ORIGINAL

Can systematic lymphadenectomy be omitted for low-risk endometrial cancer?

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Abstract : The objective of this study was to identify pathological indicators that could be used to identify a subgroup of patients with apparent stage I endometrial cancer who do require retroperitoneal lymphadenectomy. 188 T1 endometrial cancer patients underwent primary surgery at Tokushima University Hospital. We retrospectively evaluated their clinical records and histopathological factors. Systematic lymphadenectomy was performed for 149 patients, and 39 patients (grade 1 with < 5 mm of myometrial invasion) were treated without lymphadenectomy. Lymph node metastases were found in 19 (12.8%) of the lymphadenectomy cases. Twenty-four patients with a T1a endometrium-limited lesion did not exhibit lymph node metastasis. Three (3.1%) of the 95 patients with a T1a lesion exhibited lymph node metastasis, and these 3 cases exhibited approximately 50% myometrial invasion. The 39 low-risk patients who did not undergo systematic lymphadenectomy remain alive without recurrence. Systematic lymphadenectomy could be omitted for patients with a grade 1 tumor and minor myometrial invasion of less than 5mm. J. Med. Invest. 65 : 221-224, August, 2018

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INTRODUCTION

Endometrial cancer is the most common gynecological malignancy, with approximately 14,000 new cases and 2,200 related deaths occurring every year in Japan [Japanese Ministry of Health, Labour and Welfare ; Matsuda *et al*, 2012]. In 2008, the 1998 International Federation of Gynecology and Obstetrics (FIGO) criteria were revised such that stage IA includes disease that involves the endometrium and/or with < 50% myometrial invasion and stage IB includes disease with > 50% myometrial invasion. Based on the new definitions, retroperitoneal lymph node metastasis is a critical prognostic factor for patients with endometrial carcinoma [Creasman, 1989 ; Pecorelli, 2009]. Thus, the National Comprehensive Cancer Network's Clinical Practice Guidelines in Oncology recommend pelvic lymph node and para-aortic lymph node dissection, rather than nodal sampling, for patients with endometrial cancer [National Comprehensive Cancer Network]. Many studies have reported the value of lymphadenectomy when treating patients with endometrial cancer, although it is unclear whether all patients will benefit from undergoing this surgery. Therefore, we retrospectively reviewed the clinical records and histopathological factors (e.g., grade, myometrial invasion, and lymph-vascular space invasion [LVSI]) of patients with endometrial cancer who underwent surgical treatment with or without lymphadenectomy at our center.

PATIENTS AND METHODS

This retrospective study examined patients with endometrial cancer who underwent surgical treatment at the Tokushima University Hospital during 2000–2011. Informed consent for the treatment to be carried out had been given.

We identified 241 patients were treated via hysterectomy and removal of the existing adnexal structures, and had no other malignancy that was diagnosed within 5 years before or after the diagnosis of endometrial cancer. Among these 241 patients, 188 patients fulfilled our eligibility criteria : (i) magnetic resonance imaging- and computed tomography had confirmed the tumor was confined to the uterine corpus (except for occult positive lymph nodes, positive peritoneal cytology results, or both) and (ii) had not undergone preoperative therapy. Among the 188 included patients, 39 patients had only undergone hysterectomy and 149 patients had undergone hysterectomy with systematic lymphadenectomy.

In all cases, the uterus was bisected along the lateral uterine walls, and pathologists used frozen slides to determine the histological subtype, grade, and depth of myometrial invasion. Pelvic lymphadenectomy was typically performed, and para-aortic lymphadenectomy was added for patients with > 50% myometrial invasion and/or a grade 3 tumor. Among patients who underwent surgery after 2004, the lymphadenectomy was omitted for patients with minor (< 5 mm) of myometrial invasion and a grade 1 tumor. Staging was defined based on the FIGO surgical staging system [Pecorelli, 2009], and the architectural grading was based on the degree of glandular differentiation [Creasman, 1989]. After the primary operation, some patients received adjuvant chemotherapy due to their risk of recurrence (e.g., a grade 3 tumor, > 50% myometrial invasion, cervical invasion, extrauterine invasion, or positive lymph nodes). Patients who were unavailable for follow-up were not included in the analyses of survival and recurrence.

For our analyses, we extracted the tumors' characteristics from the original pathology reports. All hematoxylin and eosin-stained slides from the primary tumor were also retrospectively reviewed to confirm the original diagnosis of adenocarcinoma and to determine the FIGO grade, histological subtype, and presence of LVSI. We classified the LVSI into four categories : L0, no lymphatic and vascular invasion ; L1, a single lymphatic or vascular invasion on the slide ; L2, multiple lymphatic or vascular invasions on the slide that did not fulfil the L3 criterion ; and L3, multiple lymphatic or vascular invasions in each microscopic view (100× magnification).

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RESULTS

Based on the 2008 FIGO criteria, we included 150 patients with stage Ⅰ disease, 6 patients with stage Ⅱ disease, and 32 patients with stage Ⅲ disease. Among 188 T1 endometrial cancer patients, 38 cases had extrauterine lesions, therefore they were diagnosed as stage Ⅱ or stage Ⅲ (Table 1). As shown in Table 2, pelvic and aortic node metastases were found in 19 (12.8%) of the 149 patients who underwent hysterectomy with systematic lymphadenectomy. Sixteen (29.6%) of the 54 patients with a T1b lesion exhibited pelvic lymph node metastasis (Table 2a). The lymph node-positive rate among cases with grade 2 tumors was 10.5% (4/38). Twenty-four patients with a T1a endometrium-limited lesion did not exhibit lymph node metastasis, whereas 1 of 19 T1a myometrial invasion cases exhibited lymph node metastasis (Table 2b). Table 2c shows that the patients with < 50% myometrial invasion, a grade 1 tumor, and no LVSI did not have lymph node metastases (0/50). In patients with < 25% myometrian invasion, lymph node metastasis was not detected even though LVSI was observed. Three patients (3.1%) among the 95 patients with a T1a lesion exhibited lymph node metastasis, and these 3 patients all exhibited LVSI and approximately 50% myometrial invasion (Table 2b, Table 3). The 39 patients who did not undergo systematic lymphadenectomy are alive and without recurrence (Table 4).

Table 1. T1 patients' clinical characteristics

		Lymphadenectomy (n=149)	No lymphadenectomy (n=39)	Total (n=188)
Median age		58 (24-89)	60 (42-86)	59 (24-89)
FIGO stage, No. (%)				
ⅠA (EM only)		21 (14.1)	14 (35.9)	35 (18.6)
ⅠA (EM<)		64 (43.0)	23 (59.0)	87 (46.3)
ⅠB		28 (18.8)	0	28 (14.9)
ⅡA		2 (1.3)	0	2 (1.0)
ⅡB		4 (2.7)	0	4 (2.1)
ⅢA		9 (6.0)	2 (5.1)	11 (5.9)
ⅢB		1 (0.6)	0	1 (0.5)
ⅢC		20 (13.4)	0	20 (10.6)
4		0	0	0
Tumor histotype, grade				
Endometrioid				
Endometrioid	G1	80 (53.7)	37 (94.9)	117 (62.2)
	G2	35 (23.5)	0	35 (18.6)
	G3	10 (6.7)	0	10 (5.3)
Adenosquamous	G1	4 (2.7)	1 (2.6)	5 (2.7)
	G2	0	0	0
	G3	1 (0.6)	0	1 (0.5)
Adenoacantoma	G1	7 (4.7)	1 (2.6)	8 (4.3)
	G2	3 (2)	0	3 (1.6)
	G3	0	0	0
Serous		5 (3.4)	0	5 (2.7)
Clear cell		3 (2)	0	3 (1.6)
Mixed cell		1 (0.6)	0	1 (0.5)

EM : endometrium

Table 2-a. Myometrial invasion and Lymph node positivity of T1 patients

Myometrial invasion (%)	Pelvic LN Positivity (%)	Para-aortic LN positivity (%)	Pelvic and para-aortic LN positivity (%)
≤25	0/57 (0)	0/7 (0)	0/57 (0)
25-50	2/38 (5.2)	1/5 (20)	3/38 (7.9)
50-75	5/16 (31.2)	0/5 (0)	5/16 (31.2)
75<	11/38 (28.9)	4/25 (16)	11/38 (28.9)
Total	18/149 (12.1)	5/42 (11.9)	19/149 (12.8)

LN : lymph node

Table 2-b. Histopathologic factors on lymph node metastasis of 149 T1 patients

	LN positivity (%)	T		Lymph-vascular space invasion
Endometrioid				
grade1	8/91 (8.8)	T1a (EM only)	0/16	L0 : 0/16
		T1a (EM<)	1/48	L0 : 0/34 L1 : 0/12 L2 : 1/2
		T1b	7/27	L0 : 2/15 L1 : 4/9 L2 : 0/1 L3 : 1/2
grade2	4/38 (10.5)	T1a (EM only)	0/5	L0 : 0/5
		T1a (EM<)	1/19	L0 : 0/10 L1 : 1/6 L2 : 0/3
		T1b	3/14	L0 : 0/2 L1 : 2/7 L2 : 1/3 L3 : 0/2
grade3	4/11 (36.4)	T1a (EM only)	0/0	
		T1a (EM<)	1/3	L1 : 1/2 unknown : 0/1
		T1b	3/8	L0 : 0/2 L1 : 0/2 L3 : 3/4
Serous	3/9 (33.3)	T1a (EM only)	0/3	L0 : 0/3
Clear cell		T1a (EM<)	0/1	L0 : 0/1
Mixed cell		T1b	3/5	L0 : 1/2 L1 : 1/1 L2 : 1/1 L3 : 0/1
Total	19/149 (12.8)			

LN : lymph node
EM : endometrium

Table 2-c. Histopathologic factors on lymph node metastasis of T1 grade1 patients

Myometrial invasion (%)	LN positivity (%)	Lymphvascular space invasion
≤25	0/41 (0)	L0 : 0/36 L1 : 0/4 L2 : 0/1 L3 : 0
25-50	1/23 (4.3)	L0 : 0/14 L1 : 0/8 L2 : 1/1 L3 : 0
50-75	3/9 (33.3)	L0 : 0/6 L1 : 2/2 L2 : 0 L3 : 1/1
75<	4/18 (22.2)	L0 : 2/9 L1 : 2/7 L2 : 0/1 L3 : 0/1
Total	8/91 (8.8)	

LN : lymph node

Table 3. Characteristics of patients with lymph node metastasis

Case	Age	Histotype	T	Myometrial invasion (%)	PLN meta	PAN meta	Outcome
1	54	Endomettrioid G2,L2	T1b	53	+	–	9Y NED
2	64	Adeniacantoma G1,L2	T1a	45	+	ND	8Y NED
3	51	Endometrioid G3,L3	T1b	86	+	+	7Y7M NED
4	46	Endometrioid G2,L1	T1a	45	+	ND	7Y7M NED
5	65	Endomettrioid G1,L1	T1b	96	+	–	7Y1M NED
6	57	Endomettrioid G2L1	T1b	97	+	–	6Y6M NED
7	68	Endomettrioid G1,L0	T1b	93	+	ND	6Y2M NED
8	79	Clear cell ,L1	T1b	79	+	ND	5Y10M NED
9	66	Endomettrioid G3,L3	T1b	99	+	–	1Y2M DOD
10	52	Endomettrioid G2,L1	T1b	100	+	+	5Y8M NED
11	72	Endomettrioid G3,L3	T1b	100	+	+	5Y8M NED
12	53	Endomettrioid G1,L1	T1b	67	+	ND	5Y1M NED
13	68	Endomettrioid G1,L1	T1b	75	+	–	2Y5M DOD
14	65	Endomettrioid G1,L0	T1b	76	+	ND	4Y NED
15	73	Endometrioid G3,L1	T1a	50	–	+	2Y11M AWD
16	67	Serous, L2	T1b	98	+	+	2M10M NED
17	69	Clear cell,L0	T1b	71	+	ND	2Y DOD
18	41	Endomettrioid G1,L3	T1b	60	+	–	3Y4M NED
19	69	Endomettrioid G1,L0	T1b	78	+	–	2Y7M NED

PLN : pelvic lymph node
PAN : para-aortic lymph node
ND : not done
NED : no evidence of disease
AWD : alive with disease
DOD : died of disease

Table 4. Metastatic site after operation for patients who did or did not lymphadenectomy

Metastatic site	Lymphadenectomy (n=149)	No lymphadenectomy (n=39)
Median follow up time (months)	62 (22-138)	52 (22-145)
No metastasis No. (%)	140 (94)	39 (100)
Metastasis No. (%)	9 (6)	0
Lymph node	3	0
Lung	2	0
Intraperitoneum	3	0
Vagina	1	0
Bone	1	0

DISCUSSION

Trimble *et al*. investigated the effect of pelvic lymph node sampling on survival among women with FIGO stage I–II endometrial cancer, and reported that it increased survival among patients with stage I disease and a grade 3 tumor, but not among patients with grade 1–2 tumors [Trimble, 1998]. Cragun *et al*. have also reported that the removal of > 11 pelvic lymph nodes improved overall survival and progression-free survival among patients with poorly differentiated tumors in apparent early-stage endometrial cancer [Cragun, 2005]. However, several other reports have described no significant differences in survival and recurrence among patients with stage I endometrial cancer who did and did not undergo lymphadenectomy [Bar, 1998 ; Candiani, 1990]. Furthermore, two randomized studies have reported no significant benefits in overall or recurrence-free survival after pelvic lymphadenectomy among patients with early endometrial cancer [ASTEC study group, 2009 ; Benedetti, 2008]. Onda *et al*. have reported that aortic and pelvic lymphadenectomy followed by adjuvant chemotherapy and radiotherapy improved survival among patients with positive aortic lymph nodes [Onda, 1997]. Thus, Chan *et al*. have suggested that the extent of lymph node dissection affects survival among women with intermediate/high-risk endometrioid uterine cancer, but not among low-risk patients [Chan, 2006].

Several authors have demonstrated that primary tumor diameter and lymphatic or vascular invasion significantly affect prognosis, and that the following factors are significant predictors of a poor prognosis : ≥50% myometrial invasion, non-endometrioid histology, lymphovascular invasion, absence of associated hyperplasia, and a tumor diameter of > 2 cm [Mariani *et al*., 2000 ; Mariani *et al*., 2008]. Furthermore, those authors have reported that lymphadenectomy can be omitted for patient with disease that is confined to the uterus, histological grade 1–2, a tumor diameter of ≤2 cm, ≤50% myometrial invasion, and no metastasis [Mariani *et al*., 2000 ; Mariani *et al*., 2008]. LVSI has also been reported as a risk factor in endometrial cancer, and para-aortic lymph node metastasis is significantly affected by histological type, tumor grade, depth of myometrial invasion, cervical invasion, LVSI, serosal/adnexal invasion, and pelvic lymph node metastasis [Chang, 2011 ; Karube, 2010].

Interestingly, 37.8% of patients who undergo lymphadenectomy experience postoperative lymphedema [Todo, 2010], which may indicate that pelvic lymphadenectomy and para-aortic lymphadenectomy are excessive in low-risk cases of endometrial cancer. In the

present study, we found that 3 patients with a T1a lesion exhibited lymph node metastasis, and all 3 patients also exhibited approximately 50% myometrial invasion and LVSI. In contrast, we did not observe lymph node metastasis in patients with T1a lesions and ≤ 25% myometrial invasion, a grade 1 tumor, and the absence of LVSI. Moreover, 9 (6%) of the 149 patients who underwent lymph node dissection experienced recurrence, and the cases with recurrence exhibited approximately 50% myometrial invasion. Thus, it is necessary to carefully select low-risk cases when we omit the lymph node dissection, as the pelvic lymph nodes are the most common site of extrauterine metastasis from endometrial cancer at the initial presentation. In our institution, the pathologists diagnose the histological subtype, grade, and depth of the myometrial invasion using frozen sections during surgery, and then we determine whether lymphadenectomy is appropriate (we omit it in cases of grade 1 endometrioid adenocarcinoma with minor myometrial invasion of less than 5 mm). Based on this approach, we did not observe recurrence in the 39 cases that did not undergo lymphadenectomy, which may indicate that our criteria for omitting systematic lymphadenectomy are appropriate. However, it may be difficult to pathologically diagnose LVSI during the surgery, due to the limited number of slides. Furthermore, we observed that 1 patient with a T1a/grade 1 tumor exhibited lymph node metastasis and LVSI. Therefore, if moderate myometrial invasion or LSIV are found after the surgery, it may be appropriate to consider additional treatment. Nevertheless, it may be possible to omit lymph node dissection in cases with slight myometrial invasion, and even in cases with a grade 2 tumor. For example, given that lymph node metastasis was only observed in 1 of the 24 stage IA cases, lymph node dissection might be omitted in cases with minor myometrial invasion, even if it is difficult to differentiate between grade 1 and 2 tumors during the surgery.

CONCLUSION

Patients with stage IA endometrial cancer and a grade 1 tumor with minor myometrial invasion could be treated without retroperitoneal lymphadenectomy. However, retroperitoneal lymph node dissection should be performed as usual if the patient is considered high-risk. Moreover, we recommend performing a larger prospective randomized controlled study to identify histopathological factors that could be used to indicate the omission of selective lymphadenectomy.

DECLARATION OF INTEREST STATEMENT

The authors have no conflicts of interest.

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