynecol Oncol 2001;80(3):395–8.
[18] Timmermans A, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. Obstet Gynecol 2010;116(1):160–7.
[19] Dijkhuizen FP, et al. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. Cancer 2000;89(8):1765–72.
[20] Epstein E, et al. Dilatation and curettage fails to detect most focal lesions in the uterine cavity in women with postmenopausal bleeding. Acta Obstet Gynecol Scand 2001;80(12):1131–6.
[21] Lee DO, Jung MH, Kim HY, et al. Prospective comparison of biopsy results from curettage and hysteroscopy in postmenopausal uterine bleeding. J Obstet Gynaecol Res 2011.
[22] Hricak H, et al. MR imaging evaluation of endometrial carcinoma: results of an NCI cooperative study. Radiology 1991;179(3):829–32.
[23] Connor JP, et al. Computed tomography in endometrial carcinoma. Obstet Gynecol 2000;95(5):692–6.
[24] Kitajima K, et al. Accuracy of integrated FDG-PET/contrast-enhanced CT in detecting pelvic and paraaortic lymph node metastasis in patients with uterine cancer. Eur Radiol 2009;19(6):1529–36.
[25] Signorelli M, et al. Role of the integrated FDG PET/CT in the surgical management of patients with high risk clinical early stage endometrial cancer: detection of pelvic nodal metastases. Gynecol Oncol 2009;115(2):231–5.
[26] Park JY, et al. Comparison of the validity of magnetic resonance imaging and positron emission tomography/computed tomography in the preoperative evaluation of patients with uterine corpus cancer. Gynecol Oncol 2008;108(3):486–92.
[27] Bansal N, et al. The utility and cost effectiveness of preoperative computed tomography for patients with uterine malignancies. Gynecol Oncol 2008;111(2):208–12.
[28] Hsieh CH, et al. Can a preoperative CA 125 level be a criterion for full pelvic lymphadenectomy in surgical staging of endometrial cancer? Gynecol Oncol 2002;86(1):28–33.
[29] Soper JT, et al. Preoperative evaluation of serum CA 125, TAG 72, and CA 15-3 in patients with endometrial carcinoma. Am J Obstet Gynecol 1990;163(4 Pt 1):1204–9.
[30] Olawaiye AB, et al. Utility of pre-operative serum CA-125 in the management of uterine papillary serous carcinoma. Gynecol Oncol 2008;110(3):293–8.
[31] Creasman WT, et al. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer 1987;60(8 Suppl.):2035–41.
[32] Childers JM, et al. Laparoscopically assisted surgical staging (LASS) of endometrial cancer. Gynecol Oncol 1993;51(1):33–8.
[33] Spirtos NM, et al. Laparoscopic bilateral pelvic and paraaortic lymph node sampling: an evolving technique. Am J Obstet Gynecol 1995;173(1):105–11.
[34] Walker JL, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. J Clin Oncol 2009;27(32):5331–6.
[35] Kornblith AB, et al. Quality of life of patients with endometrial cancer undergoing laparoscopic international federation of gynecology and obstetrics staging compared with laparotomy: a Gynecologic Oncology Group study. J Clin Oncol 2009;27(32):5337–42.
[36] Palomba S, et al. Updating of a recent meta-analysis of randomized controlled trials to assess the safety and the efficacy of the laparoscopic surgery for treating early stage endometrial cancer. Gynecol Oncol 2009;114(1):135–6.
[37] Walker JL, 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(7):695–700.
[38] Boggess JF, et al. A comparative study of 3 surgical methods for hysterectomy with staging for endometrial cancer: robotic assistance, laparoscopy, laparotomy. Am J Obstet Gynecol 2008;199(4):360 [e1-9].
[39] Seamon LG, et al. Robotic hysterectomy and pelvic-aortic lymphadenectomy for endometrial cancer. Obstet Gynecol 2008;112(6):1207–13.
[40] Gehrig PA, et al. What is the optimal minimally invasive surgical procedure for endometrial cancer staging in the obese and morbidly obese woman? Gynecol Oncol 2008;111(1):41–5.
[41] Bell MC, et al. Comparison of outcomes and cost for endometrial cancer staging via traditional laparotomy, standard laparoscopy and robotic techniques. Gynecol Oncol 2008;111(3):407–11.
[42] Zivanovic O, et al. The rate of port-site metastases after 2251 laparoscopic procedures in women with underlying malignant disease. Gynecol Oncol 2008;111(3):431–7.
[43] Martinez A, et al. Low incidence of port-site metastases after laparoscopic staging of uterine cancer. Gynecol Oncol 2010;118(2):145–50.
[44] Berretta R, et al. Vaginal versus abdominal hysterectomy in endometrial cancer: a retrospective study in a selective population. Int J Gynecol Cancer 2008;18(4):797–802.
[45] Massi G, Savino L, Susini T. Vaginal hysterectomy versus abdominal hysterectomy for the treatment of stage I endometrial adenocarcinoma. Am J Obstet Gynecol 1996;174(4):1320–6.
[46] Susini T, et al. Vaginal hysterectomy and abdominal hysterectomy for treatment of endometrial cancer in the elderly. Gynecol Oncol 2005;96(2):362–7.
[47] Kilgore LC, et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. Gynecol Oncol 1995;56(1):29–33.
[48] Mariani A, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol 2008;109(1):11–8.
[49] Abu-Rustum NR, et al. The incidence of isolated paraaortic nodal metastasis in surgically staged endometrial cancer patients with negative pelvic lymph nodes. Gynecol Oncol 2009;115(2):236–8.
[50] Abu-Rustum NR, et al. Sentinel lymph node mapping for grade 1 endometrial cancer: is it the answer to the surgical staging dilemma? Gynecol Oncol 2009;113(2):163–9.
[51] Khoury-Collado F, et al. Sentinel lymph node mapping for endometrial cancer improves the detection of metastatic disease to regional lymph nodes. Gynecol Oncol 2011;122(2):251–4.
[52] Dowdy SC, et al. Extra-peritoneal laparoscopic para-aortic lymphadenectomy—a prospective cohort study of 293 patients with endometrial cancer. Gynecol Oncol 2008;111(3):418–24.
[53] Keys HM, 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(3):744–51.
[54] Abu-Rustum NR, et al. The incidence of symptomatic lower-extremity lymphedema following treatment of uterine corpus malignancies: a 12-year experience at Memorial Sloan-Kettering Cancer Center. Gynecol Oncol 2006;103(2):714–8.
[55] Todo Y, et al. Risk factors for postoperative lower-extremity lymphedema in endometrial cancer survivors who had treatment including lymphadenectomy. Gynecol Oncol 2010;119(1):60–4.
[56] Cragun JM, et al. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. J Clin Oncol 2005;23(16):3668–75.
[57] Trimble EL, Kosary C, Park RC. Lymph node sampling and survival in endometrial cancer. Gynecol Oncol 1998;71(3):340–3.
[58] Todo Y, et al. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet 2010;375(9721):1165–72.
[59] Lutman CV, et al. Pelvic lymph node count is an important prognostic variable for FIGO stage I and II endometrial carcinoma with high-risk histology. Gynecol Oncol 2006;102(1):92–7.
[60] Chan JK, et al. Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. Cancer 2006;107(8):1823–30.
[61] Benedetti Panici P, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 2008;100(23):1707–16.
[62] Kitchener H, et al. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 2009;373(9658):125–36.
[63] Creasman WT, Mutch DE, Herzog TJ. ASTEC lymphadenectomy and radiation therapy studies: are conclusions valid? Gynecol Oncol 2010;116(3):293–4.
[64] Ballester M, et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). Lancet Oncol 2011;12(5):469–76.
[65] Percorelli S, Pettersson CW, Benedet F, Sharperd JL. FIGO annual report on the results of treatment in gynecologic cancer. J Epidemiol Biostat 1998;3(35):35–62.
[66] Shih KK, et al. Surgical cytoreduction in stage IV endometrioid endometrial carcinoma. Gynecol Oncol 2011;122(3):608–11.
[67] Lambrou NC, et al. Optimal surgical cytoreduction in patients with stage III and stage IV endometrial carcinoma: a study of morbidity and survival. Gynecol Oncol 2004;93(3):653–8.
[68] Goff BA, et al. Surgical stage IV endometrial carcinoma: a study of 47 cases. Gynecol Oncol 1994;52(2):237–40.
[69] Bristow RE, et al. Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. Gynecol Oncol 2000;78(2):85–91.
[70] Campagnutta E, et al. Surgical treatment of recurrent endometrial carcinoma. Cancer 2004;100(1):89–96.
[71] Dowdy SC, et al. Radical pelvic resection and intraoperative radiation therapy for recurrent endometrial cancer: technique and analysis of outcomes. Gynecol Oncol 2006;101(2):280–6.
[72] Bristow RE, et al. Salvage cytoreductive surgery for recurrent endometrial cancer. Gynecol Oncol 2006;103(1):281–7.
[73] Barakat RR, et al. Pelvic exenteration for recurrent endometrial cancer. Gynecol Oncol 1999;75(1):99–102.