



Marguerite Bride. *Winter's End*. Watercolor, 10" × 14".

Alternative approaches to traditional laparotomy such as minimally invasive surgery can diminish procedure-related morbidity and expedite recovery for patients with endometrial cancer.

The Use of Minimally Invasive Surgery for Endometrial Cancer

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Background: Endometrial cancer is the most common gynecologic malignancy in the United States. Surgical staging is an integral component in the treatment of this disease. Minimally invasive surgical techniques have been utilized with increasing frequency in its management.

Methods: This article reviews the use of minimally invasive surgery for the treatment of endometrial cancer.

Results: Prospective trials and retrospective analyses have demonstrated the safety and feasibility of laparoscopy in performing hysterectomy, bilateral salpingo-oophorectomy, and pelvic and periaortic lymphadenectomy for surgical staging in endometrial cancer. The use of minimally invasive techniques does not appear to have an adverse impact on survival, and it improves quality of life in the postoperative period. Robotic surgery has been used in the management of this disease with promising preliminary results.

Conclusions: Laparoscopy is a safe and effective approach for surgical staging of selected patients with endometrial cancer. Further studies and cost-benefit analyses are required to determine if the use of robotics improves outcomes over standard laparoscopy and can extend the benefits of minimally invasive surgery to a larger proportion of patients with this common gynecologic malignancy.

Introduction

Minimally invasive surgery has been shown to be an appropriate, if not preferred, alternative in many wide-ranging surgical procedures. As with any procedure, careful patient selection is critical. In gynecologic oncology, the reported advantages of minimally invasive surgery include a shorter hospital stay, decreased analgesic requirements, faster recovery, lower intraoperative and postoperative complications, and improved quality

of life.^{1,2} Laparoscopy has been used extensively for the management of benign gynecologic conditions such as the evaluation and treatment of endometriosis and benign adnexal masses. Since the 1960s and 1970s, laparoscopy has been used in benign gynecology.³ Case reports in the late 1980s demonstrated the use of minimally invasive surgery in gynecologic oncology.³ As advanced laparoscopic techniques and skills have improved and as innovative technologies have become available, minimally invasive surgery has been used with increasing frequency in the treatment of gynecologic malignancies, including endometrial cancer.

Historically, endometrial cancer surgery has been performed via laparotomy. This involves carefully exploring the abdomen and pelvis, obtaining washings for

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cytology, and performing a total abdominal hysterectomy, a bilateral salpingo-oophorectomy, and pelvic and periaortic lymphadenectomy. Patients with endometrial cancer often have significant medical comorbidities such as obesity, diabetes, hypertension, and older age. Alternative techniques such as minimally invasive surgery that would diminish procedure-related morbidity and expedite recovery may be especially beneficial in this patient population.

Epidemiology

Uterine cancer is the most common gynecologic cancer in women in the United States. According to the

American Cancer Society, an estimated 40,100 women were diagnosed with uterine cancer and 7,470 died of it in 2008.⁴ Approximately 85% of endometrial cancers are of endometrioid histology. The remaining 10% to 15% include papillary serous and clear cell cancers. The adenocarcinomas are grouped into type 1 and type 2. Typically, most consider type 1 uterine cancers to be grade 1 and 2 endometrioid adenocarcinomas. Type 1 is most common in obese peri- and postmenopausal women or in women taking unopposed estrogen, and it arises on the basis of endometrial hyperplasia. Type 2 is composed of grade 3 endometrioid adenocarcinomas, papillary serous, and clear cell cancers. It is not

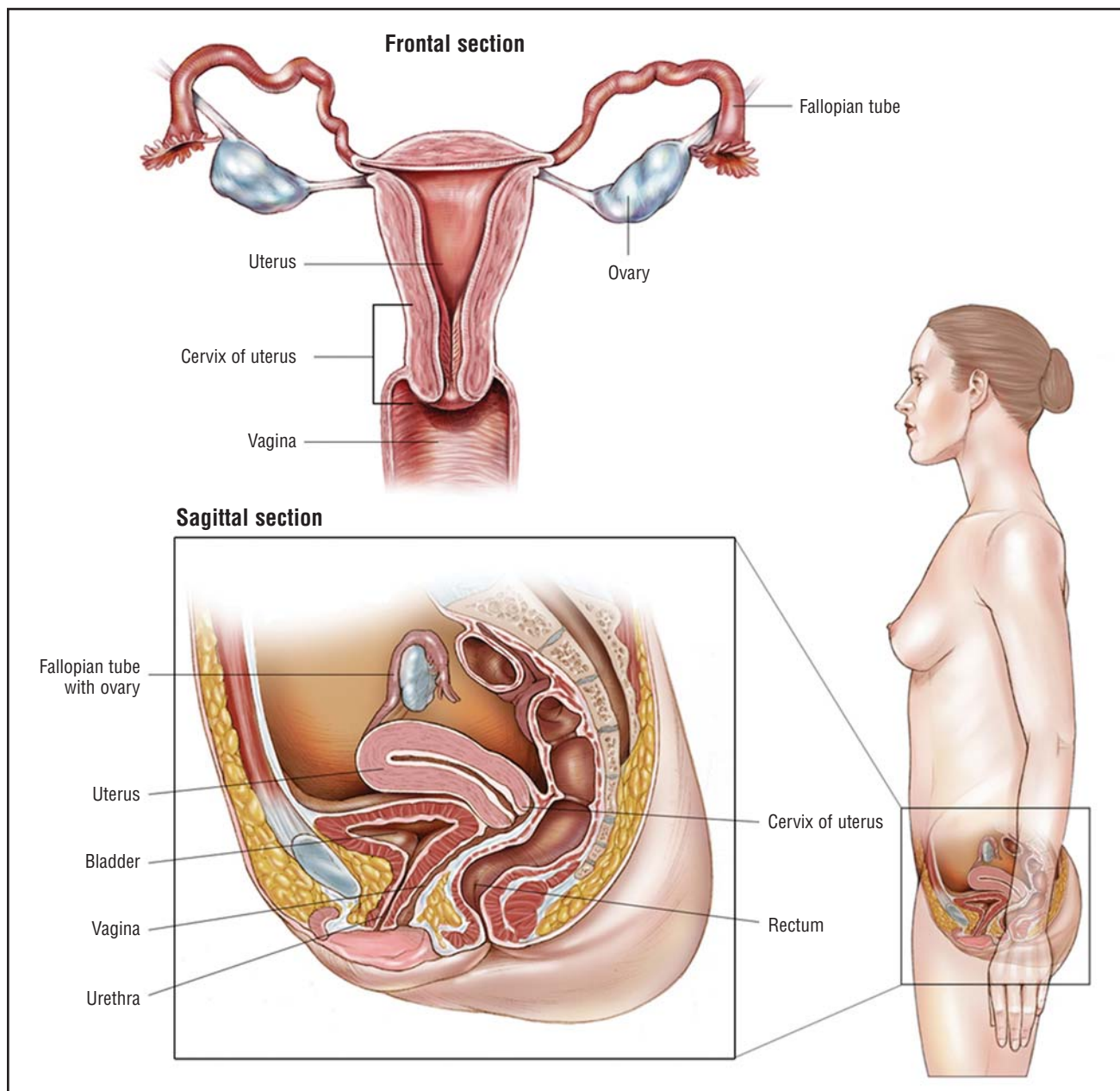


Fig 1. — Female pelvic anatomy. This figure shows the proximity of the uterus to the bladder, sigmoid colon, and vagina. From Robert Morreale, Visual Explanations, LLC. 2003. http://www.plwc.org/oncology_content/medical_illustrations/womens_print.jpg. Reprinted with permission © American Society of Clinical Oncology. All rights reserved.

associated with estrogen excess and arises in an atrophic endometrium. Such cancers are generally more aggressive with a tendency to present with advanced-stage disease.

The median age of diagnosis of endometrial cancer is 63 years, and the median age of death is 73 years. The highest incidence is in white women, with 24.3 per 100,000 per year, but the highest mortality is in black women, with 7.6 per 100,000 per year. Risk factors for the development of endometrial cancer include early menarche, late menopause, history of infertility, anovulatory cycles, nulliparity, obesity, tamoxifen use, hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome), estrogen-secreting tumors (ie, Granulosa cell), estrogen therapy, diabetes, and prior pelvic radiation.⁵

Diagnosis and Treatment

Patients with endometrial cancer usually present with abnormal vaginal bleeding. It is important to note that this is not only for postmenopausal women but also for premenopausal or perimenopausal women with prolonged menorrhagia or metrorrhagia. Prompt evaluation with endometrial sampling should be performed. This evaluation can be obtained by dilation and curettage or by endometrial pipelle.⁶ The relevant anatomy is shown in Fig 1.

Surgical Staging

Beginning in 1978, endometrial cancer was clinically staged, but over time this method was proven to be inadequate. The International Federation of Gynecologic Oncologists (FIGO) adopted a surgical staging system in 1988.⁷ The staging system incorporated the tumor grade, depth of myometrial invasion, occult extension to the cervix, adnexal involvement, peritoneal cytology, pelvic and periaortic lymph node involvement, and vaginal, inguinal, or distant metastases. Currently, the standard of care for patients with no contraindications to surgical intervention is a hysterectomy with bilateral salpingo-oophorectomy, pelvic and periaortic lymph node sampling vs lymphadenectomy. Fig 2 depicts the typical patterns of lymphatic dissemination of endometrial cancer. The extent of lymph node sampling is controversial. Some physicians perform extended staging based on frozen section analysis including grade, depth of myometrial invasion, and size of the tumor.⁸ Due to the frequency of discordance between preoperative pathology or frozen section with final pathology, others advocate complete lymphadenectomy for all patients who are medically fit.^{9,10} Whether there is a therapeutic benefit for lymphadenectomy has not been definitive determined, although retrospective analysis suggests a survival benefit.¹¹ Due to the propensity for early extrauterine dissemination in papillary serous cancers, some authors recommend performing an omentectomy as part of the

staging procedure.¹² This is debatable, however, as others state that the risk of omental disease in the absence of gross extrauterine disease is minimal.¹³ The pelvic lymph nodes include the common iliac, external iliac, internal iliac (hypogastric), and obturator nodes. The periaortic lymph nodes are sampled to the level of the inferior mesenteric artery bilaterally.⁷ The level of dissection that is considered adequate is controversial.¹⁴ Some authors suggest that the periaortic dissection should extend to the renal vessels.^{8,15}

Postoperatively, the extent of disease is categorized into a stage and grade as delineated by FIGO (Table 1), which provides prognostic information. Pathologic findings are used to determine the need for adjuvant radiation and/or chemotherapy based on risk of recurrence (Table 2).

Minimally Invasive Surgery

Whether a patient is staged via laparoscopy or laparotomy, the oncologic procedure should be identical. A careful assessment for extrauterine disease is made, obtaining pelvic cytology. A hysterectomy, bilateral-salpingo-oophorectomy, pelvic and periaortic lymph node sampling vs lymphadenectomy is performed. The majority of patients with endometrial cancer are diagnosed with early-stage

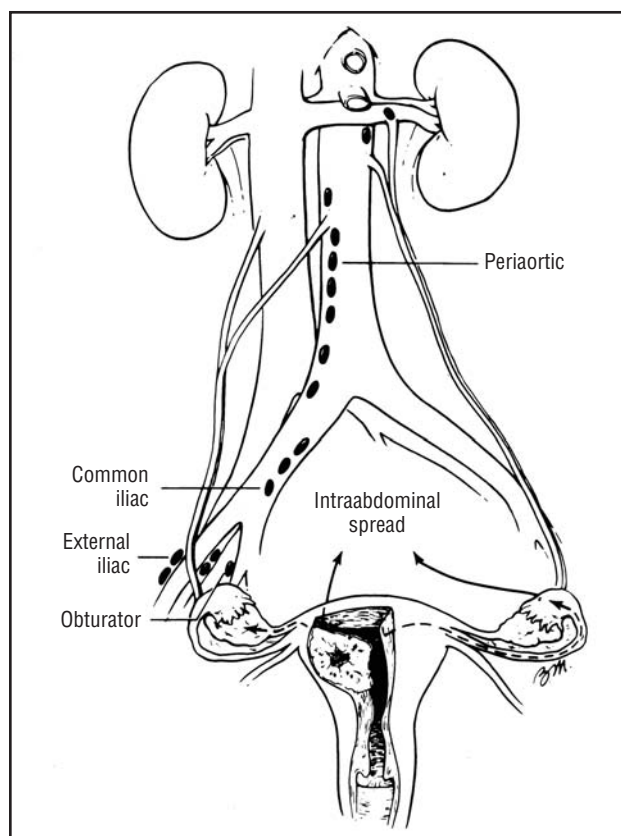


Fig 2. — Patterns of lymphatic dissemination of endometrial cancer. Endometrial cancer can spread via lymphatics to the pelvic and periaortic nodes. From DiSaia PJ, Creasman WT, eds. *Clinical Gynecologic Oncology*. 5th ed. St Louis, MO; Mosby-Year Book, Inc; 1997. © Elsevier. Reprinted with permission.

disease with a favorable 5-year prognosis. Therefore, any new surgical approach must be carefully validated to assure that the technique is at least equivalent.

A prospective German study compared laparoscopy to laparotomy in a randomized trial of 70 patients.¹⁶ The laparoscopic group included 37 patients and the laparotomy group included 33 patients. Blood loss and transfusion rates were significantly lower in the laparoscopic group. Yield of pelvic and periaortic lymph nodes, duration of surgery, and incidence of postoperative complications were similar for both groups. Overall and recurrence-free survival did not differ sig-

nificantly for both groups. In another study, these same investigators reported their experience with 650 pelvic and periaortic lymphadenectomies performed for gynecologic malignancies, 112 of which were for endometrial cancer.¹⁷ After a learning period of approximately 20 procedures, a constant number of pelvic lymph nodes (16.9 to 21.9) were removed. The number of removed periaortic lymph nodes increased over time, from 5.5 to 18.5. The number of removed lymph nodes was independent of the body mass index (BMI). Duration of pelvic lymphadenectomy was independent of BMI, but right-sided periaortic lymphadenectomy lasted significantly longer in obese women (35 vs 41 min, $P = .011$). The overall complication rate was 8.7%, with 2.9% intraoperative (vessel or bowel injury) and 5.8% postoperative complications.

A case series of 203 patients demonstrated success with laparoscopic staging.¹⁸ The conversion rate was 8% for adhesions or poor exposure, and the mean hospital stay was 2.8 days. One recent report showed a significant increase in the use of laparoscopy over a 12-year period at a single institution involving 1,312 patients.⁷

An Italian study showed that laparoscopy provides equivalent lymph node yield compared with laparotomy.¹⁹ This retrospective study identified 110 patients with apparent early-stage endometrial cancer. Fifty-five (50%) were treated by laparoscopic-assisted vaginal hysterectomy (LAVH) and 55 (50%) by total abdominal hysterectomy (TAH). All patients underwent pelvic lymphadenectomy. The mean number of lymph nodes removed was 17 for the LAVH group and 18.5 for the TAH group ($P = .294$). Compared with TAH, LAVH required a significantly longer operating time (mean 220 vs 175 min; $P < .01$) but resulted in a shorter hospital stay (mean 4 vs 8.5 days; $P < .001$) and less estimated blood loss (mean 177 cm³ vs 285 cm³; $P = .02$). Overall, fewer postoperative complications occurred in the LAVH group (6 vs 11 cases; $P < .001$). This study is limited by the biases inherent in retrospective analysis and by the lack of complete staging.

The Gynecologic Oncology Group (GOG) has completed a phase III randomized study (LAP 2) comparing laparoscopy vs laparotomy in endometrial cancer.²⁰ Laparoscopic surgical staging could be performed in 76.3% of cases. No difference in stage, positive cytology, or lymphatic metastasis could be attributed to the laparoscopic approach. Quality of life and physical functioning were improved 6 weeks postoperatively following laparoscopy, but these differences were not significant by 6 months.²¹ While laparoscopic staging may be a technically feasible option for surgical management, long-term data regarding recurrence and survival have yet to be reported.

The Laparoscopic Approach to Cancer of the Endometrium (LACE) is a randomized, controlled trial comparing total abdominal hysterectomy to total

Table 1. — International Federation of Gynecologic Oncology (FIGO) Staging for Uterine Cancer

Stage	
IA	Tumor limited to endometrium
IB	Invasion to less than one-half the myometrium
IC	Invasion to more than one-half the myometrium
IIA	Endocervical glandular involvement only
IIB	Cervical stromal invasion
IIIA	Tumor invades serosa, and/or adnexa, and/or positive peritoneal cytology
IIIB	Vaginal metastases
IIIC	Metastasis to pelvic and/or periaortic lymph nodes
IVA	Tumor invasion of bladder mucosa and/or bowel mucosa
IVB	Distant metastases including intra-abdominal and/or inguinal lymph nodes
Degree of Differentiation	
Grade 1	5% or less of a nonsquamous or nonmorular solid growth pattern
Grade 2	6% to 50% of a nonsquamous or nonmorular solid growth pattern
Grade 3	More than 50% of a nonsquamous or nonmorular solid growth pattern
Adapted with permission from the International Federation of Gynecology and Obstetrics (FIGO). Pecorelli S, Ngan HYS, Hacker NF, eds. <i>Staging Classifications and Clinical Practice Guidelines for Gynaecological Cancers</i> . London, UK: FIGO; 2006:63-83.	

Table 2. — Classification of Endometrial Cancer Risk of Recurrence and Mortality

Low Risk	
Disease confined to the uterus	
Histologic grade 1 or 2	
Endometrioid histologic subtype	
Less than 50% myometrial invasion	
High Risk	
Advanced surgical stage	
Poorly differentiated histologic grade	
Non-endometrioid histologic subtype (serous, clear cell)	
Deep myometrial invasion (> 50%)	
Lymphovascular space invasion	
Primary tumor diameter > 2 cm	
Cervical stromal invasion	
Adapted with permission from the International Federation of Gynecology and Obstetrics (FIGO). Pecorelli S, Ngan HYS, Hacker NF, eds. <i>Staging Classifications and Clinical Practice Guidelines for Gynaecological Cancers</i> . London, UK: FIGO; 2006:63-83.	

laparoscopic hysterectomy in stage I endometrial cancer patients. The ongoing study is expected to be completed in 2009 and will report on quality of life and disease-free survival in these two groups.²²

Survival outcomes with minimally invasive surgery have also been reported. A prospective, randomized study demonstrated comparable survival at a median follow-up of 44 months between laparoscopy and laparotomy.²³ Among 122 patients, the overall survival rates for the laparoscopy and laparotomy groups were 82.7% and 86.5%, respectively. These data are consistent with reported retrospective data demonstrating equivalent survival between these two groups.²⁴ The impact of laparoscopy on the incidence of positive cytology is controversial.²⁵ Some investigators report a significantly higher incidence of positive peritoneal cytology in patients undergoing laparoscopy for endometrial cancer.²⁶ This may be due to the retrograde dissemination of cancer cells into the peritoneal cavity during uterine manipulation. The clinical significance of these findings is not clear and should be individualized based on uterine pathology and lymph node status.

There are potential economic advantages to minimally invasive surgery. A retrospective report suggested that for early-stage endometrial cancer, patients treated with laparoscopy had significantly shorter hospitalization and fewer complications compared to patients treated with laparotomy, which resulted in reduced overall hospital charges.²⁷

Impact of Obesity

A retrospective study showed that obesity is not a contraindication to laparoscopic staging.²⁸ This is an important consideration, as many patients with endometrial cancer are obese. In this population (Quetelet index [QI] ≥ 28), operative time increased but hospital stay, febrile morbidity, and ileus decreased in the laparoscopy group compared with the laparotomy group. A QI ≥ 35 was associated with a decrease in success rate of completing the case laparoscopically compared with a QI < 35 (44% vs 82%, $P = .004$). A prospective study of 42 obese women treated with laparoscopy reported a 7.5% conversion rate.²⁹ Compared to historical controls from 2 years prior, women who underwent laparoscopy had a significantly longer operative time, more pelvic lymph nodes removed, and a shorter hospital stay (194.8 vs 137.7 min, $P < .001$; 11.3 vs 5.3, $P < .001$; and 2.5 vs 5.6 days, $P < .001$, respectively). Provided the patient is medically fit for the procedure, obese patients with apparent early-stage endometrial cancer can be safely and effectively managed with laparoscopy. In a prospective multicenter study, investigators evaluated outcomes in 33 obese and 32 non-obese patients undergoing laparoscopy for endometrial cancer.³⁰ They reported equivalent operating time, node counts, blood loss, and hospital stay. More complications occurred in the obese

group (8 vs 5), including pulmonary embolism, injury to the epigastric artery, bladder injury, bleeding, and conversion to laparotomy.

Incomplete Staging

Occasionally the diagnosis of endometrial cancer is not established preoperatively. To define the extent of disease, some patients may benefit from completion staging. The decision of whether to pursue a second procedure is determined by factors such as the depth of myometrial invasion, histology, grade, cervical/adnexal involvement, imaging, and medical comorbidities. Laparoscopy has been used with success in this setting, when there is a desire to minimize morbidity with a second operation.³¹ A faster recovery may also minimize delay of any adjuvant therapy that may be recommended. A recent GOG study of patients with incompletely staged gynecologic malignancies showed that laparoscopic staging was possible in 80% of patients, while 20% required laparotomy.³²

Subcutaneous Tumor Implantation After Laparoscopy

Many retrospective series have addressed the issue of trocar site metastases in women undergoing laparoscopic procedures for gynecologic cancers. The true incidence is unknown, as many cases may not be reported or are discovered in the setting of metastatic disease. A 12-year study of 1,288 patients who had laparoscopic procedures for gynecologic malignancies (including ovarian, uterine, and cervical cancer) demonstrated a rate of trocar site metastasis of 0.97%.³³ The risk of subcutaneous implantation was associated with advanced disease or carcinomatosis. Another retrospective study of 105 laparoscopic procedures performed for gynecologic malignancy demonstrated a 1% rate of abdominal wall tumor implantation.³⁴ Other investigators have reported similar rates of metastases but further defined the risk. One single-institution retrospective study identified 83 patients with port-site metastases, 39 of whom had endometrial cancer.³⁵ The overall incidence rate was 2.3%, and the risk was 5% in the setting of recurrent ovarian cancer with ascites. A review of 31 articles in 2004 identified 58 patients with port-site metastases.³⁶ Of these cases, only 4 occurred in patients with endometrial cancer. Due to the small numbers, it is difficult to draw conclusions. The etiology of port-site metastases is poorly understood. Proposed factors include a derangement of the local immune systems, impact of carbon dioxide insufflation, and the high efflux of gas from the peritoneal cavity around the trocars. Overall, the risk of abdominal implantation is low and should not preclude the use of laparoscopy in the treatment of endometrial cancer. The risk of subcutaneous implantation is likely higher in the setting of disseminated intraperitoneal disease. The GOG LAP2

study may provide a better understanding of port-site metastases in patients with endometrial cancer.

The Role of Robotic Surgery in Gynecology Oncology

The use of robotics in surgery has evolved over the past 25 years. Early passive applications were used in neurosurgery, transurethral resection of the prostate, and total hip replacement. A more active role for robotics was developed with an immersive environment that became known as robotic telepresence technology.³⁷ The predecessors to the current platform, known as Aesop and Zeus (Computer Motion Inc, Goleta, California), were applied in gynecologic procedures. These systems provided three-dimensional vision and improved dexterity.

With these technologic advancements, the use of robotics showed promise in expanding the applications of minimally invasive procedures. A significant obstacle to more widespread acceptance and application of minimally invasive surgery to advanced techniques, such as lymphadenectomy, has been a steep learning curve. Other limitations of standard laparoscopy include two-dimensional view, limited instrument dexterity, tremor amplification, and poor ergonomics. The current platform utilizes the da Vinci surgical system (Intuitive Surgical, Sunnyvale, California). This system was approved by the US Food and Drug Administration for gynecologic procedures in 2005. Using this platform, the surgeon is seated a few feet away from the patient with a console controlled by the surgeon's hands and feet (Fig 3A). The camera provides a three-dimensional view with up to 10 times magnification. There are either three or four arms, one of which holds the laparoscope. The robotic arms and instruments together provide seven degrees of freedom, replicating that of the surgeon's hand (Fig 3B).

Several investigators have reported on the use of robotics for benign indications in gynecology.³⁸⁻⁴¹ These reports have demonstrated the feasibility of hysterectomy. Others have reported the use of robotics in gynecologic oncology.^{42,43} Combined, these two studies describe the initial experience in 19 patients with gynecologic cancers, with lymph node counts ranging from 4 to 29. Another recent study evaluated surgical outcomes for 100 consecutive cases incorporating the da Vinci Surgical System.⁴⁴ Thirty-three of the patients had invasive cancer, with 20 endometrial and 9 cervical cancer cases. The patients had an average age of 55 years, with a mean BMI of 28.5 (16.1 to 52.3), and 27% had a BMI > 30 (obese). Operative time (average 128 minutes including docking time), estimated blood loss, length of stay, and complication rate did not increase using robotics. Seventeen of the 20 endometrial cases were completed robotically, and 13 of the 17 underwent concomitant lymphadenectomy with a mean yield of 15 nodes. In another study, 43 patients with clinical stage I endometrial cancer underwent staging using the da Vinci Surgical System and were compared with a historical cohort of patients who underwent laparoscopic hysterectomy with staging.⁴⁵ The average QI was 32.8 for the robotic cohort vs 29.2 in the laparoscopic cohort ($P = .008$). There were significantly more nodes recovered in the robotically staged patients (29.8 vs 23.2; $P = .004$). The mean blood loss in the robotic group was 63 mL (range 25 to 300 mL), with 45% of patients having no measurable blood loss compared with 142 mL (50 to 700 mL) in the laparoscopy group ($P = .0001$). Mean operative time was 163 minutes compared with 213 ($P = .002$). Hospital stay was 1.0 vs 1.2 days ($P = .04$). Major complications occurred in 4.6% of the robotic group and in 12.8% in the laparoscopy group. These early experiences demonstrate feasibility of applying robotics to gynecologic cancer staging.



Fig 3A-B. — The da Vinci Surgical System. (A) The surgeon is seated at the console at a short distance from the patient-side cart with the four interactive robotic arms and the vision system. (B) A robotic arm uses instruments that provide seven degrees of freedom. Photos courtesy of Intuitive Surgical, Inc, 2008.

A recent study evaluated the feasibility of training fellows in robotic-assisted laparoscopic gynecologic procedures.⁴⁶ Sixteen robotic-assisted gynecologic procedures were performed with fellows participating as the console surgeon in 9 of 16 cases. The median age was 56 years, BMI = 28.6 (range 19.4 to 43.8), estimated blood loss = 37.5 cm³ (range 25 to 200 cm³); and hospital stay = 1.0 day (range 1 to 4 days). The median total operative time for the 9 cases in which the fellow functioned as console surgeon was 168 minutes. There were no reported complications in this small series, and robotic-assisted laparoscopic training seems to be easily incorporated into gynecologic oncology training programs.

In spite of the apparent advantages, there are several important considerations. With the use of robotics, there is a loss of tactile sense that provides important feedback. The da Vinci Surgical System is bulky, interferes with vaginal access, and could potentially increase operating time with assembly of the equipment.⁴⁷ Another important factor is the significant fixed and recurring costs of the system. The cost-benefit analysis is complex, involving patient satisfaction, oncologic outcome, surgeons' experience, and hospital expenses. The role of robotics in the minimally invasive approach to endometrial cancer has yet to be determined definitively and continues to evolve. Prospective studies that compare standard laparoscopy and robotic-assisted laparoscopy are needed to help characterize any benefits offered by this innovative technology.

Conclusions

Over the past several decades, minimally invasive surgical techniques, instrumentation, and technology have improved significantly. The application of these techniques in selected women with endometrial cancer is a safe and effective alternative to laparotomy and appears to provide equivalent disease-free and overall survival rates. Patient benefit is demonstrated by faster recovery, decreased pain, and improved quality of life. As mature data from GOG LAP2 become available, the feasibility and outcomes will be further clarified. With increasing frequency, robotic technology has been used in the management of endometrial cancer with promising results. Further investigations are required to define the cost-benefit relationship between standard laparoscopy and robotics.

Disclosures

No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.

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