

Laparoscopic systemic restaging surgery for women with unexpected uterine malignancy

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Objective

We investigated the feasibility of laparoscopic restaging surgery in patients with unexpected uterine cancer.

Methods

This retrospective study included eight patients who underwent laparoscopic restaging surgery for Iran University uterine cancer after a prior hysterectomy or myomectomy.

Results

The median age of the patients and their body mass index were 55 years (range, 44-78) and 23.8 kg/m² (range, 20.75-31.89), respectively. The median interval between the prior hysterectomy and the restaging surgery was 21 days (range, 10-35). The median operating time and time for the return of bowel activity were 325 minutes (range, 200-475) and 35 hours (range, 18-50), respectively. The median numbers of harvested pelvic and para-aortic lymph nodes were 17.5 (range, 14-29) and 20.5 (range, 7-36), respectively. In seven of the eight patients, uterine extraction was performed with vaginal or electronic morcellation. The final International Federation of Gynecology and Obstetrics stage was IA in all patients. Intraoperative and postoperative complications did not occur in any of the patients, except for the need for transfusion. Patient 4 had synchronous primary cancer (stage IA) of the endometrium and left ovary. Two of the eight patients with clear cell carcinoma received chemotherapy, and none received radiotherapy. All patients survived without disease recurrence.

Conclusion

Restaging surgery might be necessary for highly selective patients with unexpected uterine malignancies. This would be an alternative surgical modality for complete staging and planning tailored adjuvant treatments. However, lymphadenectomy might not be performed in patients with early uterine cancer.

Keywords: Laparoscopy; Cancer staging; Uterine cancer

Introduction

Endometrial cancer is one of the most common gynecological malignancies in Western countries, with an increasing incidence in South Korea [1,2]. In 1988, the International Federation of Gynecology and Obstetrics (FIGO) changed the endometrial cancer staging system from a clinical to a surgical system, including pelvic and para-aortic lymphadenectomy [3]. Since then, postoperative histopathological results have been considered to be the most important factor in determining the prognosis of endometrial cancer [4]. In the recently revised FIGO staging system, pelvic lymph node (LN)

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and para-aortic LN involvement, which was previously categorized as stage IIIC, were separated into stages IIIC1 and IIIC2, respectively. These results demonstrate the different prognoses of these two conditions [5].

The procedure for endometrial cancer staging surgery includes total hysterectomy with bilateral salpingo-oophorectomy (BSO), pelvic and para-aortic sampling or systematic lymphadenectomy, and peritoneal washing cytology [6]. However, there is no consensus regarding the standard treatment for patients with unexpected uterine malignancy that was initially considered a benign gynecological condition but was diagnosed as endometrial cancer after surgery. The incidence rate of unexpected endometrial cancer reported by previous studies was 0.25-0.4% [7,8]. Although most cases are FIGO stage I cases, treatment varies from observation to staging surgery or radiotherapy. Other uterine malignancies, such as endometrial stromal sarcoma and undifferentiated endometrial sarcoma, are also rare, with incidence rates of 1.68% and 0.48%, respectively [9]. The standard treatments for uterine sarcoma are total hysterectomy and BSO [10]. However, no studies have been conducted on the standard management of unexpected uterine sarcomas.

Surgical staging is the gold standard for treating uterine malignancies. However, the reason for the various approaches to the treatment of unexpected uterine cancer is that it has not been proven whether restaging surgery, including para-aortic lymphadenectomy, should be performed in patients with suspected low-risk, early-stage disease. In addition, no clinical studies have been conducted on laparoscopic restaging surgery.

The current study aimed to examine the feasibility of laparoscopic restaging surgery in women with unexpected uterine malignancy who underwent myomectomy or hysterectomy for an initially diagnosed benign gynecological condition.

Materials and methods

We retrospectively studied patients with unexpected uterine malignancies who underwent laparoscopic restaging surgery after myomectomy or hysterectomy for benign gynecological conditions between January 2008 and August 2014. Eight patients were included in this study. For three of the eight patients who underwent hysterectomy at other institutions,

a histological review was performed by a pathologist at our hospital before the restaging surgery. We performed a radiological imaging study using computed tomography (CT), magnetic resonance imaging (MRI), or 2-deoxy-2-(¹⁸F) fluoro-D-glucose positron emission tomography (PET)-CT before restaging surgery to evaluate metastasis to other organs. Clinical data obtained from the medical records, including age, parity, menopausal status, body mass index (BMI), indication for prior surgery, type of prior surgery, and final histopathology results (cell type, grade, depth of myometrial invasion, and lymphovascular space invasion), were investigated.

For the restaging surgery, we evaluated the interval between the prior surgery and the restaging surgery, operating time, change in the hemoglobin level, time of gas out, hospital stay, and intraoperative and postoperative complications. We separately classified blood transfusions based on the operative complications. For the laparoscopic restaging surgery, we analyzed data including metastasis to other organs, the number of harvested pelvic and para-aortic LNs, the number of positive LNs, and cytology. The use of adjuvant treatment, last day of treatment and follow-up, day of recurrence, and day of death were investigated to analyze survival rates. The current study was approved by the Institutional Review Board of the Hanyang University Medical Center.

All patients underwent laparoscopic restaging surgery under general anesthesia. Four trocars were used, and the surgery was performed by experts (JS Choi, J Bae, and WM Lee). Peritoneal washing cytology was performed for all patients before full systemic retroperitoneal lymphadenectomy. During the restaging surgery, the uterus, ovary, and fallopian tube were removed if they remained intact after the previous surgery. Laparoscopic pelvic lymphadenectomy was started from the deep circumflex iliac vein and continued to the point where the ureter crossed the common iliac artery. Laparoscopic para-aortic lymphadenectomy was performed starting from that point and extending to the level of the left renal vein. Visual evaluation of the peritoneal, diaphragmatic, and serosal surfaces was performed to identify extrauterine disease, and a biopsy was performed for any suspicious lesions. Infracolic omentectomy was performed in cases of tumors involving clear cell carcinoma or synchronous ovarian cancer, and uterine extraction with morcellation was performed. The resected lymphatic tissues and organs were placed into an Endobag™ (SEJONG medical, Paju-Korea) and pulled out from the abdominal cavity through the 12-mm

port site. After all the procedures were completed, the skin incisions were sutured, and a drainage tube was placed after confirming hemostasis.

Results

The median age of the eight patients was 55 years (range, 44-78), and the median BMI was 23.8 kg/m² (range, 20.8-31.9). Uterine extraction was performed with vaginal or electronic morcellation in seven out of eight patients. The prior surgical results for all the patients are summarized in Table 1. The median operating time was 325 minutes (range, 200-475), and the median interval between the prior hysterectomy and the restaging surgery was 21 days (range, 10-35) (Table 2). Five patients underwent blood transfusions. Four patients underwent transfusion due to intraoperative hemorrhage, and patient 2 underwent transfusion after surgery due to postoperative hemoglobin change (1.2 g/dL) (Table 2). The median number of harvested LNs was 17.5 (range, 14-29) for pelvic LNs and 20.5 (range, 7-36) for para-aortic LNs (Table 3). Only one patient developed a lymphocele in the left para-aortic area, which resolved 1 year after surgery. Other patients did not experience lymphadenectomy-related complications, including lymphedema, lymphocysts, or chylous ascites. Two of the eight patients received chemotherapy, and none received radiotherapy. Patients who underwent restaging surgery survived without any recurrence at the last follow-up (Table 4).

Patient 1, aged 78 years, presented to our hospital with a high urinary frequency. A large myoma measuring 11 cm in diameter was observed on examination, and laparoscopically assisted vaginal hysterectomy (LAVH) and BSO with vaginal uterine morcellation were performed. The histopathological results revealed that the clear cell carcinoma was confined to the endometrium, and restaging surgery was performed. Although the final FIGO stage was determined to be IA based on the restaging surgery, the patient underwent adjuvant chemotherapy because of the high risk associated with clear cell carcinoma.

Patient 2, aged 58 years, was referred to our hospital due to endometrial stromal sarcoma. The patient presented with vaginal bleeding and underwent subtotal hysterectomy with electronic morcellation at another institution. A slide review revealed invasion in less than half of the myometrium. A

Table 1. Clinical characteristics of patients with unexpected uterine malignancy

Patient	Menopause	Signs/symptoms	Institute performed prior hysterectomy	Endometrial biopsy	Operative procedure	Histopathologic report	Grade	Morcellation
1	Yes	Frequency	Our hospital	No	LAVH BSO	Clear cell	3	Yes
2	Yes	Vaginal bleeding	Other	No	Subtotal hysterectomy	ESS	1	Yes
3	No	Vaginal bleeding	Our hospital	Yes	LAVH	Endometroid	2	No
4	No	Vaginal discharge	Our hospital	No	LAVH LSO	Endometroid	1	Yes
5	No	Lower abdominal pain	Our hospital	No	Laparoscopic myomectomy	ESS	1	Yes
6	Yes	Vaginal bleeding	Other	No	TLH LSO	Clear cell	3	Yes
7	No	Vaginal bleeding	Other	No	LAVH	Endometroid	2	Yes
8	No	Intermenstrual bleeding	Our hospital	No	TLH	Endometroid	1	Yes

LAVH, laparoscopically assisted vaginal hysterectomy; BSO, bilateral salpingo-oophorectomy; ESS, endometrial stromal sarcoma; LSO, left salpingo-oophorectomy; TLH, total laparoscopic hysterectomy.

Table 2. The outcomes of restaging surgery

Patient	Days between hysterectomy and restaging surgery (days)	Operating time (minutes)	Hb change (g/dL)	Gas out (hours)	Hospital stay (days)	Intraoperative complications	Postoperative complications	Transfusion (pints)
1	35	365	0.2	50	11	No	No	2
2	10	385	1.2	27	21	No	No	2
3	19	370	0.9	32	9	No	No	2
4	24	240	0.9	36	9	No	No	2
5	21	285	1.1	25	16	No	No	0
6	28	475	1.0	42	14	No	No	2
7	12	200	0.3	35	7	No	No	0
8	21	225	1.4	18	9	No	No	0

Hb, hemoglobin.

Table 3. The histopathologic results of restaging surgery

Patient	Ovary	Number of harvested pelvic LN	Pelvic LN	Number of harvested para-aortic LN	Para-aortic LN	Cytology	FIGO stage (before restaging)	Final stage
1	No malignant cell	17	No malignant cell	9	No malignant cell	No malignant cell	IA	IA
2	No malignant cell	17	No malignant cell	9	No malignant cell	No malignant cell	IA	IA
3	No malignant cell	29	No malignant cell	20	No malignant cell	No malignant cell	IA	IA
4 ^{a)}	Endometroid adenocarcinoma	24	No malignant cell	7	No malignant cell	No malignant cell	IA	IA
5	No malignant cell	28	No malignant cell	36	No malignant cell	No malignant cell	IA	IA
6	No malignant cell	20	No malignant cell	25	No malignant cell	No malignant cell	IA	IA
7	No malignant cell	14	No malignant cell	28	No malignant cell	Adenocarcinoma	IA	IA
8	No malignant cell	17	No malignant cell	21	No malignant cell	Adenocarcinoma	IA	IA

LN, lymph node; FIGO, the International Federation of Gynecology And Obstetrics.

^{a)} The final histopathologic reports of patient 4 showed synchronous primary cancer of endometrium and left ovary. Because, endometrial tumor is confined within endometrium and no lymphovascular invasion and the ovarian cancer also showed unilateral and located within parenchyma.

Table 4. Adjuvant treatment and survival outcomes after restaging surgery

Patient	Adjuvant treatment	Cycles of adjuvant treatment	Recurrence	Survival	Overall survival (months)
1	Chemotherapy	4	No	Alive	84
2	Observation	0	No	Alive	63
3	Observation	0	No	Alive	59
4	Observation	0	No	Alive	44
5	Observation	0	No	Alive	16
6	Chemotherapy	4	No	Alive	9
7	Observation	0	No	Alive	8
8	Observation	0	No	Alive	8

preoperative PET-CT scan revealed hypermetabolic lesions in both external iliac areas. The final FIGO stage was IA, without metastasis to the pelvic or para-aortic LNs.

Patient 3, aged 55 years, presented to our hospital with a 3-month history of vaginal bleeding. As the endometrial biopsy revealed atypical glandular proliferation, the patient underwent LAVH. However, the patient underwent restaging surgery because with a diagnosis of endometrioid adenocarcinoma was established based on the final biopsy results. The patient was finally diagnosed with FIGO stage IA, confined to the endometrium.

Patient 4, a 48-year-old premenopausal woman, was admitted to our hospital with lower abdominal pain. Multiple myomas measuring 5-6 cm in diameter were observed, and an LAVH with vaginal uterine morcellation was performed. A 2-cm cystic mass was observed in the left ovary during surgery, and a left salpingo-oophorectomy was also performed. Biopsy revealed endometrioid adenocarcinoma in the endometrium and left ovary. However, because the endometrial tumor was confined within the endometrium, there was no lymphovascular invasion, the ovarian cancer was unilateral and located within the parenchyma, and the diagnosis was synchronous primary cancer of the endometrium and left ovary. Pelvic CT and MRI were performed before the restaging surgery, and there was no evidence of metastasis to other organs. The final histopathological results revealed no evidence of metastasis to other organs, and the final FIGO stage was grade 1 endometrial cancer IA confined to the endometrium and grade 1 ovarian cancer IA. The patient did not receive adjuvant treatment.

Patient 5, aged 46 years, underwent laparoscopic myomectomy at our hospital for lower abdominal pain. At that time, electronic morcellation was used to remove the myoma. Histopathological examination revealed an endometrial stromal sarcoma. Preoperative PET-CT and pelvic CT revealed no evidence of metastasis to other organs. However, suspected metastatic lesions were observed in the bladder peritoneum and omentum during the restaging surgery. Partial peritonectomy and infracolic omentectomy were performed; however, malignant cells were not found in the final histopathological report. The final FIGO stage was IA.

Patient 6, aged 55 years, had a history of vaginal bleeding and underwent total laparoscopic hysterectomy (TLH) and right salpingo-oophorectomy with vaginal uterine morcellation at another institution. The patient was diagnosed with

clear cell carcinoma. Slide review revealed invasion of less than half of the myometrium and lymphovascular invasion. PET-CT revealed increased uptake in the left pelvic cavity, and the serum level of cancer antigen 125 was elevated to 202.8 U/mL. Complete obstruction of the right ureter was discovered during the restaging surgery and was considered a complication of the prior surgery. Right ureteral reimplantation and double-J catheter insertion were performed. Although the final FIGO stage was IA, adjuvant chemotherapy was administered because of clear cell carcinoma.

Patient 7, a 55-year-old premenopausal woman, complained of vaginal bleeding and was transferred to our hospital. The patient was diagnosed with endometrioid adenocarcinoma after undergoing LAVH with vaginal uterine morcellation at another institution. Slide review revealed grade 2 disease and invasion of less than half of the myometrium. Although malignant cells were observed on cytology, the final FIGO stage was determined to be IA as a result of the restaging surgery.

Patient 8, a 44-year-old premenopausal woman, visited our hospital for evaluation of intermenstrual bleeding. Transvaginal ultrasonography revealed a 3-cm submucosal myoma and a 6-cm intramural myoma. The patient underwent TLH with vaginal uterine morcellation. Based on the biopsy results, endometrioid adenocarcinoma with the invasion of less than half of the myometrium was diagnosed, and the patient underwent restaging surgery. Although the cytology results were positive, the final FIGO stage was determined to be IA.

Discussion

According to the National Comprehensive Cancer Network (NCCN) guidelines, restaging surgery is recommended for patients with unexpected endometrial cancer classified as FIGO stage IA disease that presents as myometrial invasion when abnormal findings are observed in an imaging study [11]. The NCCN guidelines recommend that when the imaging study is negative, either observation or radiotherapy can be performed. However, these guidelines do not provide definite recommendations. In another study, four of nine patients diagnosed with unexpected endometrial cancer underwent restaging surgery [8]. Two of these patients whose disease was upstaged to IIIC showed tumor recurrence. The five other patients did not undergo restaging surgery, and one

patient died because of disease progression. Four patients received adjuvant radiotherapy. These results highlight the lack of guidelines for patients with unexpected endometrial cancer because various treatments have failed to demonstrate profound therapeutic benefits.

Although restaging surgery remains controversial, the results of several studies on the clinical implications of pelvic and para-aortic lymphadenectomy suggest that this procedure should be performed in patients with unexpected uterine malignancies. There are several reasons for this finding. First, the extent of the disease can be precisely assessed through surgical staging, and the patient's prognosis can be predicted based on the results. The final histopathological results enable tailored therapy for each patient and avoid unnecessary adjuvant treatment. An Italian group reported that lymphadenectomy did not affect survival [12]. However, the results of the Italian group demonstrated that radiotherapy was performed significantly more often in patients who did not undergo lymphadenectomy than in those who underwent lymphadenectomy. Another study reported that as the FIGO stage increased, patients treated without lymphadenectomy were more likely to receive whole-pelvic lymphadenectomy than those treated without lymphadenectomy [13]. In contrast, among the patients who underwent lymphadenectomy, a higher percentage of patients underwent vaginal brachytherapy than those who underwent whole-pelvic radiotherapy. These outcomes indicate that unnecessary adjuvant radiotherapy may be performed when the disease extent is not accurately determined. Based on the restaging results, focused vaginal brachytherapy can be performed to avoid whole-pelvic radiation. In the current study, increased uptake in the pelvic area was observed in the PET-CT performed before the restaging surgery in two patients. However, after surgery, the disease was confirmed as FIGO stage IA, and additional treatment was not necessary. Without restaging surgery, they would have had a high chance of receiving adjuvant radiotherapy based on their PET-CT scans.

The procedure must include lymphadenectomy, washing cytology, and inspection of the peritoneal cavity, followed by multiple biopsies, particularly if electronic morcellation is performed prior to surgery to determine the extent of the disease. A recent meta-analysis reported that uterine morcellation increases the risk of intra-abdominal recurrence of unexpected uterine malignancy [14]. Another study suggested that immediate surgical re-exploration is mandatory because

morcellation alters the natural history of the disease [15]. In the current study, uterine morcellation was performed in seven of the eight patients. Fortunately, no patient was up-staged because of peritoneal seeding of fragments. However, morcellation may be the reason two patients had positive cytology results, although they had stage IA disease.

Second, pelvic and para-aortic lymphadenectomy has a therapeutic role, which increases the possibility of survival gain. In another study, systematic lymphadenectomy increased the 5-year overall survival rate among patients with early-stage endometrial cancer (91.6% vs. 70.6%, $P=0.0095$) [16,17]. Patients who underwent systematic pelvic and para-aortic lymphadenectomy had a significantly higher overall survival rate than those who underwent pelvic lymphadenectomy alone.

Third, the possibility of undertreatment can be prevented by locating and removing isolated para-aortic LNs, which manifest only as para-aortic LN involvement without pelvic LN involvement. The incidence of isolated para-aortic LN involvement has been reported to be 7-16% [18,19]. In this study, we performed para-aortic lymphadenectomy at the level of the left renal vein because LN metastasis is most prevalent in the para-aortic LNs and the superior area of the inferior mesenteric artery [19].

Fourth, although imaging studies are most often used for evaluating metastasis, these modalities cannot detect all metastatic lesions. PET-CT is the most useful diagnostic tool [20]. The overall sensitivity, specificity, and accuracy of PET-CT have been reported to be 55.3%, 99.6%, and 97.8%, respectively [21,22]. However, the ability of PET-CT to detect lesions in LNs is largely associated with lesion size, and detecting lesions smaller than 5 mm is challenging [23]. The CT and MRI detection of metastases is based on their size. The most acceptable criterion is a lesion size of 8-10 mm, with a sensitivity and specificity of 27-66% and 73-99%, respectively [24].

However, despite the importance of lymphadenectomy, recent studies have reported that it must be minimized in patients with early endometrial cancer. A Cochrane review of lymphadenectomy for managing endometrial cancer revealed that there was no significant benefit in survival gain between the lymphadenectomy and no lymphadenectomy groups in the early stage. In addition, adverse effects of lymphadenectomy were found between the two groups such as a higher risk of surgery-related morbidity, lymphedema, and lympho-

cyst [25]. Other studies have shown no differences in the overall survival between the two groups [26].

It is debatable whether restaging surgery is necessary for patients with unexpected uterine malignancy, and whether the laparoscopic approach would be the best option for such patients. However, laparoscopic restaging surgery should be performed by experienced surgeons to prevent postoperative complications. Additionally, lymphadenectomy increases the risk for higher risk of surgery-related morbidity, lymphedema, and lymphocysts [27].

In conclusion, restaging surgery may be performed in highly selected patients with unexpected uterine malignancy. However, this procedure might be omitted in patients suspected of early uterine cancer.

Conflict of interest

We have no conflicts of interest.

Ethical approval

The study was approved by Institutional Review Board of the Hanyang University Medical Center (HYUH 2014-12-024).

Patient consent

Informed consent was waived owing to the retrospective nature of the study.

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