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Early-Stage Endometrial Cancer: Surgery

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Abstract

Endometrial cancer typically presents at an early stage, and surgery alone can be curative in many of these cases. Traditionally, surgery for early-stage disease has been carried out using an open approach; however, the use of minimally invasive surgery has rapidly grown in the field of gynecologic oncology. Multiple studies have demonstrated its feasibility, and oncologic outcomes continue to be validated.

Keywords

Endometrial cancer • Surgery • Laparoscopy

Introduction

Endometrial cancer remains the most common gynecologic malignancy in the USA, and it ranks as the fourth most common cancer among American women. There will be an estimated 54,870 newly diagnosed cancers of the uterine corpus and 10,170 deaths from this disease in 2015 [1]. Fortunately, the vast majority of endometrial cancers are detected at early stages; approximately 75 % of these cancers are limited to the uterus at time of discovery. This is in large part due to the early warning sign of abnormal uterine bleeding present during the early stages of the disease.

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Endometrial cancer has traditionally been classified into two types [2], although some have proposed an integrated classification system incorporating molecular and clinicopathologic features [3]. Type I cancers are more common and are associated with increased levels of circulating estrogen. These tumors usually begin as endometrial hyperplasia and progress to cancer. They tend to occur at a younger age and are less aggressive (typically grade 1 and 2 endometrioid adenocarcinomas). Type II cancers are of higher grade, more aggressive, and tend to arise in a background of atrophic endometrium. Histologically, they encompass serous, clear cell, and grade 3 endometrioid adenocarcinomas. They occur in older patients and do not have an estrogen-related precursor.

Fortunately, early-stage type I endometrial cancers comprise the vast majority of cases

and can be cured. The surgical treatment of early-stage type I cancers is the focus of this chapter.

Surgical Therapy

With the change of the staging system for this disease from a clinical to a surgical evaluation, primary treatment for women with endometrial cancer begins with surgery. Prior to undergoing a major surgical procedure, and given that this disease is associated with surgical risk factors such as obesity, hypertension, and diabetes, all patients should undergo a thorough history and physical examination. Physical examination should include areas of potential tumor spread: enlarged supraclavicular and inguinal lymph nodes, signs of intra-abdominal disease or ascites, and close inspection of the cervix and vagina. Chest radiography has traditionally been obtained to rule out any pulmonary spread. Other imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scan, are usually obtained when findings on history and physical examination warrant further investigation. Serum CA-125 has been shown to be elevated in patients with advanced disease, and this may provide additional information if intra-abdominal spread is suspected [4].

The standard surgical approach to the patient with endometrial cancer clinically confined to the uterus entails an exploration of the peritoneal cavity, biopsies of any suspicious lesions, total hysterectomy, bilateral salpingo-oophorectomy (BSO), and selected pelvic and para-aortic lymph node sampling.

After entering the peritoneal cavity, a thorough exploration is performed. Any suspicious lesions should be biopsied. Although no longer required for surgical staging, obtaining peritoneal washings is still recommended; washings are acquired by instilling approximately 100 cm^3 of saline into the pelvis and aspirating for cytological analysis. An extrafascial hysterectomy with BSO can then be performed.

Once the primary specimen has been removed, the pelvic ± para-aortic lymph nodes should be sampled. This is an area that remains controversial in the management of endometrial cancer. The basis for lymph node sampling arose from Gynecologic Oncology Group (GOG) protocol 33 [5]. This study demonstrated that the incidence of pelvic and para-aortic lymph node metastasis was higher for patients with high-grade and deeply invasive tumors. Low-grade tumors with no or only superficial myometrial invasion were associated with a very low incidence of lymph node spread.

Intraoperative Management

In the absence of obvious extrauterine spread, some have advocated using a combination of preoperative tumor grade, intraoperative assessment of myometrial invasion, and clinical evaluation of the lymph nodes to determine if lymph node assessment should be undertaken. Mariani et al. [6] prospectively examined 281 patients undergoing lymphadenectomy at the time of surgery for endometrial cancer. They found that 22 % of patients with high-risk disease had lymph node metastases. They also identified a low-risk group consisting of patients with low-grade disease (grade 1 or 2, endometrioid histology), with $\leq$50 % myometrial invasion and tumor size $\leq$2 cm, who probably do not benefit from lymphadenectomy. Using the "Mayo Criteria" at time of frozen section to omit lymphadenectomy does rely on several pathologic uncertainties (assessing tumor grade and depth of myometrial invasion) that may vary from institution to institution. Tumor grade cannot be accurately determined using office biopsy or curettage. In a retrospective study by Obermair et al. [7], the preoperative histologic grade of the curettage specimen was compared with that of the final specimen. Only 78 % of well-differentiated tumors diagnosed on curettage maintained the same histologic grade on final analysis. Similar results of the inaccuracy of preoperative grade assessment have been demonstrated by other authors [8–10].

Accurately assessing depth of myometrial invasion by either intraoperative visual inspection or frozen-section analysis can be difficult. Intraoperative visual examination can correctly predict the degree of myometrial invasion in 87 % of grade 1 tumors, 65 % of grade 2 tumors, and 31 % of grade 3 tumors [11]. The use of frozen-section analysis to assess myometrial invasion has been advocated by some [12]. In a recent study of 153 patients with grade 1 or 2 endometrioid endometrial cancer, Frumovitz et al. [13] compared preoperative grade and intraoperative myometrial invasion with final pathology. Forty-nine patients (32 %) had a discrepancy between preoperative and final histology. Thirty-seven patients (27 %) had their lesions upgraded or were found to have disease of histology other than endometrioid adenocarcinoma. Twenty-six percent of Pipelle biopsies and 23 % of curettage specimens were upgraded on final pathology. The authors concluded that a clinically significant number of patients will be found to have more advanced disease than can be predicted using preoperative and intraoperative prognostic factors, and these should not be relied upon for staging. Palpation of the retroperitoneal nodes can be inaccurate even in experienced hands. In one study of 126 women, assessment by palpation alone would have missed 36 % of positive nodes [14]. Others have also demonstrated this inaccuracy [15]. Additionally, over one-third of lymph nodes may have only microscopic metastasis [16].

Routine Staging

Since intraoperative assessment of pathologic risk factors for extrauterine spread is not perfect, many have advocated the routine use of surgical staging for all patients. In a large population-based study of more than 10,000 patients, Trimble et al. [17] demonstrated the impact of lymph node sampling on survival in women with International Federation of Gynecology and Obstetrics (FIGO) stage I and II endometrial adenocarcinoma. Five-year relative survival was not significantly improved in stage I patients who underwent lymph node sampling. When stage I patients were stratified by histologic grade, lymph node sampling was associated with an increased survival in patients with grade 3, but not grade 1 or 2, tumors. This may have been due to the identification of women with more advanced disease. The American College of Obstetricians and Gynecologists recently published its clinical management guidelines for endometrial cancer and recommended systemic surgical staging for most women with endometrial cancer. Exceptions to this approach were made after consultation with a gynecologic oncologist [18].

Lymph Node Evaluation

The extent of lymph node sampling required for accurate staging is debatable. Improved outcomes have been associated with an increased number of nodes removed. Kilgore et al. [19] reviewed their experience on 649 patients with adenocarcinoma of the endometrium. Patients were categorized into one of three groups: multiple-site pelvic node sampling, limited pelvic node sampling, and no sampling. Patients in whom multiple-site sampling, which was defined as having at least four sites sampled, was performed had a significantly better survival than patients who had no sampling. Patients with limited or less than four sites sampled did not have a significantly better survival compared with patients who did not undergo sampling. Cragun et al. [20] recently published a single-institution series on selective lymphadenectomy in apparent early-stage endometrial cancer. An improvement in overall and progression-free survival was seen in patients with poorly differentiated tumors and more than 11 nodes removed. This survival advantage was not seen in patients with grade 1 or 2 tumors. These retrospective data suggest a therapeutic value to performing a lymphadenectomy, and some have advocated the routine use of lymphadenectomy in the management of these patients. Complete lymphadenectomy can provide excellent local control (Table 1) [21–26].

Table 1 Recurrences in moderate and high-risk patients treated with lymphadenectomy without whole-pelvic radiation

Author	Number of patients	Mean number of pelvic nodes	Mean follow-up (months)	Postoperative brachytherapy	Number of local recurrences	Number of distant recurrences
Fanning et al. [21]	22	28	34	Yes	0	1
Orr et al. [22]	115	24	39	Yes	0	7
Larson et al. [23]	105	N/A	43	No	4	4
Mohan et al. [24]	63	33	96	Yes	0	5 (1 site unknown)
Seago et al. [25]	23	N/A	26	Yes	0	2
Berclaz et al. [26]	19	18	54	Yes	1	0

One potential explanation for the therapeutic benefits of lymphadenectomy may be the removal of any subclinically involved nodes. Girardi et al. [16] reported on their experience with systematic pelvic lymphadenectomy in the treatment of endometrial cancer. A mean of 37 pelvic nodes were removed, and 27 (36 %) of 76 patients were upstaged based on lymph node metastases. Thirty-seven percent of lymph node metastases were $\leq$2 mm in diameter. Additionally, Yabushita et al. [27] demonstrated that up to 38 % of patients with stage I endometrial cancers were found to have metastatic disease detectable by immunostain only. Removal of this otherwise undetectable disease can be performed with low morbidity [22, 28] and may explain the potential therapeutic benefit to lymphadenectomy in early-stage endometrial cancer.

Alternatively, inadequate evaluation of the lymph nodes may lead to missed metastasis and undertreatment of more advanced disease [29]. Inadequate nodal evaluation may account for the difference in survival observed in cases that are at higher risk for spread. In a retrospective study of 467 patients with FIGO stage I and II endometrial cancers, a pelvic lymph node count of $\geq$12 nodes was associated with an improved survival only in cases with high-risk histology. The authors suggested that this observation was a result of improved staging in patients with higher node counts who were at higher risk for spread [30].

Despite these data supporting the use of routine lymphadenectomy, there has been no randomized trial showing a benefit in early-stage endometrial cancer. There have been two randomized trials demonstrating a lack of benefit for routine surgical staging. Panici et al. [31] reported on 514 women with clinical stage I endometrial cancer who were randomized to either systemic lymphadenectomy or no lymphadenectomy. No improvement in disease-free or overall survival was found between the two groups. Similarly, a large multicenter European trial randomized 1408 women with clinical stage I endometrial cancer to surgery with or without routine pelvic lymphadenectomy. The design of this trial was flawed, but similar to the Italian study, the performance of routine pelvic lymphadenectomy did not impact disease-free or overall survival [32].

Since the identification of nodal metastases has profound effects on postoperative management and adjuvant therapy, novel techniques have been studied to obtain this valuable information. A more targeted approach to lymph node evaluation may eventually do away with the need to perform lymph node sampling to any degree. Sentinel lymph node mapping for endometrial cancer was first reported in 1996 [33], and over time, feasibility studies have begun to appear in the literature [34–37]. Sentinel lymph node mapping has become a topic of debate in the management of endometrial cancer; however, it may provide diagnostic accuracy while minimizing the morbidity associated with complete lymphadenectomy [38]. Although there have not been any large randomized studies to support the use of sentinel lymph node mapping

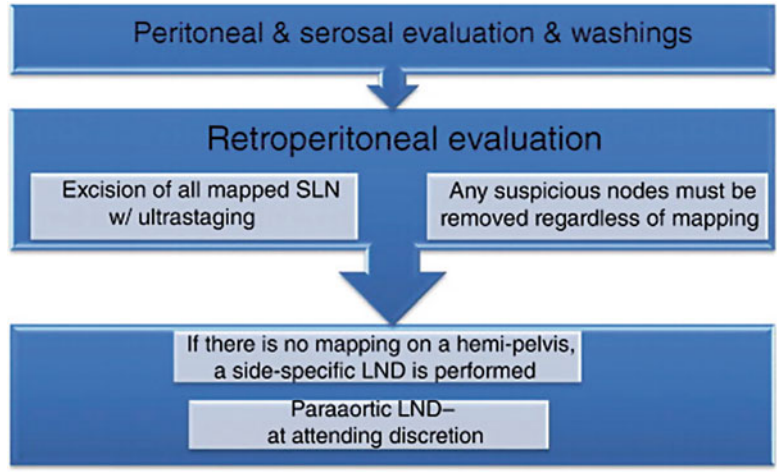

Fig. 1 Sentinel lymph node mapping algorithm for the staging of endometrial cancer

for apparent early-stage endometrial cancer, there are data that seem to support this novel technique.

The Senti-Endo study was conducted to assess the detection rate and diagnostic accuracy of sentinel lymph node mapping for early-stage endometrial cancer. Sentinel lymph node mapping was performed using a cervical dual injection technique with technetium patent blue dye. Completion pelvic lymphadenectomy was performed in all patients. The authors reported that 111 of the 125 eligible patients had at least one sentinel node detected. Seventeen percent (19 of 111 patients) were found to have a positive pelvic node and 5 % (5 of 111 patients) had a positive aortic node. The reported negative predictive value for each hemipelvis was 100 %, and the sensitivity was also 100 %. When evaluating the patients, the negative predictive value was 97 %, and the sensitivity was 84 %. The authors concluded that sentinel lymph node biopsy could be a trade-off between systematic lymphadenectomy and no dissection in patients with low- and intermediate-risk endometrial cancer [39].

Barlin et al. [40] published on the use of a sentinel lymph node mapping algorithm for endometrial cancer staging. The specific algorithm consists of (1) peritoneal and serosal evaluation and washings; (2) retroperitoneal evaluation including excision of all mapped sentinel nodes and suspicious nodes regardless of mapping; and (3) if there is no mapping on a hemipelvis, a site-specific pelvic common iliac and internal iliac lymph node dissection is performed. Para-aortic lymph node dissection is performed at the surgeon's discretion (Fig. 1). Over a 6-year period, 498 patients underwent sentinel lymph node mapping with a cervical injection of blue dye. Eighty-one percent of the patients had at least one lymph node removed, and the sentinel lymph node correctly identified 40 of 47 patients with nodal metastases. The false-negative rate was 15 %; however, when applying the described algorithm to these patients, the false-negative rate was decreased to 2 %. The authors concluded that satisfactory sentinel lymph node mapping for endometrial cancer requires the use of a sentinel lymph node mapping algorithm in which side-specific lymphadenectomy is performed when a sentinel lymph node is not identified. The use of this algorithm does not appear to compromise the detection rate of lymph node metastases. In a retrospective study of 507 patients, Leitao et al. [41] demonstrated that the incorporation of the described sentinel lymph node mapping algorithm resulted in a decreased nodal count while maintaining the same detection rate of lymph node metastases.

Different techniques have been described for sentinel lymph node mapping in endometrial cancer. There have been three injection sites described for sentinel lymph node mapping in

endometrial cancer. A cervical, a subserosal/myometrial, and a hysteroscopic endometrial injection have all been described. A cervical injection appears to be the easiest and most convenient technique; however, some have questioned its accuracy. Abu-Rustum et al. [42] compared the sentinel lymph node detection of a subserosal and cervical injection with a cervical-alone injection, and found comparable rates. Newer techniques of sentinel lymph node mapping, such as the use of near infrared imaging with indocyanine green, appear to yield higher rates of detection and bilateral mapping compared with blue dye alone or in combination with technetium [43].

Surgery is the mainstay treatment of this disease. Yet, surgeons specifically trained for the surgical management of this disease, gynecologic oncologists, are only involved in the care of 40 % of women with this disease [44]. Thus, a significant portion of patients diagnosed with endometrial cancer will not have appropriate surgery, as gynecologic oncologists are 2.5 times more likely to perform complete surgical staging compared with general obstetrician/gynecologists [44]. Such figures have led the Society of Gynecologic Oncology (SGO) to issue statements advising that patients with a primary diagnosis of endometrial cancer or recurrent disease be referred to a gynecologic oncologist to assist in determining the most appropriate surgical approach as well as extent of surgery and the potential benefits of adjuvant therapy [45].

Laparoscopic Surgery and Endometrial Cancer

Minimally invasive surgery has been incorporated into the management of gynecologic malignancies. Vaginal hysterectomy has been used in the management of endometrial cancers in certain situations [46]. However, the vaginal route does not allow for the evaluation of the peritoneal cavity or the retroperitoneal lymph nodes. With the development of improved instruments and surgeon skill, laparoscopic surgeons began to perform more complicated procedures, including sampling of the retroperitoneal lymph nodes.

Childers et al. [47] first reported on the combined use of laparoscopy with vaginal hysterectomy for the treatment of early-stage endometrial cancer. This group later reported on a series of 59 patients with clinical stage I endometrial cancer who were staged by this new procedure. Their technique included an inspection of the peritoneal cavity, intraperitoneal washings, and a laparoscopically assisted vaginal hysterectomy (LVAH). Patients with preoperative grade 2 or 3 tumors or grade 1 tumors with > 50 % myometrial invasion underwent laparoscopic pelvic and para-aortic lymphadenectomy. Six patients had intraperitoneal disease. Two patients could not undergo laparoscopic lymphadenectomy secondary to obesity, and two patients required conversion to laparotomy for intraoperative complications.

Advances in minimally invasive surgical techniques have allowed the use of laparoscopy in endometrial cancer surgery. Many studies have described the use of a combined laparoscopic and vaginal approach to perform all of the procedures involved in endometrial cancer staging, including a complete assessment of peritoneal surfaces and retroperitoneum [48–51]. Total laparoscopic hysterectomy (TLH) has also been well described as a technique that eliminates the need for vaginal surgery during the procedure [52].

Despite many early reports of the potential benefits of laparoscopy, it was only recently that the GOG LAP 2 trial established this as a standard approach to the management of early-stage endometrial cancer. In their initial report, Walker et al. [53] reported the initial findings of 2616 patients who were enrolled in this large randomized multi-institutional study. Patients were randomly assigned to laparoscopy or open surgery including hysterectomy salpingo-oophorectomy, pelvic cytology, and pelvic and para-aortic lymphadenectomy. In the trial, 1682 patients were assigned to laparoscopic surgery, and 1248 (74.2 %) had their surgery completed without conversion to laparotomy. Laparoscopy

resulted in fewer moderate-to-severe postoperative adverse events compared with open surgery. Hospitalization was also shorter. Although there was a larger number of patients in the laparoscopic arm who did not have an adequate number of pelvic and para-aortic nodes removed (8 % in the laparoscopic arm vs. 4 % in the laparotomy arm, $p < 0.0001$), there was no difference in the detection of advanced-stage disease. The authors concluded that laparoscopic surgical staging was feasible and safe, with fewer complications and shorter hospital stay. The oncologic outcomes were recently reported. With a median follow-up of 59 months, the 3-year recurrence rates were comparable among the two arms (11.4 % with laparoscopy and 10.2 % with laparotomy). The estimated 5-year overall survival was 89.8 % in both arms [54]. These results and the improved quality of life demonstrated with laparoscopy [55] help support the acceptance of laparoscopy in the management of early-stage endometrial cancer.

A robotic platform for performing minimally invasive surgery has made a significant impact on the management of patients with early-stage endometrial cancer. Robotically assisted surgery has allowed surgeons to overcome many of the technical difficulties associated with traditional laparoscopy, such as lack of depth perception, two-dimensional optics, and limited range of motion. The learning curve for robotic hysterectomy and lymphadenectomy is faster compared with that of laparoscopic hysterectomy and lymphadenectomy, with comparable adequacy of surgical staging between the two techniques. Several surveys of the SGO demonstrated an increasing trend in the use of laparoscopy for the management of endometrial cancer over an 8-year period. In 2004, 10 % of respondents identified endometrial cancer surgery as the most commonly performed laparoscopic procedure compared with 70 % of respondents in 2012. Much of this may be related to the increase in use of robotic surgery, which increased from 29 % in 2007 to 97 % in 2012 among respondents [56–58].

Gaia et al. [59] performed a systematic review of eight studies with 1591 patients who underwent surgical staging for endometrial cancer (robotic, 589; laparoscopic, 396; and laparotomy, 606). The pooled mean number of aortic and pelvic lymph nodes was similar when comparing the robotic approach to laparotomy and the robotic approach to laparoscopy. Estimated blood loss was less with robotic hysterectomy compared with laparoscopy and laparotomy. Robotic and laparoscopic surgery were associated with a shorter length of stay but longer operative time compared with laparotomy. The authors concluded that perioperative outcomes were similar for the robotic and laparoscopic approach. The robotic approach had the lowest blood loss.

This may also be accomplished with decreased pain requirements. In a retrospective study of 475 patients with endometrial cancer who underwent robotic or laparoscopic surgery, the robotic approach was associated with a significantly lower total dose of fentanyl used [60]. In a time of cost containment in medicine, robotic surgery may also be attractive. Leitao et al. conducted a cost analysis of three surgical approaches (laparoscopy, robotic, and laparotomy) of patients with endometrial cancer over a 2-year period. Although laparoscopic surgery was associated with the lowest cost compared with the robotic and open approaches, the non-amortized cost was comparable between laparoscopy and the robotic platform after the initial learning period. The authors saw a shift from laparotomy to robotic surgery during their study period, leading them to conclude that there is cost neutralization with the robot when it helps to decrease laparotomy rates [61].

Surgery for Stage II Disease

Extrafascial hysterectomy is usually employed in the surgical management of endometrial cancer. However, when there is known or suspected cervical involvement, radical hysterectomy can be used to effectively control local disease. In a retrospective series of 202 patients with cervical involvement from endometrial cancer, Boente et al. [62] defined five treatment groups: radical

hysterectomy ± radiation, TAH/BSO, radiation therapy alone, radiation therapy followed by TAH/BSO, and TAH/BSO followed by radiation therapy. Despite having more frequent adverse prognostic factors, patients treated with radical hysterectomy had an 86 % 5-year actuarial survival rate. This was in contrast to 5-year survival rates of 38 % and 19 % in the radiation group followed by TAH/BSO and TAH/BSO ± radiotherapy groups, respectively. Although formal statistical comparisons were not made, the authors supported the use of radical hysterectomy in patients with stage II endometrial cancer.

Improved outcomes with radical hysterectomy were described by Mariani et al. [63] in a review of 82 patients with cervical involvement. Although this study included both stage II and III patients, a subgroup analysis of only patients with stage II disease treated with radical hysterectomy demonstrated superior results. Both disease-related and recurrence-free survival rates were 100 % in patients treated with radical hysterectomy compared with 80 % and 73 %, respectively, in patients treated with simple hysterectomy. Thus, treatment of patients that have known cervical extension using radical hysterectomy appears to be a reasonable approach.

Surgery in the Morbidly Obese Patient

Obesity is a major risk factor for the development of endometrial cancer, and many patients will present with a high body mass index (BMI) (also described as Quetelet Index [QI]). Patients classified as morbidly obese can be technically challenging to surgically manage. This subclassification of patients may comprise over one-quarter of patients with endometrial cancer [64]. These patients require longer operating times and experience greater blood loss when compared with patients with BMIs $< 30\ kg/m^2$. However, hospital stay and perioperative complications do not appear to be increased.

Consideration may be given to performing a panniculectomy in these patients. In a retrospective series of patients undergoing panniculectomy for endometrial neoplasms, the procedure was associated with a higher para-aortic node count compared with that of matched controls [65]. The procedure was not associated with an increase in perioperative morbidity. Although pelvic node count was not higher, the authors suggested that panniculectomy may enhance operative exposure and facilitate the staging procedure.

While technically challenging, obesity may not be an absolute contraindication to performing a laparoscopic staging procedure. Scribner et al. [66] reported on their experience of laparoscopic pelvic and para-aortic lymphadenectomy in obese patients. In 55 patients, laparoscopic staging was completed in 82 % of those with a QI < 35 compared with only 44 % of those with a QI ≥ 35 ($p = 0.004$). Despite this difference, these authors and others concluded that obesity is not an absolute contraindication to laparoscopic staging [67, 68]. Robotic surgery may expand the role of minimally invasive surgery in this patient population. In a study of obese and morbidly obese patients with endometrial cancer, Gerhig et al. [69] demonstrated that the use of robotic surgery in this population was associated with shorter operative times, reduced blood loss, and a shorter hospital stay compared with traditional laparoscopy. Similarly, Seamon et al. [70] concluded that robotic hysterectomy and lymphadenectomy for endometrial cancer could be performed in heavier patients compared to laparoscopy, with shorter operating room times and hospital stay, decreased transfusion rates, and fewer conversions to laparotomy.

Conclusions

- Early-stage endometrial cancer is surgically treated, yielding valuable information for diagnostic and therapeutic purposes.
- The potential variability between preoperative and final histologic grade, depth of invasion, and other prognostic factors mandates that surgical staging be performed in the majority of patients with early-stage cancer.
- A sentinel lymph node mapping algorithm appears to be a promising approach for staging patients.

- Advances in minimally invasive techniques, skills, and instrumentation offer many potential benefits to patients undergoing surgical management. Some anatomic barriers, however, such as large fibroid uteri, are contraindications to laparoscopic surgery in the presence of endometrial cancer.
- The equivalency of outcome with the abdominal approach, when applying such laparoscopic procedures, has been demonstrated by the Gynecologic Oncology Group. The laparoscopic approach is associated with improved patient satisfaction, decreased morbidity, and comparable survival, and should be considered the main treatment option in patients with early-stage endometrial cancer.
- The introduction of a robotic platform has expanded the role of minimally invasive surgery and may be particularly helpful in the obese patient population.

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