Volume Index is a Risk Factor for Recurrence Even in Patients with Clinical Stage IA Endometrial Cancer Undergoing either Laparotomy or Laparoscopy: A Retrospective Study

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Abstract

Objectives: The objective of the study was to investigate the long-term outcomes, in particular, recurrence risk, especially tumor volume, for Stage IA endometrial cancer and to identify the risk factors for recurrence.

Materials and Methods: This single-center retrospective study analyzed women who underwent primary surgical treatment for the International Federation of Gynecology and Obstetrics Stage IA (Grade 1 or 2) endometrioid carcinoma at our institute between January 2010 and July 2018. Patients’ demographic characteristics, including age, operative time, number of lymph nodes, final stage, volume index as tumor volume, and final histological type, were reviewed. A total of 168 patients were enrolled, with 95 and 73 patients in the laparotomy and laparoscopy groups, respectively. The Cox proportional hazards model was used to adjust for prognostic factors in the analysis including upstaged patients, tumor histology, lymphovascular invasion, and volume index.

Results: There was no difference in the recurrence rate between laparoscopic and open surgeries for Stage IA endometrial cancer. The operative time was longer, and the amount of blood loss was lesser in the laparoscopy group than in the laparotomy group. For all patients undergoing either laparoscopy or open surgery, upstaged ≥IB, nonendometrioid Grade 1 or 2, lymphovascular invasion, and volume index ≥36 were significant independent recurrence risk factors.

Conclusion: Laparoscopic surgery for Stage IA endometrial cancer is technically and oncologically safe. Patients with a high-volume index have a higher recurrence risk. Furthermore, the volume index can be a recurrence predictor in low-risk endometrial cancer patients.

Keywords: Endometrial cancer, laparoscopy, recurrence, tumor volume

INTRODUCTION

Laparoscopic surgery for endometrial cancer is feasible and safe because of its short-term outcomes such as shorter operative time, a lesser amount of blood loss, fewer complications, and a shorter hospital stay than laparotomy.1,2 A previous meta-analysis reported that laparoscopic surgery for endometrial cancer is more feasible in terms of short-term outcomes, progression-free survival, and overall survival (OS) than laparotomy.3 A Lap2 randomized controlled trial on laparoscopic surgery for endometrial cancer reported laparoscopy feasibility and a nonsignificant difference between laparoscopy and laparotomy recurrence rates.1,4 However, the prior statistical boundaries for noninferiority were not reached.4 Conventional laparoscopic surgery, which is a minimally invasive but nonrobotic-assisted technique for endometrial cancer, is feasible and safe and is preferred by many patients.3 However, the risk of recurrence is a concern, especially when patients undergo either laparotomy or laparoscopy. The volume index is a recurrence predictor in low-risk endometrial cancer patients.3

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cancer, was accepted under the national health insurance system in Japan in 2014. Only the preoperative diagnosis of clinical Stage IA endometrial cancer is covered by the national insurance. Furthermore, the national health insurance system only covers the laparoscopic surgery for pelvic lymphadenectomy but not for paraortic lymphadenectomy. In Japan, laparoscopic surgery for gynecologic disorders is mainly performed by a reproductive medicine and endocrinology specialist, and reports are mainly on laparoscopy. A majority of gynecological oncologists perform cancer surgery cases by open laparotomy. Thus, data on the recurrence rate of laparoscopic surgery are limited, and only one study has reported its short-term operative outcomes such as the amount of blood loss, operative time, and complications. In fact, recently, the high recurrence rate of cervical and endometrial cancers following minimally invasive procedures is frequently reported. Accumulating Japanese domestic data on the outcomes of laparoscopic surgery for endometrial cancer is necessary, especially on the long-term recurrence risk and the recurrence risk factors. The preoperative risk factors for recurrence are the presence of nonendometrioid carcinoma, deep myometrial invasion, and CA125 >35 U/ml. Moreover, the volume index, a quantity indicator of tumor volume, is reported as a risk factor for recurrence. The volume index is also a risk factor of lymph node metastasis; thus, tumor volume should be considered as a risk factor for prognosis.

We aimed to investigate the long-term outcomes, mainly the recurrence risk, for clinical Stage IA endometrial cancer – which reportedly has a low recurrence rate – and the clinical significance of a large tumor volume index. Second, we studied the oncologic feasibility of laparoscopic surgery for endometrial cancer.

**Materials and Methods**

This single-center retrospective study analyzed women who underwent primary surgical treatment of the International Federation of Gynecology and Obstetrics clinical Stage IA endometrioid carcinoma of Grade 1 or 2 at our institute between January 2010 and June 2018. Patients were allocated to the laparoscopy group or laparotomy group. The decision to perform either laparoscopy or laparotomy was a historical control because laparoscopy was only covered by the national health insurance system in Japan in 2014.

Lymphadenectomy was omitted in patients suspected of having myometrium invasion by magnetic resonance imaging (MRI). Paraortic lymphadenectomy was not performed in the laparoscopic group as it was not covered by the national health insurance system in Japan. When patients were treated with adjuvant therapy, chemotherapy with paclitaxel and carboplatin was administered in six cycles. Patients without recurrence were considered successfully treated on 5 years of follow-up postsurgery, regardless of open laparotomy or laparoscopy. The institutional review board provided ethical approval (approval number: S19-127) for the trial and waived the need for obtaining patients’ informed consent because of the retrospective study design.

**Eligibility criteria**

Women aged ≥20 years who underwent laparoscopy or laparotomy in our institute during the study period for preoperatively diagnosed clinical Stage IA endometrial cancer were enrolled in this study. Patients with a history of other cancers were excluded from the study.

**Volume index**

The included patients underwent MRI preoperatively. The primary outcome was recurrence-free survival (RFS). Demographic characteristics, including age, operative time, number of lymph nodes, the final stage, volume index, and final histological type, were reviewed. Volume index was evaluated in either the T2-weighted magnetic resonance images or gadolinium-enhanced T1-weighted images. Volume index was defined as the product of the maximum longitudinal diameter along the uterine axis, the maximum anteroposterior diameter (thickness) in a sagittal section image, and the maximum horizontal diameter in a horizontal section image. We used a volume index cutoff value ≥36 as a recurrence risk factor because it was reported as a prognostic factor in previous studies.

**Statistical analysis**

JMP for Windows, version 10.0.0 (SAS Institute Japan, Minato, Japan) was used for the statistical analyses. For variables with normal distribution, continuous data were compared using the Student’s t-test. For variables with nonnormal distribution, data were compared using the Wilcoxon signed-rank test. Fisher’s exact test was used to study the associations among the demographic parameters. RFS was analyzed with the Kaplan–Meier method, using log-rank tests because of the short-term study duration. The Cox proportional hazards model was used to adjust for prognostic factors in the analysis including upstaged patients, tumor histology, lymphovascular invasion, and volume index. For all statistical tests, a two-sided P < 0.05 was considered statistically significant. For the hazard ratio, 95% confidence intervals (95% CIs) were estimated. For all statistical tests, a two-sided P < 0.05 was considered statistically significant. For the odds ratio, 95% CIs were estimated.

**Results**

A total of 168 patients were enrolled including 95 and 73 patients in the laparotomy and laparoscopy groups,
respectively. In the laparoscopic group, a uterine manipulator was used in 13 patients (17.8%), it was not used in 42 (57.5%), and whether it was used was unknown in 18 (24.7%). Among the patients in whom a uterine manipulator was not used, a trocar at the right side of the umbilicus was used for uterus manipulation.[16] To establish a firm fix on the uterus, the trocar was placed on the right side of the umbilicus, and we used Johann forceps with a long jaw (4 cm) (Olympus, Tokyo, Japan), allowing for a gentle and firm grasp with a ratchet. This allowed for counter traction and several positions required during surgery without using an intrauterine manipulator [Figure 1].[16]

Table 1 shows the patients’ characteristics. Lymphadenectomy was omitted in patients suspected of having myometrium invasion by MRI.[14] Lymphadenectomy was not performed in 49 (51.6%) and 62 (84.9%) patients in the laparotomy and laparoscopy groups, respectively. In the laparotomy group, both pelvic and paraaortic lymphadenectomy was performed on 26 patients (27.4%). In the laparoscopy group, paraaortic lymphadenectomy was not performed. The operative times of both the procedures without lymphadenectomy and with pelvic lymphadenectomy were significantly longer in the laparoscopy group than in the laparotomy group (99.7 ± 41.0 vs. 128.2 ± 44.2 min, \( P = 0.001 \) and 148.0 ± 59.1 vs. 229.4 ± 44.4 min, \( P < 0.0001 \), respectively). In contrast, the amount of blood loss during the procedures without lymphadenectomy was significantly lesser in the laparoscopy group than in the laparotomy group (188.6 ± 184.6 vs. 121.7 ± 134.4 g, \( P = 0.029 \)). The postoperative pathology was not consistent among 14 patients, with ten patients having Grade 3 endometrioid carcinoma, three patients having serous carcinoma, and one patient having squamous cell carcinoma.

The perioperative complications are shown in Table 2. There was no significant difference in the perioperative complications between the laparotomy and laparoscopy groups. There was no case of organ injury in either group. Five (5.3%) and one (1.4%) patients received blood transfusions in the laparotomy and laparoscopy groups, respectively.

The RFS rates for the laparotomy and laparoscopy groups are presented in a Kaplan–Meier curve [Figure 2]. There was no significant difference in the RFS rate between the two groups (5-years RFS for the laparotomy vs. laparoscopy were 93.5% vs. 91.0%, respectively, \( P = 0.465 \)). Moreover, there was no significant difference in the OS between the two groups (5-years OS laparotomy vs. laparoscopy were 97.4% vs. 95.4%, respectively, \( P = 0.42 \)). The median follow-up durations were 62 and 59 months in the laparotomy and laparoscopy groups, respectively.

We studied all the patients; those in the laparoscopy and laparotomy groups were considered together as one group for prediagnosis of endometrial cancer IA to determine the prognostic factors for RFS and OS. The Cox hazard ratio of RFS is shown in Table 3. In the univariate analyses, upstaged, nonendometrioid Grade 1 or 2, significant factors were lymphovascular invasion, positive ascitic cytology results, volume index ≥36, and adjuvant chemotherapy. In the multivariate analyses, upstaged, nonendometrioid Grade 1 or 2, and volume index ≥36 remained significant factors.

Table 4 shows the Cox hazard ratio of OS. In the univariate analyses, upstaged, nonendometrioid Grade 1 or 2, significant factors were a volume index ≥36, and adjuvant chemotherapy. In the multivariate analyses, the only significant factor was the volume index.

Eleven patients including five and six patients in the laparotomy and laparoscopy groups, respectively, had recurrence. Two out
of five patients in the laparotomy group had recurrence at the stump \((n=1)\) and dissemination \((n=1)\). Two out of six patients in the laparoscopy group had recurrence at the stump \((n=1)\) and dissemination \((n=1)\). The other patients had distant metastasis.

**Discussion**

Our study suggests that there was no difference in the recurrence rate between laparoscopic and open surgeries in patients with clinical Stage IA endometrial cancer, which is covered by the national insurance in Japan. The operative time was longer with less blood loss in the laparoscopy group than that in the laparotomy group. Upstaged ≥IB, nonendometrioid Grade 1 or 2, lymphovascular invasion, and volume index ≥36 were significant independent risk factors for recurrence. Volume index ≥36 was the only significant risk factor for OS. This volume index has been reported as a risk factor for advanced and high-risk endometrial cancer. Whereas, in our study, it was found to be a risk factor for recurrence in patients with early and low-risk endometrial cancer. Laparoscopy is not a risk factor for recurrence. The volume index is useful information and can be calculated preoperatively.

Similar to the findings of past studies and a meta-analysis, laparoscopy was not a significant risk factor for recurrence in patients with Stage IA endometrial cancer.\cite{1,2,4,17} Moreover, our study and previous reports showed similar results in relation to the perioperative complications and technical feasibility of laparoscopy.\cite{12,2,4,18} It is essential to report the long-term survival outcomes and technical feasibility of new treatments, including laparoscopic procedures, which have only been introduced in Japan recently. Our data showed that clinical Stage IA endometrial cancer is safely managed with laparoscopy. Although laparoscopic procedures for endometrial cancer have been reported in previous studies,\cite{1,3} laparoscopy for endometrial cancer has only recently been introduced to the national health insurance system in 2014 in Japan;\cite{5} thus, its long-term survival outcomes have not yet been reported. It is important to investigate the safety and long-term prognosis of laparoscopy for endometrial cancer in countries that have only newly introduced such a procedure.

A volume index ≥36 is an independent significant risk factor for recurrence and OS, which is a novel finding of our study.

**Table 1: Patient’s characteristics**

|                      | Laparotomy \((n=95), \, n (%)\) | Laparoscopy \((n=73), \, n (%)\) | \(P^*\) |
|----------------------|---------------------------------|---------------------------------|---------|
| Age (mean±SD)        | 61.3±11.7                       | 58.1±13.1                       | 0.090   |
| BMI (kg/m\(^2\))     | 25.2±5.39                       | 26.4±6.82                       | 0.223   |
| No lymphadenectomy   | 49 (51.6)                       | 62 (84.9)                       | <0.0001*|
| PLN was performed    | 20 (21.1)                       | 11 (15.1)                       | <0.0001*|
| PLN + PAN was performed | 26 (27.4)                      | 0                               | <0.0001*|
| Number of lymph nodes removed in PLN | 26.6±9.14             | 18.5±6.42                       | 0.015*  |
| Operative time (min; without lymphadenectomy) | 99.7±41.0             | 128.2±44.2                     | 0.001   |
| Blood loss (g; without lymphadenectomy) | 188.6±184.6             | 121.7±134.4                     | 0.029*  |
| Operative time (min; with PLN) | 148.0±59.1           | 229.4±44.4                     | <0.0001*|
| Blood loss (g; with PLN) | 284.1±146.0          | 184.6±103.1                    | 0.055   |
| Upstaged after surgery | 6 (6.3)                        | 9 (12.3)                       | 0.186   |
| Volume index ≥36     | 6 (6.3)                         | 5 (6.8)                        | 1       |
| Nonendometrioid carcinoma Grade 1 or 2 | 10 (10)                  | 4 (5.5)                        | 0.275   |
| Adjuvant chemotherapy performed | 15 (15.8)             | 6 (8.2)                        | 0.164   |

*\(P<0.05\). SD: Standard deviation, BMI: Body mass index, PLN: Pelvic lymphadenectomy, PAN: Paraortic lymphadenectomy

**Table 2: Perioperative complications**

|                      | Laparotomy \((n=95), \, n (%)\) | Laparoscopy \((n=73), \, n (%)\) | \(P^*\) |
|----------------------|---------------------------------|---------------------------------|---------|
| Re-bleeding          | 3 (3.2)                         | 2 (2.7)                         | 1       |
| Lymphocele           | 5 (5.3)                         | 1 (1.4)                         | 0.235   |
| Ileus                | 4 (4.2)                         | 0                               | 0.133   |
| Surgical site infection | 2 (2.1)                     | 3 (4.1)                         | 0.654   |
| Blood transfusion    | 5 (5.3)                         | 1 (1.4)                         | 0.233   |
| Organ injury         | 0                               | 0                               |         |

*The significance of \(P\) value was set at <0.05 in this study

**Figure 3:** Overall survival rates for laparotomy and laparoscopy are presented in a Kaplan–Meier curve.
Volume index is an independent risk factor for lymph node metastasis and disease progression. However, past reports focused on advanced endometrial carcinoma. In this study, we enrolled patients prediagnosed with Stage IA endometrial cancer. Our data suggested that the volume index is an important factor for predicting prognosis even in the early stages of endometrial cancer. Furthermore, our data showed that upstaged ≥IB, nonendometrioid Grade 1 or 2, lymphovascular invasion, and volume index ≥36 were significant independent risk factors for recurrence. Among these risk factors, only the volume index could be measured preoperatively.

Tumor volume is associated with the stage, prognosis, and metastasis of many cancers. Mariani et al. reported a significant prognostic difference between tumors <2 cm diameter and tumors ≥2 cm diameter in patients with low-risk endometrial cancer. A previous study reported on the role of tumor diameter in predicting lymph node metastasis. In our study, even those with the early preoperative Stage IA endometrial cancer had a recurrence risk with large tumor volume. In these patients, we should perform pelvic and paraaortic lymphadenectomy to confirm disease staging to ensure that they do not miss adjuvant therapy.

Our study has some limitations. This was a retrospective study and since it was based on Japan’s health insurance system, patient enrollment in this study based on laparotomy and laparoscopy procedures was not equal, especially in cases of paraaortic lymphadenectomy. Performing a lymphadenectomy or not might influence the outcome. However, it is worthwhile to report no significant difference in prognosis in the laparoscopy group after omitting paraaortic lymphadenectomy compared to the prognosis in the laparotomy group. Endometrial cancer was accepted under the national health insurance system in Japan in 2014, and this information about the long-term outcome report is essential for current clinical practice. Tumor spillage, which is argued to be a risk factor for recurrence, should have also been analyzed in the study. In future, further studies are warranted to validate our results.

**Conclusion**

Laparoscopic surgery for clinical Stage IA endometrial cancer is technically and oncologically safe. Patients with a high volume index have a high recurrence risk. Moreover, the volume index was found to be a significant independent recurrence and OS risk factor, even in patients with low-risk endometrial cancer. Further data collection on the recurrence risk after laparoscopic surgery is necessary for future studies. Our data will be helpful to institutions using laparoscopy to treat endometrial cancer.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Walker JL, Piedmonte MR, Spirito NM, Eisenkop SM, Schlaerth JB, Mannel RB, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. J Clin Oncol 2009;27:5331-6.
2. Terai Y, Tanaka T, Sasaki H, Kuwaguchi H, Fujiwara S, Yoo S, et al. Total laparoscopic modified radical hysterectomy with lymphadenectomy for endometrial cancer compared with laparotomy. J Obstet Gynecol Res 2014;40:570-5.
3. Galaal K, Donkers H, Bryant A, Lopes AD. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. Cochrane Database Syst Rev 2018;10:CD006655.
4. Walker JL, Piedmonte MR, Spirito NM, Eisenkop SM, Schlaerth JB, Mannel RS, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 Study. J Clin Oncol 2012;30:695-700.
5. Deura I, Shimada M, Azuma Y, Komatsu H, Nagira K, Sawada M, et al. Comparison of laparoscopic surgery and conventional laparotomy for surgical staging of patients with presumed low-risk endometrial cancer: The current state of Japan. Taiwan J Obstet Gynecol 2019;58:99-104.
6. Chikazawa K, Yoshida C, Kuwata T, Konno R. Vaginal incision during total laparoscopic hysterectomy may cause severe bradycardia and cardiac arrest. Taiwan J Obstet Gynecol 2018;57:468-9.
7. Tanaka T, Terai Y, Hayashi S, Aoki D, Miki K, Kobayashi E, et al. Comparison between laparoscopy and laparotomy in systematic para-aortic lymphadenectomy for patients with endometrial cancer: A retrospective multicenter study. J Gynecol Surg 2017;33:105-10.
8. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med 2018;379:1895-904.
9. Song J, Le T, Hopkins L, Fung-Kee-Fung M, Lupe K, Gaudet M, et al. A comparison of disease recurrence between robotic versus laparotomy approach in patients with intermediate-risk endometrial cancer. Int J Gynecol Cancer 2020;30:160-6.
10. Kang S, Nam JH, Bae DS, Kim JW, Kim MH, Chen X, et al. Preoperative assessment of lymph node metastasis in endometrial cancer: A Korean Gynecologic Oncology Group study. Cancer 2017;123:263-72.
11. Todo Y, Watari H, Okamoto K, Hareyama H, Minobe S, Kato H, et al. Tumor volume successively reflects the state of disease progression in endometrial cancer. Gynecol Oncol 2013;129:472-7.
12. Todo Y, Sakuragi N, Nishida R, Yamada T, Ebina Y, Yamamoto R, et al. Combined use of magnetic resonance imaging, CA 125 assay, histologic type, and histologic grade in the prediction of lymph node metastasis in endometrial carcinoma. Am J Obstet Gynecol 2003;188:1265-72.
13. Todo Y, Okamoto K, Hayashi M, Minobe S, Nomura E, Hareyama H, et al. A validation study of a scoring system to estimate the risk of lymph node metastasis for patients with endometrial cancer for tailoring the indication of lymphadenectomy. Gynecol Oncol 2007;104:623-8.
14. Nagase S, Katabuchi H, Hiura M, Sakuragi N, Aoki Y, Kigawa J, et al. Evidence-based guidelines for treatment of uterine body neoplasm in Japan: Japan Society of Gynecologic Oncology (JSGO) 2009 edition. Int J Clin Oncol 2010;15:531-42.
15. Todo Y, Choi HJ, Kang S, Kim JW, Nam JH, Watari H, et al. Clinical significance of tumor volume in endometrial cancer: A Japan-Korea cooperative study. Gynecol Oncol 2013;131:294-8.
16. Imai K, Chikazawa K, Ito T, Kuwata T, Konno R. Manipulating the uterus without a manipulator or human hands: A resolution using retractor and forceps tied with gauze. J Minim Invasive Gynecol 2020;27:1461-2.
17. Lee CL, Kusunoki S, Huang KG, Wu KY, Huang CY, Yen CF. Long-term survival outcomes of laparoscopic staging surgery in treating endometrial cancer: 20 years of follow-up. Taiwan J Obstet Gynecol 2016;55:545-51.
18. Chu LH, Chang WC, Sheu BC. Comparison of the laparoscopic versus conventional open method for surgical staging of endometrial carcinoma. Taiwan J Obstet Gynecol 2016;55:188-92.
19. Writtekind C, Greene FL, Hutter RV, Klimpfinger M, Sobin LH. TNM Atlas: Illustrated Guide to the TNM Classification of Malignant Tumours. 5th ed. Heidelberg: Springer-Verlag; 2005.
20. Kaschelny S, Tubiana M, Lé MG, Valleron AJ, Mouriès H, Contesso G, et al. Breast cancer: Relationship between the size of the primary tumour and the probability of metastatic dissemination. Br J Cancer 1984;49:709-15.
21. Mariani A, Webb MJ, Keeney GL, Haddock MG, Calori G, Podratz KC. Low-risk corpus cancer: Is lymphadenectomy or radiotherapy necessary? Am J Obstet Gynecol 2000;182:1506-19.
22. Milam MR, Java J, Walker JL, Metzinger DS, Parker LP, Coleman RL, et al. Nodal metastasis risk in endometrioid endometrial cancer. Obstet Gynecol 2012;119:286-92.
23. Kanao H, Matsuo K, Aoki Y, Tanigawa T, Nomura H, Okamoto S, et al. Feasibility and outcome of total laparoscopic radical hysterectomy with no-touch technique for FIGO IB1 cervical cancer. J Gynecol Oncol 2019;30:e71.
24. Melamed A, Margul DJ, Chen L, Keating NL, Del Carmen MG, Yang J, et al. Survival after minimally invasive radical hysterectomy for early-stage cervical cancer. N Engl J Med 2018;379:1905-14.