

A cohort study evaluating paraaortic lymphadenectomy in endometrial cancer

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Abstract. The current study sought to assess the role of paraaortic lymphadenectomy (LNE) in females with endometrial cancer. A retrospective analysis of patients diagnosed with endometrial cancer of stage IA to II preoperatively, between 2009 and 2011 was conducted. Patients were included who had suffered from endometrial cancer without preoperative adjuvant therapy and who underwent hysterectomy plus systematic pelvic LNE and paraaortic LNE by laparoscopy or laparotomy. A total of 54 patients who underwent surgery for preoperative endometrial cancer were selected. All patients underwent LNE. The incidences of pelvic and paraaortic lymph node metastases were 11.1% (6/54) and 7.4% (4/54), with a total positive lymph node rate of 14.8% (8/54). In addition, among the 8 positive cases, 5 patients underwent laparotomy and 3 underwent laparoscopy; 3 cases were classified as stage I and 5 as stage II preoperatively. Of these, 7 patients were identified with pathology-related risk factors, including low differentiation or clear cell adenocarcinoma postoperatively. Discordance of pathological differentiation between the pre- and postoperative stages reached 57.1% (4/7). The results revealed the high occurrence of positive lymph nodes in endometrial cancer which demonstrate the importance of systematic LNE. Additionally, no severe complications were caused by LNE besides lymph cysts. In summary, it is necessary to perform LNE, particularly the removal of the paraaortic lymph node, in patients with endometrial cancers in order to improve postoperative therapy. Laparoscopy has similar surgical effects as laparotomy, but has a number of advantages.

Introduction

Endometrial cancer is the most common gynecological malignancy in developed countries (1). Standard management includes the surgical removal of the uterus, Fallopian tubes and ovaries (2). Metastasis to the pelvic lymph nodes (PLN) or paraaortic lymph nodes (PAN) is one of the most significant factors associated with the determination of the clinical stage and prognosis of endometrial cancer. The reported frequency of PLN and/or PAN metastasis ranges from 5 to 20% (3-6) and patients with retroperitoneal lymph node metastasis are classified as stage IIIC. Thus, it is important to evaluate the presence or absence of PAN metastasis when surgically staging this disease and predicting its prognosis.

However, in previous years, the issue of the therapeutic effect of lymphadenectomy (LNE) in endometrial cancer has been debated. LNE and PAN dissection are not routine operative procedures at present. Certain authors view it as a curative approach in retrospective studies, while others consider the value of LNE as a purely diagnostic measure and others doubt the therapeutic significance of this surgery (7-9). However, there is an agreement that pelvic and/or PAN involvement worsens the prognosis of endometrial carcinoma significantly (10-13). Knowledge of lymph node involvement or other extrauterine spread generally affects postoperative treatment in the form of irradiation or chemotherapy. It appears unreasonable that systematic LNE does not include regional lymph node dissection, involving either the biopsy of enlarged nodes only, selective nodal sampling, or complete LNE.

To date, there are no studies on LNE in patients with endometrial cancer from China, particularly the paraaortic LNE by laparoscopy. Our hospital is one of the first centers in China to initiate the use of laparoscopy in the gynecological field, particularly in gynecological tumors. The patients with endometrial cancer who underwent hysterectomy and systematic LNE plus paraaortic LNE by laparoscopy or laparotomy were retrospectively analyzed. The diagnostic significance of paraaortic LNE for patients with or without intermediate- or high-risk endometrial cancer was identified, based on the hypothesis that the PAN area is susceptible to recurrence if omitted from surgery and metastasis to the PAN area influences adjuvant treatment. It is not possible to accurately stage endometrial malignancies if the PAN area is neglected, and this is likely to aggravate radiotherapy. Therefore, this study

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Abbreviations: LNE, lymphadenectomy; PLN, pelvic lymph nodes; PAN, paraaortic lymph nodes

Key words: lymphadenectomy, endometrial cancer, paraaortic

Table I. Total LN and positive LN counts.

	Number of cases	Total LN count, average (%)		Positive LN count	
		Pelvic	Para-aortic	Pelvic	Para-aortic
Stage					
IA	8 (T) + 24 (L)	644 (20.1)	129 (4.0)		
IB	6 (T) + 4 (L)	228 (22.8)	43 (4.3)		
II	2 (T) + 1 (L)	64 (21.3)	11 (3.7)		
IIIA	1 (L)	17 (17)	2 (2)		
IIIC	5 (T) + 3 (L)	159 (19.8)	22 (2.8)		
Surgery pathway					
Laparotomy	21	453 (21.6)	72 (3.4)	7	5
Laparoscopy	33	659 (20.0)	135 (4.1)	9	2
Total				16	7

LN, lymph node; T, laparotomy; L, laparoscopy.

intends to analyze the positive rate of PAN metastasis in patients with endometrial cancer in our hospital and compare the difference between laparoscopy and laparotomy. The aim of the current study was to investigate the importance of para-aortic LNE in endometrial cancer and the advantage of laparoscopy over laparotomy.

Patients and methods

A total of 54 patients were selected who had undergone hysterectomy plus systematic pelvic LNE and para-aortic LNE by laparoscopy or laparotomy in the previous two years, dating from 12/1/2009 to 23/5/2011, in the Obstetrics and Gynecology Hospital of Fudan University (Shanghai, China). This study was approved by the Ethics Committee of the Obstetrics and Gynecology Hospital of Fudan University. Written informed consent was obtained from all patient's family. In total, 33 cases were laparoscopic and 21 cases were laparotomic. Lymph node count and status, escalation of stage, histology type, duration of surgery, estimated blood loss, peri- and postoperative complications, postoperative hospitalization and recovery and history of irregular menstrual cycle and menopausal vaginal bleeding were recorded. All surgical procedures were performed by experienced gynecological oncologists at the Obstetrics and Gynecology Hospital of Fudan University. All diagnoses of cancer were histologically confirmed. Furthermore, the duration of surgery and blood loss were evaluated to judge the feasibility of the para-aortic LNE and compare the two surgery pathways technically. Data were collected in an intent to treat manner and then analyzed using SAS 9.2 (SAS Institute, Cary, North Carolina). The t- and wilcox-tests were used to assess the differences between the laparoscopy and laparotomy cohorts.

Results

Lymph node count and status. We calculated the total lymph node count in various stages and various surgery pathways. The average para-aortic lymph node count of the laparotomy

Table II. Positive LN status.

PAN status	PLN status	Incidence (%)
+	+	2/54 (3.7)
+	-	4/54 (7.4)
-	+	2/54 (3.7)
Total		8/54 (14.8)

LN, lymph node; PAN, para-aortic lymph nodes; PLN, pelvic lymph nodes.

group was 3.14, while the laparoscopy group was 2.40. No statistical difference was observed between the two groups of the PANs. The lymph node status was also analyzed. A total of 8 cases (14.8% of patients) were identified as positive for either PAN or PLN metastasis. No other high-risk factors were identified in 4/8 patients prior to surgery, with the exception of invasive depth $>1/2$ myometrial layer (19 patients were identified with invasive depth $>1/2$ myometrial layer in total). Low differentiation was identified by curettage in 2 patients. The final 2 patients were free of high-risk factors. A positive lymph node status was not predictable based on the preoperative status as there is no definite method for predicting lymph node metastasis, therefore systematic pelvic LNE and para-aortic LNE should be performed to make staging more precise and to guide the postoperative therapy, particularly radiation (Tables I and II).

Pre- and postoperation stage. According to the FIGO guidelines, the stage of endometrial cancer is mainly categorized by pathological status. Therefore, occasionally there is an elevation of stage following surgery, as the status of the lymph node cannot be precisely predicted prior to surgery. It has been reported that a substantial number of patients with grade 1 endometrial cancer based on pre- and intraoperative assessments have a higher grade of disease at final pathology. In the

Table III. Postoperative histology distribution of the endometrial cancer.

Histology	No. patients	Incidence, n (%)	PAN, n (%)	PAN/PLN, n (%)	PLN, n (%)
Endometrioid adenocarcinoma					
Grade 1	20	1 (5)	0 (0)	0 (0)	1 (5)
Grade 2	15	1 (6.7)	1 (6.7)	0 (0)	2 (13.3)
Grade 3	9	1 (11.1)	1 (11.1)	2 (22.2)	4 (44.4)
Serous adenocarcinoma	5	1 (20.0)	0 (0)	0 (0)	1 (25.0)
Clear cell adenocarcinoma	5	0 (0)	0 (0)	0 (0)	0 (0)

PAN, paraaortic lymph nodes; PLN, pelvic lymph nodes.

Table IV. Average blood loss and duration of surgery.

Characteristic	Number of cases	Average blood loss (ml)	P-value	Average operating time (h)	P-value
Stage					
I	32	342.19	0.2918 (t-test)	3.92	0.6823 (t-test)
II, III	22	459.09	0.4278 (Wilcoxon test)	4.04	0.4227 (Wilcoxon test)
IA	8	375	0.6564 (t-test)	3.73	0.6176 (t-test)
IB	24	331.25	0.5361 (Wilcoxon test)	3.98	0.8106 (Wilcoxon test)
Surgery pathway					
Laparotomy	21	500	0.1198 (t-test)	3.90	0.7189 (t-test)
Laparoscopy	33	319.7	0.1385 (Wilcoxon test)	4.01	0.9363 (Wilcoxon test)

current study, 20.4% (11/54) were upgraded at final pathology with 13.0% (7/54) characterized as grade 2 disease and 7.4% (4/54) characterized as grade 3. Overall, 22.2% (12/54) had an advanced stage disease. A total of 42.2% (19/45) of patients with disease limited to the uterus had adverse features, including high risk histological variants, grade 3 disease, myometrial invasion N1/2 and/or cervical involvement. Among the 8 positive cases, 3 were classified as stage I and 5 as stage II preoperatively. Although LNE does not affect survival rate, as reported, it may identify patients with advanced disease and assist in tailoring adjuvant therapy for those with adverse risk factors. These results suggest the importance of paraaortic LNE in endometrial cancer.

Histological type. Postoperative histological analysis revealed that tumors with lower differentiation, including G3, tend to metastasize via the lymph system. Among the 8 positive cases, 7 patients were identified with pathology-related risk factors, including low differentiation or clear cell carcinoma postoperatively. Discordance of pathological differentiation between the pre- and postoperative stages reached 57.1% (4/7). Among the 5 clear cell adenocarcinomas, no incidence of positive lymph node metastasis was observed. Clear cell adenocarcinoma is considered to be invasive even in the early stages; the deviation may be demonstrated to be corrected by future studies involving a large number of patients. Of note, one case was staged as IA preoperatively, with no high-risk factors and was revealed to be PAN-positive but PLN-negative and G1 postoperatively (Table III).

Surgery duration and blood loss. The average surgery duration of laparotomy was 3.90 h and of laparoscopy was 4.01 h. No statistical difference was observed in operating time between the two groups. The estimated blood loss was also evaluated as being on average 500 ml for laparotomy and 319.7 ml for laparoscopy; there was no statistical significance between the two groups. The estimated blood loss during the LNE for the majority of patients was 20-40 ml. A longer duration of surgery and more blood loss occurred only among the cases in which radical cervical resection was performed when the cervix was invaded. Stage did not affect the average blood loss or average operating time. The comparison between stage IA and IB and between I and II plus III revealed no statistical difference in blood loss or duration of surgery. The comparison of distribution of stages between the two surgery pathways revealed that the distribution has no effect (Table IV).

Complications, postoperative hospitalization and recovery. There were no clear complications caused by the surgery, with the exception of lymph cysts. The formation of lymph cysts may be partially explained by the backing pathways of lymph fluid in the pelvis being widely blocked after the LNE. The majority of patients had no symptoms and only a few patients complained of slight discomfort in the legs. The large abdominal incision created by laparotomy causes acute pain and carries a risk of a slow healing wound, particularly for obese patients. Postoperative hospitalization was much shorter in duration for the laparoscopic group, with a maximum of 7-8 days, than that of the laparotomic group,

with a maximum of 12-15 days. Furthermore, the majority of patients in the laparoscopic group were able to dismount the bed freely 2-3 days following surgery, while in the latter group, patients were in pain, felt weak and were not willing to dismount the bed in the first week following surgery. The comparison between the two surgery pathways demonstrates that laparoscopy correlates with a shorter hospitalization and recovery period. The two surgeries have similar surgical effects for the patients when taking into consideration surgery duration, blood loss, lymph node count and status and complications.

History of irregular menstrual cycles and menopausal vaginal bleeding. The majority of patients with endometrial neoplasms had a history of irregular menstrual cycles or menopausal vaginal bleeding. In the present study, the shortest history of abnormal menstruation was one month. This 49-year-old patient was first diagnosed as stage II and was identified as G3 histologically post-surgery. This patient had no high risk factors, as assessed prior to surgery. Low differentiation of endometrial cancer cells manifests a strong malignant capacity, with minor symptoms; this may cause late stage damage of the patients, even if they are diagnosed early. The shortest duration of menopausal vaginal bleeding was 5 days. The patient had a 2-year history of hypertension and 4-year history of menopause and was diagnosed as having endometrioid cancer, characterized as stage IA and G1 following surgery. Among the non-menopausal females, 26.3% (5/19) had a history of irregular menstrual cycles of less than 4 months, with 1 of the 5 cases identified as PAN-positive and 47.4% (9/19) patients had a history of irregular menstrual cycles of less than 10 months. Among the menopausal females, 42.9% (15/35) had a history of menopausal vaginal bleeding for less than 3 months, with 1 of the 15 cases demonstrated to be PAN-positive. Close follow-ups and curettages of females with a history of irregular menstrual cycles and menopausal vaginal bleeding were performed, whether high risk factors were present or not.

Discussion

The metastasis to lymph nodes is a major prognostic factor among females with endometrial cancers. Therefore, careful assessment of the pathological nodal status is an integral part of the management of these patients. Histopathological examination provides the most accurate method of ascertaining the degree of metastatic spread to the lymph nodes, although the complications and practical significance of LNE remain controversial. Certain researchers have reported a low therapeutic significance of LNE, however, it causes unavoidable complications that affect the quality of life of the patients (14,15), while others argue that it aids in obtaining a systematic stage for the patient, particularly from the histological aspect (16). Beside the histological type and the invasion depth of the myometrial layer, the lymph node status is extremely significant in the determination of postoperative treatment, particularly radiotherapy (17,18). It has been suggested that surgery with systematic pelvic and paraaortic LNE followed by adjuvant chemotherapy improved the long-term survival rate in patients with PAN metastasis (19,20). These results demonstrate that

laparoscopic LNE advances minimally invasive diagnostics in endometrial cancers and may allow for a more precise prognostic assessment.

In previous years, the concept of minimally invasive surgery in the management of gynecological malignancies has gradually evolved from almost impossible to a fully realized optimal choice for a number of patients. Laparoscopy for gynecological malignancies is now used worldwide (21-23). It has been established that laparoscopy induces fewer adhesions than open dissection. The laparotomy approach subjects the patient to the morbidity associated with a large incision and consequently more complications. Recognized advantages of laparoscopy include less pain, smaller incisions, quicker recovery, shorter hospital stays, decreased blood loss, equivalent nodal counts and, in certain studies, similar survival rates. This has been confirmed in the current study.

With regard to the retrieved nodes, laparoscopic lymph node dissection has been demonstrated to be comparable to laparotomy in terms of node counts. In the current study, the mean number of nodes obtained by the laparoscopic approach was 24.1. The node count using the laparoscopic extraperitoneal approach had been shown to be comparable to that of a transperitoneal approach. This number included patients with grossly involved nodes who had a selective lymph node removal. It was also in agreement with other reports evaluating paraaortic LNE.

LNE is associated with significant operative risks in certain patients, however there were no incidences of pelvic organ trauma and little blood loss during LNE in the current study. The low incidence of postoperative complications allows prompt resumption of daily activities and the early initiation of adjuvant therapy. Lymph cysts are the most common complication post surgery, whichever surgical pathway is used, laparotomy or laparoscopy. There are no clear symptoms caused by lymph cysts. The majority of pelvic lymphocysts appear within 3 to 4 weeks following surgery, with an incidence varying from 1.5 to 25.3%. In the current study, the incidence of lymphocysts was 18.5% (10/54). This difference may be due to the variable degree of complete LNE or the various methods used to perform the procedure. Although the exact mechanism of the formation of pelvic lymphocysts is not known, the majority of lymphocysts cause slight symptoms and may be treated conservatively.

In conclusion, laparotomic and laparoscopic surgeries may be successfully performed. The feasibility of performing laparoscopic LNE in endometrial cancer has been demonstrated. Laparoscopy had a similar duration of surgery and blood loss, but had an improved influence on the patients with potentially fewer complications and faster recovery. The postoperative duration in hospital was markedly longer among the patients who underwent laparotomy. It is a safe procedure with an acceptable nodal yield, blood loss, short operating duration and low complication rate. It is effective in tailoring the field of adjuvant radiotherapy in endometrial cancers. Therefore, we consider that it is a useful tool for completing staging and confirming the adequate treatment for endometrial cancer in various stages. In the future, further experience and a longer follow-up period are required to confirm that this approach is safe and feasible.

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