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Is Adjuvant Chemotherapy Necessary in Patients with Early Endometrial Cancer?

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ABSTRACT

Background We investigated whether there was a difference in prognosis between patients with stage IA endometrial cancer with and without lymphovascular space invasion.

Methods We enrolled patients with stage IA (pT1aN0M0) endometrial cancer admitted to our hospital from 2009 to 2018. All patients underwent hysterectomy, bilateral salpingo-oophorectomy, and systematic pelvic lymphadenectomy. We immunopathologically evaluated the presence or absence of lymphovascular space invasion in the tumor tissue using hematoxylin and eosin, Elastica-van Gieson, and podoplanin staining. We analyzed disease-free and overall survival and calculated patients' survival distribution using the Kaplan–Meier method and log-rank test. The multivariate analysis was performed to determine the prognostic factors.

Results A total of 116 patients were included. The median age of the patients was 57 (range, 30–78) years, and the histological subtype revealed 98 and 18 cases of types 1 and 2, respectively. The median follow-up period was 71.9 (range, 10.8–149) months, and the 3-year disease-free and 3-year overall survival rates were 94% and 99%, respectively. The disease-free and overall survival rates were significantly shorter in type 2 patients than in type 1 patients (type 2 vs. type 1; 77% vs. 97%, $P < 0.01$, 94% vs. 100%, $P = 0.014$, respectively). The univariate and multivariate analyses showed that there were no significant differences in disease-free survival between the lymphovascular space invasion-positive and -negative groups among type 1 cases.

Conclusion There was no difference in prognosis between patients with stage IA and type 1 endometrial cancer with and without lymphovascular space invasion.

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Abbreviations: CI, confidence interval; FIGO, Federation of Gynecology and Obstetrics; LVSI, lympovascular space invasion; MI, myometrial invasion; NA, not available; SweGCG, Swedish Gynecologic Cancer Group

Key words endometrial cancer; lymphovascular space invasion; prognosis; recurrent risk

The incidence of endometrial cancer has been increasing worldwide; it also has higher morbidity than other gynecological cancers in Japan.[1] Endometrial cancer is often diagnosed at an early stage because it usually presents with abnormal vaginal bleeding; thus, endometrial cancer has a good prognosis (in Japan, the 5-year survival rate for International Federation of Gynecology and Obstetrics (FIGO) stage IA endometrial cancer is 97.0%).[2]

Endometrioid carcinoma grades 1 and 2 are classified as type 1 endometrial cancer and the others as type 2 endometrial cancer. Patients with type 2 endometrial cancer have a worse prognosis than those with type 1 endometrial cancer.[3] Although the risk of recurrence is classified through postoperative pathological assessment, the prognosis of early endometrial cancer is good even with surgery alone.[4] Previous studies reported that lymphovascular space invasion is a risk factor for the recurrence of endometrial cancer.[5–7] The National Clinical Practice Guidelines in Oncology recommend that high- or intermediate-risk cases should receive postoperative radiotherapy or chemotherapy.[8] However, previous studies had some limitations, for example, the inclusion of patients with stage IB-IV endometrial cancer and the lack of evaluation of lymph node metastasis.

At our hospital, postoperative adjuvant chemotherapy has not been performed for patients with stage IA endometrial cancer with endometrioid grade 1 or 2, regardless of the presence or absence of lymphovascular space invasion. In our daily clinical practice, we rarely encountered recurrent cases, even though we failed to properly assess lymphovascular space invasion.

Thus, in this study, we investigated whether there was a difference in prognosis between patients with stage IA endometrial cancer with and without lymphovascular space invasion.

SUBJECTS AND METHODS

Study population

The patients with FIGO 2009 stage IA (pT1aN0M0) endometrial cancer who underwent surgery from January

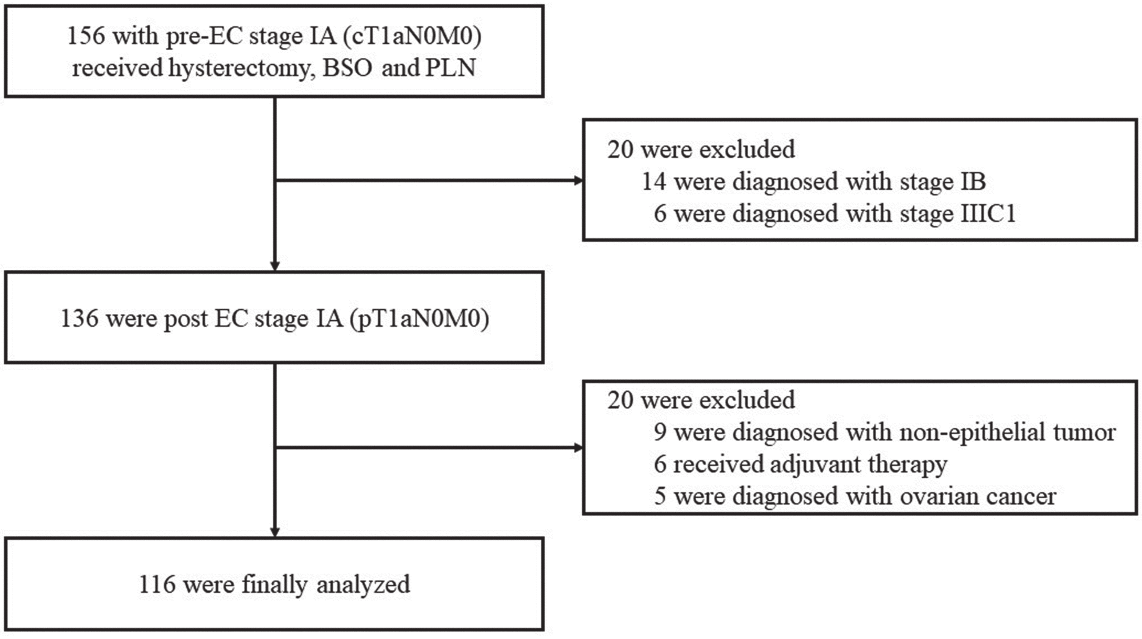

Fig. 1. Flow chart of the enrollment process. BSO, bilateral salpingo-oophorectomy; EC, endometrial cancer; PLN, pelvic lymphadenectomy.

2009 to August 2018 at Tottori University were enrolled in this study.[9] The main exclusion criteria were as follows: no lymphadenectomy, stage IB or higher, positive peritoneal cytology, and receiving adjuvant therapy. No postoperative treatment was administered to patients with or without lymphovascular space invasion. The primary outcomes were 3-year disease-free and 3-year overall survival. The secondary outcomes were prognostic factors relating to survival endpoints.

Surgical procedures

The surgeries performed on the patients were hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, and systematic pelvic lymphadenectomy, in addition to para-aortic lymphadenectomy and omentectomy in type 2 endometrial cancer cases. The extent of the systematic pelvic lymphadenectomy was from the common iliac nodes to the supra-inguinal nodes. Lymph node sampling and sentinel lymph node dissection were not performed. We performed chest radiography, electrocardiography, spirometry, intravenous pyelography, computed tomography, and magnetic resonance imaging preoperatively.

Pathological diagnosis

We immunopathologically evaluated the presence or absence of lymphovascular space invasion in tumor tissue samples using hematoxylin and eosin, Elastica-van Gieson, and podoplanin staining. Lymphovascular space invasion was evaluated by an expert pathologist. Lymphovascular space invasion is a pathologic finding defined by the presence of tumor cells within lymphatic vessels and/or small capillaries, outside the main tumor.[7]

Statistical analysis

We analyzed the type of recurrence, disease-free survival, and overall survival. Patients' survival distribution and multivariate analysis were calculated using the Kaplan–Meier method, log-rank test, and Cox proportional hazards models.[10] The significance of the survival distribution in each group was assessed using the log-rank test. *P*-values < 0.05 were considered to indicate statistical significance. Statistical analyses were performed using EZR software, version 1.54, 2020.[11] This study was approved by the Institutional Review Board of Tottori University Hospital (IRB number: 19A198). All patients provided opt-out consent in accordance with the institutional guidelines.

RESULTS

Patient characteristics

A total of 116 patients with FIGO stage IA endometrial cancer were included (Fig. 1). The characteristics of patients in this study are shown in Table 1. In all cases, the median age of the patients was 57 (range, 30–78) years. Their median body mass index was 23.5 (range, 15.6–46.6) kg/m^2. The median number of resected lymph nodes was 26 (range, 10–59). Eighty-four patients

Table 1. Patients' characteristics

		Type 1 (n = 98)	Type 2 (n = 18)
Age† (years)		57 (30–78)	63 (34–77)
BMI† (kg/m^2)		23.3 (15.6–46.6)	23.8 (19.4–39.8)
Number of lymph nodes†		25 (10–59)	26 (15–41)
Type of surgery			
Laparotomy		70 (71%)	17 (94%)
Laparoscopy		28 (29%)	1 (6%)
Histological subtype			
Type 1	Endometrioid grade 1	85 (73%)	
	Endometrioid grade 2	13 (11%)	
Type 2	Endometrioid grade 3		10 (9%)
	Clear cell		3 (3%)
	Other		5 (4%)
Myometrial invasion			
MI		57 (58%)	13 (72%)
No-MI		41 (42%)	5 (28%)
LVSI			
Positive		9 (9%)	6 (33%)
Negative		89 (91%)	12 (67%)
Tumor size			
≥ 2 cm		35 (36%)	9 (50%)
< 2 cm		63 (64%)	9 (50%)
Follow-up time† (months)		71.1 (11.5–150)	72.2 (10.3–130)

†Median (range). BMI, body mass index; LVSI, lymphovascular space invasion; MI, myometrial invasion.

(72%) reached menopause. The distribution of the histological subtypes was as follows: 85, 13, and 10 cases of endometrioid carcinoma grades 1, 2, and 3, respectively. Regarding the non-endometrioid subtype, three cases were clear cell carcinomas and five cases were other subtypes.

We performed 87 laparotomies and 29 laparoscopic surgeries. No deep (< 50%) myometrial invasion (MI) was observed in 70 cases (60%), while 15 cases (13%) had lymphovascular space invasion. The median follow-up time was 71.9 (range, 10.3–149) months. We will provide our data for the reproducibility of this study in other centers if such is requested.

Survival endpoints

In the type 1 group, recurrence was noted in three cases (3.1%), including two cases in the pelvis and one case in the vaginal stump. All of them had no lymphovascular space invasion. In contrast, in the type 2 group, four cases (22%) had recurrence, including three in the peritoneum and one in the vaginal stump. The 3-year disease-free and 3-year overall survival rates in all cases were 94% and 99%, respectively. The 3-year disease-free and 3-year overall survival rates in the type 2 group were significantly lower than those of the type 1 group (type 2 vs. type 1; 77% vs. 97%, $P < 0.01$, 94% vs. 100%, $P = 0.014$) (Figs. 2a and b). There were no significant differences in the 3-year disease-free and 3-year overall survival rates between the groups with and without MI in < 50% of the myometrium (MI vs. no-MI; 93% vs. 96%, $P = 0.53$, 99% vs. 100%, $P = 0.35$). There were no significant differences between the groups with and without lymphovascular space invasion in terms of the 3-year disease-free and 3-year overall survival rates (lymphovascular space invasion (+) vs. lymphovascular space invasion (–); 87% vs. 95%, $P = 0.2$, 93% vs. 100%, $P = 0.27$). There were no significant differences between tumor size ≥ 2 cm and tumor size < 2 cm in the 3-year disease-free and 3-year overall survival rates (tumor size ≥ 2 cm vs. < 2 cm; 93% vs. 94%, $P = 0.75$, 100% vs. 99%, $P = 0.95$, respectively).

In addition, the 3-year disease-free and 3-year overall survival rates in the only type 1 group with lymphovascular space invasion did not differ from those in the group without such invasion [lymphovascular space invasion (+) vs. lymphovascular space invasion (–); not available (NA) vs. 97%, $P = 0.58$, NA vs. 100%, $P = 0.75$] (Figs. 3a and b). In the multivariate analysis for disease-free survival, lymphovascular space invasion was not an independent prognostic factor in this study (Tables 2-a and b). The multivariate analysis for overall survival was not performed because of the small number of events and cases.

DISCUSSION

This study showed that there was no difference in prognosis between patients with stage IA endometrial cancer (pT1aN0M0) (grade 1 or 2) with and without lymphovascular space invasion. Multivariate analysis showed that only histological subtype was a prognostic factor. Therefore, patients with stage IA and type 1 endometrial cancer may not require adjuvant chemotherapy even if lymphovascular space invasion is present.

The risk factors for recurrence in stage I endometrial cancers are age, histological subtype, MI depth, tumor size, and positive ascites cytology.[5, 12] In particular, the histological subtype and MI are prognostic factors and important recurrent risk factors.[13, 14] Keys et al. reported that patients with lymphovascular space involvement were included in an intermediate-risk group;

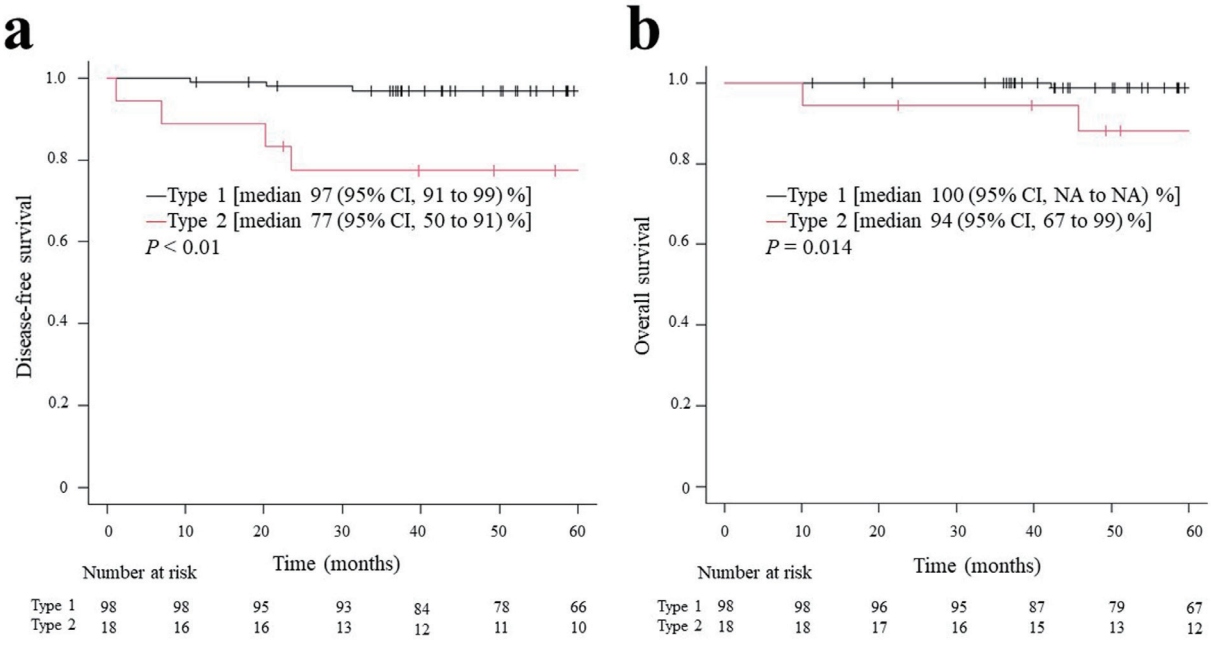

Fig. 2. Histological subtypes and prognosis. **a)** 3-year disease-free survival and prognosis. **b)** 3-year overall survival and prognosis. The 3-year disease-free and 3-year overall survival rates in the type 2 group were significantly shorter than those in the type 1 group. CI, confidence interval; NA, not available.

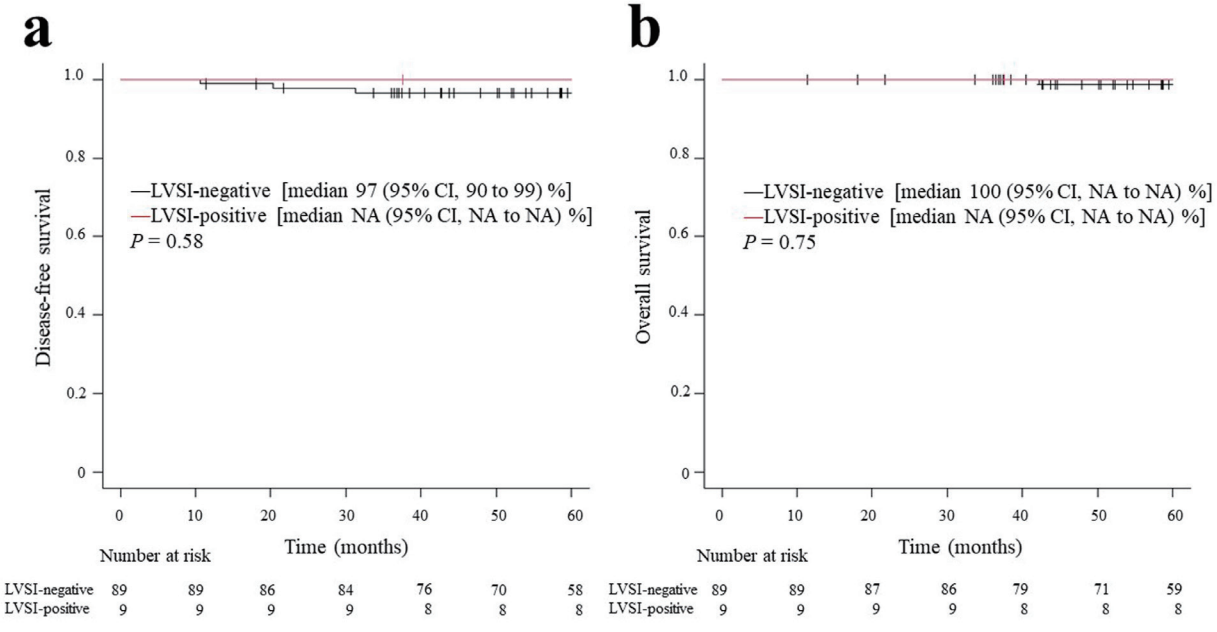

Fig. 3. Lymphovascular space invasion and prognosis among type 1 endometrial cancers. **a)** 3-year disease-free survival. **b)** 3-year overall survival. The data of the group with LVSI were not different from those of the group without LVSI. CI, confidence interval; LVSI, lymphovascular space invasion; NA, not available.

Table 2-a. Multivariate analysis for disease-free survival in all patients

Variable		Multivariate analysis	
		Relative risk (95% CI)	*P*
Histological subtype	Type 2 vs type 1	7.82 (1.56–42.1)	0.014*
Myometrial invasion	Not deep myometrial invasion vs none	1.41 (0.21–11.5)	0.72
LVSI	Positive vs negative	1.35 (0.17–8.7)	0.75
Tumor size	≥ 2 cm vs < 2 cm	0.76 (0.14–4.1)	0.75

Table 2-b. Multivariate analysis for disease-free survival in type 1 patients

Variable		Multivariate analysis	
		Relative risk (95% CI)	*P*
Age (years)	Age ≥ 65 vs Age < 65	1.3 (0.05–15)	0.84
Myometrial invasion	Not deep myometrial invasion vs none	1.4 (0.06–19.8)	0.8
LVSI	Positive vs negative	4.9 (0.2–64)	0.23
Tumor size	≥ 2 cm vs < 2 cm	3.9 (0.33–94.2)	0.29

*$P < 0.05$. CI, confidence interval; LVSI, lymphovascular space invasion.

therefore, adjuvant therapy was recommended for these patients.[5, 6] However, in general, the patient's quality of life worsens after adjuvant therapy. We must consider the need for adjuvant therapy in cases of lymphovascular space invasion.

Li et al. reported that lymphovascular space invasion was a poor survival risk factor, but this study noted lymphovascular space invasion in multiple stages of endometrial cancer.[15] Cusano et al. reported a higher mortality rate in lymphovascular space invasion-positive cases. However, this study only analyzed stage I endometrial cancer cases as a whole, rather than classifying patients into stages IA and IB.[16] In our study, we analyzed only stage IA endometrial cancer cases and appropriately evaluated lymph node metastasis in all cases.

Recently, although some studies have assessed patients with stage IA and type 1 cancers, for example, Stålberg et al. reported that the presence of lymphovascular space invasion in low-risk cases (histologic grade 1 or 2, no deep MI, and diploid tumors) was associated with poor overall survival (hazard ratio 1.69, 95% confidence interval 1.00–2.86),[8] this study and some previous research included patients whose pathological lymph node metastases were not evaluated.[7, 17] Briët et al. have reported that lymph node metastasis increases with lymphovascular space invasion.[18] Therefore, the number of cases with occult lymph node metastasis proportionately increases with the number of cases with positive lymphovascular space invasion. We predicted that these previous study populations could have included cases of mixed occult lymph node metastasis. Aslan et al. pointed out that including patients who have not undergone lymph node evaluation is an important confounding effect.[19] Therefore, our study revealed important data because we evaluated all patients who were identified as having FIGO stage IA endometrial cancer through the pathological evaluation of tissue using systematic lymphadenectomy. To the best of our knowledge, this is the first study to investigate all cases of stage IA (pT1aN0M0) and type 1 endometrial cancer after systematic lymphadenectomy specifically.

This study had some limitations. First, the study examined a total of 116 cases, and only 15 cases had lymphovascular space invasion. Although the number of cases was small and the detection power was low, these may have led to wrong conclusions. Therefore, we need to analyze more cases to confirm the statistical differences observed in this study. Second, this was a retrospective study; therefore, all data could not be collected. Third, a selection bias could have occurred as our study was a single-institution trial.

We intend to conduct studies involving more patients with systematic lymphadenectomy in a multi-institutional collaboration in the future. We also hope to evaluate the histological classification with more accurate grouping using central judgment.

This study examined the difference in prognosis between patients with stage IA and type 1 endometrial cancer who underwent pelvic lymphadenectomy with

the presence or absence of lymphovascular space invasion. Although the number of cases was small and the detection power was low, no significant prognostic differences were identified between the cases with and without lymphovascular space invasion. Patients with stage IA endometrial cancer had a good prognosis, and the only prognostic factor was the histological subtype. Therefore, patients with stage IA and type 1 endometrial cancer may not require adjuvant chemotherapy even if lymphovascular space invasion is present.

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The authors declare no conflicts of interest.

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