Laparoscopic surgery for endometrial cancer: long-term results of a multicentric study

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Summary

Purpose of investigation: Surgical treatment of endometrial cancer was traditionally done by laparotomy, however the laparoscopic approach has gained wider acceptance by gynecologic surgeons.The primary aim of the study was to report the perioperative and postoperative outcomes of laparoscopic surgery in a major group of patients with endometrial cancer. The second aim was to study the long-term results of laparoscopic surgery in patients with endometrial cancer.

Material and method: A prospective multicentric study was conducted at three oncolaparoscopic centres; 221 women who had undergone laparoscopic (177 women) or abdominal (44 women) hysterectomy with bilateral salpingo-oophorectomy and lymphadenectomy were included in the study. Women with stage IA, grade 1 did not undergo lymphadenectomy unless they had a high risk histologic tumor type. Lymph node dissection was performed in 145 women with disease greater than IA or grades other than 1.

Results: The mean age and weight were similar in the compared laparoscopic and open groups. Perioperative blood loss was comparable in both groups (211.2 ml vs 245.7 ml, respectively) without any significant consecutive changes in serum hemoglobin values. Although the length of operating time for the laparoscopic surgery was significantly longer than the time for the laparotomy procedure (163.3 min vs 114.7 min, $p < 0.0001$), the laparoscopic patients were discharged from hospital much earlier at 3.9 days (range 2-16) after the laparoscopic procedure compared with 7.3 days (range 5-16) after the abdominal procedure ($p < 0.0001$). The difference in surgical complications between groups was statistically insignificant ($p = 0.58$). Similar long-term results were noted in both groups. With a median follow-up of 33.6 months for the laparoscopy group and 45.2 months for the open group, there were no significant differences in tumor recurrence ($p = 0.99$] or recurrence-free survival ($p = 0.86$) between the two groups.

Conclusion: The study illustrates that laparoscopically assisted surgical staging of endometrial cancer is safe as an open procedure.The laparoscopic approach may also be considered for endometrial malignancy which typically occurs in obese and elderly, high-risk women. Our analysis showed no difference with respect to recurrence or survival between the compared laparoscopic and the open group.

Key words: Endometrial carcinoma; Surgery; Laparoscopy; Hysterectomy; Complications; Recurrence; Survival.

Introduction

Endometrial cancer (EC) is the most common gynaecological cancer, with an incidence of 30 cases per 100,000 women in the Czech Republic in 1999. Surgical treatment was traditionally done by laparotomy, however the laparoscopic approach has gained wider acceptance by gynecologic surgeons. Laparoscopically assisted surgical staging (LASS) of endometrial cancer has been reported in several case series totaling more than 600 cases [1-9].

A phase III prospective randomized trial of laparoscopically assisted vaginal hysterectomy and laparoscopic surgical staging versus traditional abdominal hysterectomy and staging for the management of patients with endometrial cancer was undertaken by the Gynecologic Oncologic Group (GOG). Patients were evaluated for differences in important variables such as completeness of surgical staging, hospital stay and quality of life [10, 11].

Based on the above criteria, the Czech multicentric prospective trial (CZEMPT) began in 1996 and the preliminary results were reported [7]. The primary aim of the study was to report the perioperative and postoperative outcomes of laparoscopic surgery in a major group of patients with endometrial cancer. The second aim was to study the long term results of laparoscopic surgery in patients with EC.

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Subjects and method

This study was conducted at three oncolaparoscopic centres in the Czech Republic. We identified 332 patients who underwent surgery for early stage endometrial cancer between April 1996 and March 2001. Only 221 women who had undergone laparoscopic (177 women) or abdominal (44 women) hysterectomy with bilateral salpingo-oophorectomy (BSO) and lymphadenectomy were included in the study. A group of 44 abdominally treated patients from Hospital Kladno was used as a control (open group). The vaginally and abdominally treated patients from other centres or patients with incomplete records were excluded.

Selection criteria for the laparoscopic approach included clinician suspicion of early stage endometrial cancer,

regardless of grade or histopathology and myoinvasion, as well a mobile uterus amenable to a laparovaginal approach for hysterectomy. The decision concerning the extent of laparoscopic surgery was based on the guideliness suggested by Childders *et al.* [1] and arranged in protocol of CZEMPT [7]. Women with stage IA, grade 1 did not undergo lymphadenectomy unless they had a high-risk histologic tumor type (e.g. papillary serous or clear cell carcinoma). Pelvic lymphadenectomy was performed in all women with disease greater than IA or grades other than 1. Para-aortic lymph node dissection was performed in women with grade 3 tumors and any degree of myometrial invasion, and those with high-risk histologic tumor types. The decision to perform lymphadenectomy was based on the preoperative endometrial biopsy, ultrasound (US), computerized tomography (CT) or magnetic resonance imaging (MRI), and in some cases frozen section.

The patients who underwent abdominally assisted surgical staging (AASS) had a standard open procedure with a vertical midline incision, total extrafascial hysterectomy, bilateral salpingo-oophorectomy, peritoneal washing, pelvic lymph node dissection, and in the presence of selected high risk factors, para-aortic sampling as well. For the open procedure patients who were not suitable for laparoscopic surgery were selected because of following reasons: concurrent illness that does not allow the use of the Trendelenburg position, high anesthesiology risk according to classification ASA (American Society of Anesthesiologists) III and a more enlarged myomatous uterus, in which the necessity of morcellation can be a prerequisite due to a history of repeated laparotomies for peritonitis.

Perioperative surgical complications were defined as adverse events such as bladder, ureteral, bowel or vascular injuries, estimated blood loss over 1,000 ml, and significant abdominal wall bleeding. Postoperative complications were defined as adverse events occurring within 30 days of surgery as a result of the procedure and were considered major if they resulted in a blood transfusion, patient readmission or a secondary surgical procedure. All the procedures were carried out by one of three experienced oncogynecological surgeons. A video recording was taken for each patient. A case record form was completed containing patient identification data, preoperative staging (ultrasound, CT, MRI and biopsy), surgical/pathological information (grading, myometrial invasion, typing histology and cytology), and the definitive staging. Surgical staging was performed according to the Federation of Gynecology and Obstetrics (FIGO) staging system. The types of surgery and characteristics of the women are shown in Table 1.

The study protocols were approved by the Scientific Committee on Human Research at the Czech Endoscopic Society and by the Regional Committee on Human Research at Hospital Kladno. The participants gave informed consent at enrollment.*

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Table 1. — *Types of surgery and patient characteristics.*

Type of surgery	Laparoscopy	Open	Totals
HYE, BSO, lavage	32 (18.0%)	19 (43.1%)	51 (23.1%)
HYE, BSO, PLN, lavage	114 (64.4%)	22 (50.0%)	136 (61.5%)
HYE, BSO, PLN, PALN	29 (16.4%)	2 (4.5%)	31 (14.0%)
HYE, BSO, PLN, PALN + omentectomy	2 (1.1%)	1 (2.2%)	3 (1.5%)
Totals	177 (80.1%)	44 (19.9%)	221 (100%)
Patients characteristics			p value
Mean weight (kg)	81.0	81.8	NS
Range	(51-130)	(52-110)	
Mean age (years)	61.8	63.6	NS
Range	(42-79)	(44-85)	

Abbreviation: HYE = hysterectomy, BSO = bilateral salpingo-oophorectomy, PLN = pelvic lymph node dissection, PALN = para-aortic lymph node dissection.

Laparoscopic operative technique

Laparoscopy was carried out using video monitoring equipment with the patient in the lithotomy position. The telescope was inserted at the subumbilical site and one 10-mm port of entry was made suprapubically and medially. Finally, two or three 5-mm ports were placed in each of the lower quadrants at the lateral edge of the rectus muscle. Bipolar and monopolar electrocauters (Karl Storz Endoscope, Tuttlingen, Germany) were used in most cases, whereas a harmonic scalpel and laparosonic coagulating shears (LCS-K5), (Ultracission, Ethicon Endo Surgery, Johnson & Johnson Ltd, Cincinnati, Ohio, USA) were applied in one center only (Kladno Hospital).

Laparoscopically assisted surgical staging required a complete inspection of the whole peritoneal cavity. Intraperitoneal fluid was aspirated in each of four quadrants for cytological investigation. A second-look laparoscopy was then performed to secure or confirm hemostasis and an intraperitoneal drain was left in situ until the next day. All patients received thrombosis prophylaxis in a form of low molecular heparin and also perioperative prophylactic antibiotics.

Transperitoneal pelvic lymph node dissection (PLN)

The dissection was begun by opening the broad ligament and lateral pelvic peritoneum between the round ligament and the infundibulopelvic ligament. The lymph nodes bearing the adipose tissue were excised from the obturator fossa after mobilization of the external and internal iliac vessels and obturator nerve and vessels, as well. We dissected the lymph nodes up to the level of bifurcation of the iliac vessels superiorly and to the femoral canal inferiorly. The paravesical and pararectal spaces were opened with a blunt and sharp dissection. The ureter was visualized along the medial leaf of the pertitoneum at the level of the bifurcation of the common iliac artery.

Transperitoneal para-aortic lymph node dissection (PALN) or sampling (PALS)

The para-aortic lymph node dissection was initiated by incising the peritoneum, which lies over the right common iliac artery, extending the incision cranially along the aorta up to the level of the inferior mesenteric artery. From the para-aortic fields between the level of the inferior meseneteric artery and the level of the renal artery lymph node sampling only was performed. Para-aortic dissection was done after the pelvic lymph node dissection. The nodal package was removed from the operative field through the suprapubic 10-mm trocar.

Laparoscopically assisted vaginal hysterectomy (LAVH)

The anterior peritoneum of the broad ligament was dissected towards the bladder. After the dissection of the bladder from the lower uterine segment, an inspection was carried out on each side to visualize the ureter and uterine artery. In most cases we carried out desiccation of the uterine artery only and did not transect the uterine vessels during the laparoscopic part of the procedure. Dissection of the uterine artery originating from the hypogastric artery was performed in some cases during pelvic lymphadenectomy. Clips or needle sutures were used only in some cases, whereas bipolar and monopolar diathermy or harmonic scalpel were effective in most cases. The remainder of the hysterectomy was performed as follows. The uterus, tubes and ovaries were removed vaginally after the anetrior and posterior cul du sac were opened by sharp and blunt dissection. The cut and suture ligation of the uterine vessels and cardinal and uterosacral ligaments were done as in a conventional hysterectomy.

Statistical analysis

Results from the laparoscopy and open group were analyzed using an unpaired Wilcoxon rank sum test. The distribution of the time to recurrence and survival data were estimated using the Kaplan-Meier analysis [12], and compared using the log-rank test. A p value less than 0.05 was considered as significant.

Results

The results are summarized in Tables 2-5. Laparoscopic procedures were completed successfully in 171 women (96.6%). The electrosurgical procedure of laparoscopy was carried out in 153 patients and the ultrasonic operative technique with a harmonic scalpel and shears was used in one center only (24 women).

The mean age and range of age distribution were similar in the two groups (Table 1). The mean age in the laparoscopic group was 61.8 years, compared to 63.6 years in the open group. The difference in the weight between groups was not substantial: mean 81.0 kg in the laparoscopic group versus 81.8 in the open group. The heaviest woman (130 kg) successfully underwent laparoscopically assisted vaginal hysterectomy, pelvic and paraaortic lymph node dissection. Almost half the patients in the laparoscopic group (49.6%) were obese and weighed more than 81.7 kg/180 lb. There was no significant difference in duration of surgery between both groups (obese, 166.8 min vs non-obese 159.8 min, p = 0.38).

Table 2. — *Outcome and length of hospital day.*

Variable	Laparoscopy	Open	p value
Mean duration of surgery (min)	163.1	115.1	p < 0.0001
Range	(45-360)	(50-180)	
Mean number of lymph nodes recovered	16.8	14.3	NS
Range	(4-36)	(4-22)	
Mean estimated blood loss (ml)	211.2	245.7	NS
Range	(50-1600)	(50-1200)	
Mean hospital stay (days)	3.9	7.3	p < 0.0001
Range	(2-16)	(5-19)	

Table 3. — *Results of histopathological examination.*

Histological type	Laparoscopy	Open
Adenocarcinoma	161 (90.9%)	39 (88.6%)
Adenoacanthoma	5 (2.8%)	1 (2.2%)
Papillary carcinoma	3 (1.7%)	1 (2.2%)
Adenosquamous carcinoma	3 (1.7%)	1 (2.2%)
Clear-cell carcinoma	1 (0.5%)	1 (2.2%)
Carcinosarcoma	4 (2.2%)	1 (2.2%)
Surgical stage (FIGO) (n)		
IA	51 (28.8%)	4 (9.0%)
IB	79 (44.6%)	10 (22.8%)
IC	26 (14.6%)	21 (42.7%)
IIA	1 (0.5%)	2 (4.5%)
IIB	0	1 (2.2%)
IIIA	6 (3.4%)	3 (6.8%)
IIIB	0	0
IIIC	14 (7.9%)	3 (6.8%)
Grading (n)		
1	72 (40.6%)	10 (22.7%)
2	64 (36.1%)	14 (31.8%)
3	41 (23.2%)	20 (45.4%)

Adenocarcinoma was the most common histology found in both groups (Table 3). The difference in the frequency of poorly differentiated lesions (Grade 2,3), (laparoscopy group 59.3% versus open group 77.2%) was statistically insignificant. Of the 145 patients who underwent laparoscopic lymphadenectomy, 31 patients also had para-aortic lymph node dissection or sampling with seven positive results for metastasis. We found malignant changes of lymph nodes in 14 women (7.9%) in the laparoscopic group versus three women (6.8%) in the open group. Positive lymph nodes were always associated with undifferentiated tumor (grade 3). The mean numbers of removed lymph nodes in our groups were comparable (16.8 laparoscopy group vs 14.3 open group, p = 0.28) (Table 2).

The blood loss was minimal and only three units of transfusion were required in the three patients with conversion for uncontrolled intraoperative bleeding. Peri operative blood loss was comparable in both groups (211.2 ml vs 245.7 ml in the laparoscopic and open group, respectively) without any significant consecutive changes in the serum hemoglobin value (Table 2). Although the length of operating time for laparoscopic surgery was significantly longer than the time for the laparotomy procedure (163.1 min vs 115.1 min, p < 0.0001), the laparoscopy patients were discharged from hospital much earlier, at 3.9 days (range 2-16) after the laparoscopic procedure, compared with 7.3 days (range 5-16) after the abdominal procedure (p < 0.0001).

We converted to laparotomy in six patients: one woman had uncontrolled bleeding from a branch of the iliac vein, two obese patients had oxygen hypoventilation during anesthesia and three others sustained an injury to the epigastric artery or had extensive fibrotic adhesions and uncontrolled bleeding. An overview of peri-and postoperative complications is shown in Table 4. The difference

Table 4. — *Complications.*

Variable	Laparoscopy	Open
Surgical complications		
Bladder injury	2	1
Epigastric artery injury	3	0
Obturator nerve injury	1	0
Transfusion	3	1
Conversion	6	0
Postoperative complications		
Fever	5	2
Hematoma	2	1
Cellulitis cuff	1	0
Wound abscess (resuturing)	0	3
Pelvic abscess	1	0
Ureteral fistula	1	0
Trombophlebitis	1	1
Pulmonary artery microembolism	1	0
Total	27	9

in the surgical complications between groups was statistically insignificant (laparoscopy group 8.7% vs open group 4.5%, p = 0.58) .

The number of postoperative complications was similarly distributed in both groups (Table 4). Among the women who underwent laparoscopy, 12 (6.8%) developed significant postoperative complications which included ureteral fistula (n = 1), cuff cellulitis requiring re-admission (n = 1), pelvic hematoma (n = 2), trombophlebitis (n = 1), pulmonary artery microembolism (n = 1), fever (n = 5) and pelvic abscess (n = 1). Seven (15.8%) women who underwent laparotomy had significant postoperative complications which included wound abscess requiring secondary surgery (three patients), fever (two patients), pelvic hematoma (one patient) and trombophlebitis (one patient).

All patients, regardless of surgical approach chosen, were treated postoperatively on the same clinical pathways. Similar long-term outcomes were noted for both groups (Table 5). With a median follow-up of 33.6 months for the laparoscopy group (range 9-69 months) and 45,2 months for the open group (range 9-69 months), there was no significant difference in tumor recurrence between the groups (p = 0.99), (Figure 1). None of the patients who underwent laparoscopic surgery developed tumor recurrence in the laparoscopic trocar sites or in the vaginal cuff; all recurrences in the laparoscopic group occurred as distant metastases. One patient from the open group developed local recurrence in the vaginal cuff. Table 5 and Figure 2 show survival analysis of the studied groups. There was no significant difference in the recurrence-free survival between the two groups

Table 5. — *Survival and recurrence.*

Variable	Laparoscopy	Open
Mean follow-up (months)	33.6 (range 9-69)	45.2 (range 9-69)
Recurrences	11	3
Recurrence-related death	8	2
Non-recurrence related death	1	0
Recurrence free survival	93.7%	93.2%, p = 0.99
Overall survival	94.9%	95.5% p = 0.96

Table 6. — *Review of reports regarding laparoscopic surgery in women with endometrial cancer.*

Reference	No. of patients	Follow-up	MNLN	Conversion (%)	Complications (%)
Current sudy	177	34	16.8	3.4	15.2
Childers *et al.*	59	–	–	13.6	5.1
Gemignani *et al.*	69	18	7.0	4.3	5.8
Eltabbakh *et al.*	86	17	10.8 (2.7*)	5.8	10.5
Magrina *et al.*	56	28	19.4	4.3	23.2
Malur *et al.*	37	16.5	16.1 (9.6*)	0	29.7
Scribner *et al.*	95	–	23.2 (6.8*)	29.1	19.6

MNLN = mean number of lymph nodes
* mean number of para/aortic lymph nodes

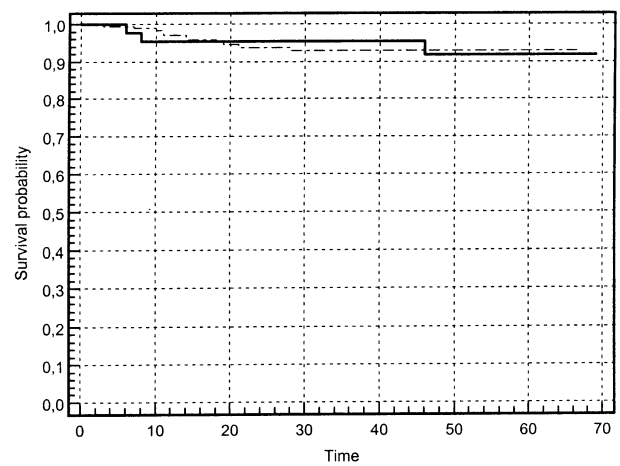

Figure 1. — Kaplan-Meier analysis of the reccurrence-free interval in compared groups. Solid line = open group, dotted line = laparoscopy group. Time interval in months.

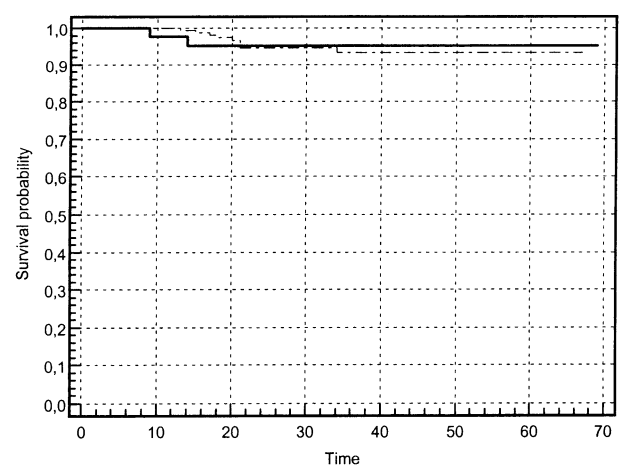

Figure 2. — Kaplan-Meier analysis of survival in compared groups. Solid line = open group, dotted line = laparoscopy group. Time interval in months.

($p = 0.86$). One patient in the laparoscopic group died as a result of a pelvic abscess and cardiac disorder two weeks after surgery.

Discussion

Several studies (Table 6) have evaluated the feasibility of laparoscopic surgery in women with endometrial cancer, but in only three of these studies are survival data reported. In a retrospective study of Gemignani *et al.* [3], 69 patients treated by LAVH had significantly shorter hospitalization and fewer complications, resulting in less overall hospital charges when compared to 251 patients treated by laparotomy. Long-term outcome was similar. In another retrospective study early recurrences and survival rates appear to be similar to those reported for laparotomy patients [6]. The 3-year recurrence rate for 45 patients with surgical stage I endometrial cancer treated by laparoscopy and vaginal or laparoscopy hysterectomy was 2.5%. In a previous study from the Mayo Clinic involving 577 patients with stage I cancer (1971 FIGO staging) treated by laparotomy, there were 52 recurrences, for a recurrence rate of 9% [11]. Malur *et al.* [4] reported in a prospective randomized study ($n = 70$) no significant differences in disease recurrence and long-term survival between the laparoscopy and laparotomy group (97.3% vs 93.3% and 83.9% vs 90.9%, respectively). In seven patients death was related to cardiac or pulmonary disorders and in two patients death was tumor associated. In our prospective multicentric study no significant differences in tumor recurrence and long-term survival were found between the laparoscopy and open group ($p = 0.99$ and $p = 0.86$, respectively).

Childers *et al.* [1] reported on a series of 59 patients considered as candidates for laparoscopically assisted surgical staging for management of their clinical stage I endometrial adenocarcinoma. Several authors concluded that that removal of regional lymph nodes can be done laparoscopically even in obese patients [8, 13, 14, 15]. In our previous study we assessed differences in duration of surgery, number of excised lymph nodes, blood loss, and hospital stay after LASS in two groups of women of different weight with endometrial cancer [14]. A surprising outcome was that the duration of surgery was shorter by six minutes for obese compared to non-obese patients. The results of duration of laparoscopic surgery in the current study were similar (obese group 166.8 min vs the non-obese group 159.8, $p = 0.38$). However, morbid obesity is a limiting factor to laparoscopy because of the inability of these women to tolerate the steep Trendelenburg position. We were unable to finish complete laparoscopic lymph-node dissection in two obese women due to oxygen hypoventilation during anesthesia. On the contrary, laparoscopic surgery in the remaining 86 (97.7%) obese patients was successful .

We found that laparoscopic surgery required on average 50 minutes more to perform than laparotomy. Although the length of the operative time for laparoscopy was significantly longer ($p < 0.0001$) than the time of the open procedure, the laparoscopic group of patients were discharged from hospital significantly earlier ($p < 0.0001$). Similar findings have bee reported by other surgeons [2, 3, 9]. The results of our study showed that laparoscopy and the open procedure were similar in terms of perioperative outcomes in blood loss and the number of nodes recovered. No significant difference in number of removed lymph nodes either by laparoscopy or by laparotomy is reported in the literature, which is accordance with our findings [3, 4, 5]. The total rate of major and moderate complications was higher in the control open group (20.5% vs 15.2%), but the difference was statistically insignificant. In six cases the laparoscopic procedure was converted to laparotomy. In one patient the injury of iliac vein branch was followed by laparotomy and multiple complications were induced (wound abscess, resuturing and pulmonary artery microembolism). In one patient of the laparoscopy group the nervus obturatorius was irritiated during pelvic lymphadenectomy.

Among the 88 patients in the laparoscopic group with higher stage grade and myoinvasion, only PLN was carried out in 63 and both PLN and PALN or PALS were also done in 25. In this high risk group malignant changes of the lymph nodes were confirmed in 13 women (8,9%) and in only one patient in the group of 57 women with low grade and myoinvasion less than 50%. The total number of women with pathologic lymph nodes and positive cytology was 20 (13.8%). We found only one case of positive aortic nodes without involvement of the pelvic nodes which is in accordance with reports of others [8, 16]. This finding supports the idea of Homesley *et al.* [17], that pelvic-node metastasis is a better criterion for aortic lymphadenectomy than myometrial invasion.

Port-site metastasis (PSR) is discussed as a problem of laparoscopic surgery in patients with uterine malignancy [18, 19, 20] but is also associated with open surgery. We did not observe metastasis in any incision in the group of 177 laparoscopically treated patients. Muntz *et al.* [18] reported successfully treated case of port-site recurrence after laparoscopic surgery for endometrial cancer. We suppose that the modified laparoscopic surgical technique can decrease the likelihood of PSR using clips to occlude the Fallopian tubes and minimal manipulation with the uterus.

Our study illustrates that laparoscopically assisted surgical staging of endometrial cancer is safe as an open procedure. The laparoscopic approach may also be considered for the endometrial malignancy which typically occurs in obese, elderly, high-risk women. Laparoscopy affords a surgeon the ability to avoid abdominal incision wound infections in these patients. Our analysis showed no difference with respect to recurrence or survival between the compared laparoscopic and open groups. Survival data from a GOG study, though not a primary outcome measure, may be available for analysis as the trial matures [10]. The women who underwent the laparoscopic procedure had similar nodal counts, short postoperative stays in hospital and acceptable complications. This approach also allows the women to have all the benefits of laparoscopic surgery, such as less pain, less scarring, and shorter recovery time, but with a higher financial cost [2].

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