Gynecol Surg (2006) 3: 245–252
DOI 10.1007/s10397-006-0223-z

REVIEW ARTICLE

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Laparoscopic management of early endometrial cancer: current status

Received: 9 March 2006 / Accepted: 8 June 2006 / Published online: 5 August 2006

Abstract Endometrial cancer is the most common form of gynaecological cancer. Laparotomy has traditionally been the surgical treatment of choice, but the laparoscopic approach is gaining wider acceptance by gynaecologic surgeons, and an abundance of clinical information is currently available on all aspects of this approach. Whether in combination with laparoscopic-assisted vaginal or total laparoscopic hysterectomy, laparoscopic staging, including salpingo-oophorectomy and regional lymph-node dissection, is a major component of the treatment of patients with early endometrial cancer. This review examines the various options to treating endometrial cancer and proposes that laparoscopically assisted surgical staging of endometrial cancer is both a feasible and safe option. Comparative analyses of survival and recurrence rates for patients treated by laparoscopy and laparotomy have shown similar survival results. It remains to be proven if these laparoscopic techniques are associated with greater benefits.

Keywords Endometrial cancer · Laparoscopy · Management

Introduction

Endometrial cancer (EC) is the most common form of gynaecological cancer with an incidence of 48.7 cases per 100,000 women in the USA and 32,00/100,000 in the Czech Republic [1, 2]. Fortunately, most women present with early-stage disease and have an excellent prognosis. For the medically operable candidates with early-stage disease, surgery is the treatment of choice, with laparotomy being the traditional approach. However, the laparoscopic approach is gaining wider acceptance by gynaecologic surgeons. Laparoscopy offers a number of major advantages over laparotomy for patients undergoing surgical treatment for benign gynaecological disorders. Similar advantages have been found in women undergoing laparoscopic radical surgery for uterine malignancies. Consequently, there is a growing body of evidence in the literature favouring laparoscopic techniques over the standard laparotomy approach for patients with endometrial cancer [3]. Since the first report by Childers et al. [4] on laparoscopically assisted surgical staging (LASS) several reports have followed.

The following review will update our present knowledge as to the benefits and results of laparoscopy in the treatment of women with surgically manageable early endometrial cancer.

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Laparoscopic surgical techniques

Whether in combination with laparoscopic assisted vaginal hysterectomy (LAVH) or total laparoscopic hysterectomy (TLH), laparoscopic staging, including lymphadenectomy, is a major component in the treatment of patients with early-stage endometrial cancer. It remains to be proven which of these techniques is associated with the greatest benefits [5]. The standard approach to the surgical management of early-stage endometrial carcinoma has been to perform the primary surgery via an open technique. Peritoneal washing is obtained for cytology, a thorough exploratory laparotomy is performed and an extrafascial hysterectomy and bilateral salpingo-oophorectomy (BSO) are carried out. Pelvic and para-aortic lymph node dissections complete the surgical staging.

Laparoscopic hysterectomy and bilateral salpingo-oophorectomy

The traditional surgical approach to EC has been an abdominal hysterectomy (AH) and adnexectomy, which is the current gold standard of care as documented by

Patridge et al. [6]. This surgical procedure has been performed on 80% of American women with endometrial cancer. Vaginal hysterectomy has long been viewed as an acceptable alternative for some women with endometrial cancer for whom total abdominal hysterectomy might be difficult or risky [7]. However, it may be difficult or impossible to inspect the peritoneal cavity, obtain peritoneal cytology and perform salpingo-oophorectomy and lymph node dissection by means of the vaginal approach. The shortcomings of the pure vaginal approach have recently been documented in a study on laparoscopy [8]. Laparoscopic-assisted vaginal hysterectomy combined with laparoscopic lymphadenectomy in the management of endometrial cancer has been reported in several series totalling over 600 patients [9]. Most of the gynaecologic surgeons performing laparovaginal hysterectomy, particularly LAVH, find this approach to be safer and shorter than a purely laparoscopic approach [10, 11].

Although various techniques of TLH have been reported [12–14], no prospective or randomised studies have reported on its efficiacy in the management of endometrial cancer. In a retrospective study Manolitsas and McCartney [14] compared TLH with open hysterectomy in the management of endometrial carcinoma. The authors developed a safe and efficient technique for performing TLH using a specially designed silicone, transvaginal tube. The low incidence of port-site metastases was reported by Obermaier et al. [12] in a group of 226 women with early-stage endometrial cancer treated by TLH. These authors concluded that TLH management does not seem to worsen the prognosis of patients with EC. A comparison of TLH and abdominal hysterectomy for obese women with endometrial cancer revealed that wound infection occurred in 48.8% patients in the abdominal group and in 2.1% in the TLH group. All other morbidity, as well as patterns of recurrence and survival rates, were similar in both groups. These data justify a prospective randomised trial comparing TLH with abdominal hysterectomy for the treatment of endometrial cancer.

However, other surgical approaches are also able to achieve the standard recommendation for the management of early-stage endometrial cancer. Fagotti et al. [15] suggest that mini-laparotomy is a feasible alternative to the standard treatment in endometrial cancer patients as it offers the patient a cost-effective procedure that avoids many of the potential complications of standard therapy.

Laparoscopic lymph node dissection

Given that lymphadenectomy is accepted as standard management of uterine cancer, there is no reason for not replacing the classical open procedure with the laparoscopic one. Two laparoscopic approaches to lymphadenectomy have been developed: extraperitoneal and transperitoneal. The extraperitoneal approach was the first to be developed, and it may offer some advantages over the transperitoneal approach. It has been experimentally demonstrated that the extraperitoneal approach generates significantly fewer adhesions than the transperitoneal technique, which allows adjuvant radiotherapy to be started sooner with reduced morbidity [16, 17]. On the other hand, the transperitoneal approach is the most extended technique among laparoscopic surgeons and, consequently, this approach allows lymphadenectomy and hysterectomy to be combined with salpingo-oophorectomy.

The area in which the superiority of the laparoscopic tool has been clearly demonstrated is with the prevention of postoperative adhesions. This is a significant advantage in the management of endometrial cancer because patients who are considered to be at risk for recurrence after lymphadenectomy are subjected to radiotherapy. For radiotherapy, the complication of greatest concern is radiation enteritis, a complication that is linked to peritoneal adhesions' limiting the mobility of the intestinal loops and exposing them to excessive irradiation [8].

A retrospective comparative study by Leblanc et al. [19] found six severe complications in 26 patients irradiated following open pelvic dissection, versus one complication for 26 patients irradiated after laparoscopic dissection. Although the laparoscopic approach to lymph node dissection seems to be better than the open approach, laparoscopic dissection could be improved if limited to the sentinel lymph node biopsy. This issue is discussed in the following section.

Laparoscopic pelvic and para-aortic lymphadenectomy

Laparoscopic pelvic lymphadenectomy was first reported in 1991 by Querleu et al. [20] in a series of 39 patients with cervical cancer in. One year later Nezhat et al. [21] described para-aortic lymphadenectomy for the first time.

The number of reports on the use of laparoscopy in lymph node dissection in endometrial cancer remains surprisingly low [4, 8, 10–13, 16–20, 22–24]. Childers et al. [4] reported on a series of 59 patients considered to be candidates for LASS for the management of clinical stage I adenocarcinoma of the endometrium. These authors carried out pelvic and para-aortic lymphadenectomy on 23 patients, but were unable to perform the common iliac and para-aortic lymphadenectomy by laparoscopy in two other patients because of obesity. Several authors have concluded that removal of both the pelvic and para-aortic lymph nodes can be accomplished laparoscopically even in obese patients [10, 13, 25, 26]. However, at present, there is no consensus on indication and extent with regard to lymphadenectomy. Even in the presence of other pelvic pathology, obesity does not seem to limit pelvic lymphadenectomy, thus allowing these women with endometrial cancer to be candidates for the laparoscopic procedure [25]. In addition, primary removal of the aortic nodes is not warranted in most women with endometrial carcinoma and should be restricted to the pelvic lymph nodes [27].

Holub et al. [28] reported the findings of a Czech multicentric study in which transperitoneal lymph node dissection was used. Among the 69 patients in the laparoscopic group with higher stage grading and deep myometrial invasion, pelvic node dissection only was

carried out in 44 patients, and both pelvic and para-aortic lymphadenectomy were also done in 25 of the patients. Malignant changes in the lymph nodes were confirmed in ten of these women (14.5%) and in one woman in the group of patients with low grading and a myometrial myoinvasion of less than 50%. The total number of women with pathologic lymph nodes and positive peritoneal cytology was 14 (15.2%). In such cases as these clinical evaluation alone may lead to understaging of the disease. In a retrospective chart review of 320 patients with early-stage endometrial cancer treated by laparoscopic hysterectomy and lymphadenectomy or total abdominal hysterectomy and lymphadenectomy described by Gemignani et al. [29], no significant difference existed between either method in mean lymph node yield. However, pelvic node metastasis was found to be a better criterion for aortic lymphadenectomy than myometrial invasion. According to the findings of Benedetti-Panici et al. [30], the superficial obturator nodes in the pelvic area were frequently involved. Evaluation of these nodes alone identified 71% of patients with positive nodes. On the other hand, when the external iliac and superficial common iliac nodes were evaluated together with the superficial obturator group, all patients with metastases were identified.

In one randomised prospective clinical trial, 37 patients with EC were treated with a laparoscopic assisted approach and 33 patients with an abdominal approach [11]. In the first group of patients, pelvic lymphadenectomy was performed in 25 women and para-aortic lymphadenectomy in 20. In the second group, pelvic and para-aortic lymphadenectomy were performed in 24 and 20 patients, respectively. No major intra-operative complications occurred in either group, and conversion was not necessary. Postoperative complications were not severe and were distributed similarly in both groups.

According to the recommendation of the FIGO Committee on Gynecologic Oncology [31], indication for aortic lymph node dissection would include suspicious aortic or common iliac nodes, grossly positive adnexa, grade 3 and any grade of tumour showing the outer half of myometrial invasion. Patients with clear cell papillary serous or carcinosarcoma histologic subtypes are also candidates for aortic sampling.

Although mandated through the staging system, lymphadenectomy of the pelvis and para-aortic areas remains controversial, with most individuals using selective node sampling and reserving regional total lymphadenectomy for cases with certain high-risk features.

Laparoscopic uterine sentinel lymph node (SLN) biopsy

The presence of lymph-node metastases has a major impact on the prognosis of women with uterine cancer. One of the cornerstones of gynaecologic cancer surgery is the assessment and removal of the regional lymph nodes. However, the most appropriate and reliable technique for assessing regional pelvic and para- aortic node remains uncertain [32]. The sentinel node is the first lymph node to receive cancer cell metastasis from the primary tumour. Sentinel lymph node dissection and intra-operative lymphatic mapping were, therefore, designed as a less invasive alternative to the routine elective lymph-node dissection in patients with early-early- stage cutaneous melanoma [33]. To date very few reports of cases of sentinel lymph node dissection in endometrial cancer have been published: approximately seven published studies (Table 1) are currently available that provide investigators with information which addresses the various questions concerning the detection of the SLN and its negative predictive value. The answers to these questions will determine the role of laparoscopic SLN biopsy in the management of early endometrial cancer.

Targeting the nodes

The sentinel node is targeted by injecting the marker close to the tumour. Injections in the fundus itself (using laparotomy, laparoscopy or hysteroscopy) have a higher detection rate but a lower predictive value [32, 34, 35]. In patients with endometrial cancer the injections can be made in the cervix as well. The technique as well as the medium used are important variables. Two types of media are used as a marker: blue dyes and radioisotopic colloids. The blue dyes [Lymphazurin or Patent Blue Dye (PBD)] can be used in undiluted or diluted form. The main reason for failure of the SLN PBD technique is likely to be the insufficient quantity of injected blue dye. A dose of at least 2 ml PBD in 7 ml isotonic solution) is required. The site of injection also plays an important role. The depth of the injection should be 2–5 mm (the level of the sub-epithelial network). The observation reported by Dargent et al. [39] in patients with cervical cancer has bee confirmed by others in cases of

Table 1 Literature concerning SLN biopsy in early endometrial cancer

Author (reference)	Number of patients	Injection technique[a]	Surgical technique	SLN detection (%)	Average number of SLN
Burke et al. [32]	18	PBD	Laparotomy	67.0	2.0
Holub et al. [31]	25	PBD	Laparoscopy	84.0	2.0
Pelosi et al. [34]	16	PBD+RGD	Laparoscopy	94.0	1.5
Barranger et al. [35]	17	PBD+RGS	Laparoscopy	94.1	2.6
Lelievre et al. [36]	12	PBD+RGS	Laparoscopy	91.6	3.0
Niikura et al. [37]	28	RGS	Laparotomy	2.0	3.1
Raspagliesi et al. [38]	18	RGS	Hysteroscopy	100.0	3.0

[a]RGS, Radio-guided surgery; BPD, Blue Patent Dye

endometrial cancer [40]: successful SND detection depends on both the sites of injection and the volume of BPD.

Albumin and synthetic colloidal particles are used as radiocolloids. No matter which colloid is used, however, the detection rate is higher and the number of detected nodes is greater with the radioisotopic technique than with the blue dyes, although the false negative rate may also be higher with the former. The combination of blue dye and isotopes is obviously the most productive tool [18].

Locating and removing the nodes

Following the injection of the radioisotopic colloid the targeted nodes can be located transcutaneously by means of scintigraphy. The most common isotope used for linking to the colloid particles is technetium 99. The surgical localisation of the SLN can be undertaken up to 12 h after the injection of the colloid, but with the injection of blue dye, which Marchiole and Dargent [18] recommend in addition to the colloid, localisation must be made within minutes prior the beginning of surgery. The first step of the combined procedure recommended by these authors is a transperitoneal assessment. The laparoscope is introduced as usual. If the injection of BPD has been done correctly, the blue channels are located through the dorsal leaf of the broad ligament. The most frequent location is between the vein and the obturator nerve. In 85% of cases the targeted node lies in the interiliac area.

Assessing the nodes

The technique adopted for assessing the nodes has a major influence on the negative predictive value of the sentinel node biopsy. Although many different methods exist, these can be grouped into four categories: (1) frozen section, (2) unilevel sectioning and standard staining, (3) multilevel sectioning and histo-immunochemical staining and (4) molecular biology [18].

Unilevel sectioning and staining is the most commonly used tool, but true lymph node metastasis – a fortiori, micrometastases (tumour deposits less than 2000 μm in size) and especially submicrometastases (tumour deposits less than 200 μm in size) – can escape the assessment [18]. Multilevel sectioning is the answer to the inadequacy of classical techniques. A good compromise is editing two or three adjacent vignettes at selected 200-μm intervals, a distance that theoretically avoids missing even submicrometastases. Immunohistochemical staining increases the sensitivity of the assessment.

Table 2 Comparison of perioperative laparoscopy and laparotomy data for endometrial cancer[a]

Author (year and reference)	Number of patients	Operating time (min)	Blood loss (ml)	Number of lymph nodes	Hospital days
Laparoscopy					
Magrina et al. (1995; [22])	15	174	272	18.5	3.4
Spirtos et al. (1996; [56])	13	–	–	28.0	2.4
Holub et al. (1998; [58])	11	153	130	–	4.7
Gemignani et al. (1999; [29])	69	214	211	7.0	2.9
Scribner et al. (2001; [57])	19	237	350	34.0	3.7
Eltabbakh et al. (2000; [26])	40	195	318	11.3	2.5
Holub et al. (2002; [31])	177	163	211	16.8	3.9
Langebrekke et al. (2002; [46])	27	143	–	6.8	4.3
Eltabbakh et al. (2001; [8])	100	–	200	13.5	2.0
Litta et al. (2003; [24])	29	186	125	14.2	2.5
Occelli et al. (2003; [16])	69	164	–	15.8	4.0
Zapico et al. (2003; [48])	38	165	–	15.1	5.0
Laparotomy					
Magrina et al. (1995; [22])	15	142	502	23.5	6.6
Spirtos et al. (1996; [56])	17	–	–	29.0	6.4
Holub et al. (1998; [58])	26	127	150	–	7.7
Gemignani et al. (1999; [29])	251	144	209	6.0	6.7
Scribner et al. (2001; [57])	17	157	344	30.0	5.2
Eltabbakh et al. (2000; [26])	86	–	250	10.5	5.0
Holub et al. (2002; [31])	44	115	246	14.3	7.3
Langebrekke et al. (2002; [46])	24	87	–	5.6	6.2
Eltabbakh et al. (2001; [8])	40	138	303	5.3	6.5
Litta et al. (2003; [24])	30	152	153	13.4	6.4
Occeli et al. (2003; [16])	58	123	–	11.0	9.0
Zapico et al. (2003; [48])	37	130	–	13.5	7.0

[a]The basic data were extracted from paper published by Magrina [3] with this author's permission

Pros and cons: systematic versus sentinel lymph node dissection

The aim of the sentinel node dissection is to avoid systematic lymphadenectomy in the lymph node-negative patient. Therefore, the SLN biopsy must meet two requirements. The first is surgical: the SLN biopsy must be less deleterious than the systematic dissection. The second is oncologic: the negative predictive value of the SLN assessment must be 100%. The SLN biopsy is obviously more rapid and simpler than the systematic dissection, and the detection rate is between 90 and 100%. The negative predictive value of the SLN assessment in most of the series reported in the literature is close to 100%. On the other hand, systematic lymph node dissection, which, if done by laparoscope, is no more dangerous than the simple SLN biopsy, which is part of surgery for early-stage endometrial cancer.

Laparoscopy versus laparotomy

Perioperative data

Initial data reported by Magrina et al. [22] in comparing laparoscopy with laparotomy for the surgical treatment of patients with endometrial cancer revealed a number of advantages for the laparoscopic group. Additional studies have duplicated these preliminary results. A comparison of the perioperative data between laparoscopy and laparotomy for endometrial cancer is shown in Table 2. There is a general agreement that, relative to patients undergoing a laparotomy, laparoscopy patients have slightly longer operating times, reduced mean blood loss and hospitalisation and a similar, or larger, number of retrieved lymph nodes [3]. Of interest, consistently similar findings were also observed for both treatment groups when only patients with body mass indices (BMIs) between 28 and 60 were included [26]. Operating times, to no surprise, are in correlation with the surgeon´s experience with this procedure. Decreasing operating times and an increased number of retrieved lymph nodes have been reported to be correlated with the increasing experience of the surgeon. The learning curve is believed to level off after 25–30 laparoscopic staging procedures for endometrial cancer [41].

Conversion to laparotomy and postoperative complications

Laparoscopic conversion rates to laparotomy range from 0 to 12.4% when all causes for conversion – severe adhesions, heavy bleeding, difficult exposure, obesity and intolerance to increased intra-abdominal pressure – are taken into consideration [3, 18, 26, 29]. Of the TLH procedures 4–10.6% were converted to open hysterectomy [12, 14]. However, conversion rates due to intraoperative complications are lower (0–5.3%) [22–24, 29, 42, 43]. When the rate of postoperative complications are compared between laparotomy and laparoscopy techniques, similar or lower rates are noted for laparoscopy patients. The incidence of reported complications range from 0 to 17.5% [23, 24].

Table 3 Follow-up and disease-free survival (DFS) for laparoscopy-treated women with endometrial cancer[a]

Author (reference)	*n*	Mean follow up (months)	DFS (%)
Magrina et al. [43]	45	76.0	94.7
Lim et al. [44]	40	29.5	92.6
Malur et al. [18]	37	16.5	97.3
Holub et al. [42]	177	33.6	93.7
Eltabbakh et al. [45]	100	27.0	93.0
Langebrekke et al. [46]	27	12.0	100.0
Liauw et al. [47]	30	15.5	100.0
Kuoppala et al. [23]	40	34.0	100.0
Zapico et al. [48]	38	53.2	81.6
Tozzi et al. [49]	63	44.0	87.4
Total and range	597	12–76	81.6–100.0

[a]The basic data were extracted from paper published by Magrina [3] with this author's permission

Survival and recurrence

Several studies have evaluated the feasibility of laparoscopic surgery in women with endometrial cancer, but survival data are reported in only ten of these [18, 24, 42–49] (Table 3). The disease-free survival (DFS) rate for a total of 597 patients followed up for a mean of 12–76 months ranged from 81.6–100%. These values are not significantly different statistically from from laparotomy survival and recurrence rates (Tables 4 and 5). In a prospective randomised study (n=70) Malur et al. [18] found no significant differences in disease recurrence and long-term survival between the laparoscopy and laparotomy groups (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 it was tumour-

Table 4 Comparison of DFS between laparoscopy- and laparotomy-treated women with endometrial cancer[a]

Author (reference)	DFS (%)			
	n	Laparoscopy	*n*	Laparotomy
Malur et al. [18]	37	97.3	37	93.3
Holub et al. [42]	177	93.7	44	93.2
Eltabbakh et al. [45]	100	90.0	86	92.0
Langebrekke at al. [46]	27	100.0	24	95.9
Kuopalla et al. [23]	40	100.0	40	95.0
Zapico et al. [48]	38	81.6	37	81.1
Tozzi et al. [49]	63	87.4	59	91.6

[a]The basic data were extracted from paper published by Magrina [3] with this author's permission

Table 5 Comparison of recurrence after treatment for endometrial cancer by laparoscopy and laparotomy[a]

Authors (reference)	Recurrence (%)			
	n	Laparoscopy	*n*	Laparotomy
Eltabbakh et al. [45]	100	7.0	86	10.5
Holub et al. [42]	177	6.2	44	6.8
Langebrekke et al. [46]	26	0	22	4.1
Kuoppala et al. [23]	40	2.5	40	2.5
Zapico et al. [48]	38	5.2	37	5.4

[a]The basic data were extracted from paper published by Magrina [3] with this author's permission

associated. In the Czech prospective multicentric study [42] no significant differences in tumour recurrence or long-term survival were found between laparoscopy and open surgery (p=0.99 and p=0.86, respectively).

Port-site metastases or recurrence

The finding of tumour growth at the site of a previous laparoscopic trocar placement, commonly known as a port-site metastases (PSM), is one of the most feared complications of a laparoscopic procedure in gynaecologic cancer treatment. Port-site recurrence (PSR) has been reported in association with endometrial cancers managed laparoscopically; however, the mechanism of development is not fully understood [50, 51]. In most cases these recurrences occur in association with advanced stage disease [41]. No patient in the reviewed series reported here experienced a trocar site recurrence (Tables 3 and 5). Muntz et al. [52] reported successfully treating a case of PSM after laparoscopic surgery for uterine cancer. Wilkinson et al. [53] concluded that laparoscopic PSR can be reproduced using the transplantable VX-2 rabbit carcinoma model. In the VX-2 model, trocar recurrence was the result of direct contamination via surgical instrumentation of viable cancer cells. The effect of the pneumoperitoneum or intra-peritoneal cytological spillage (indirect contamination) did not have any effect on trocar recurrence. However, the reported outcomes of studies on the impact of the pneumoperitoneum on tumour growth are controversial. Watson et al. [54] suggests that the excision of port-site wounds following laparoscopy for cancer in an experimental model does not prevent the subsequent development of port-site tumours. Most reports refer to the recurrence within the first 2 years. Two PSR reported by Sanjuan et al. [55] were discovered 39 and 48 months after first diagnosis, which is not frequent. The delay of these recurrences highlights the necessity of a randomised trial with longer follow-up.

Conclusion

This review illustrates that laparoscopic management of endometrial cancer is safe as an open procedure and that the survival and recurrence rates by this procedure are comparable to those of laparotomy. The laparoscopic approach may also be considered for endometrial malignancy which typically occur in obese, elderly, high-risk women. Laparoscopy affords a surgeon the ability to avoid abdominal incision wound infection in these patients. The laparoscopic approach also allows the women to have all of the benefits of minimally invasive surgery, such as less pain, less scaring, and a shorter recovery time. However, the relative difficulty for surgeons to develop advanced laparoscopic surgical skills is a limitation to the widespread use of laparoscopy.

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