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ORIGINAL ARTICLE

Histologic grade and peritoneal cytology as prognostic factors in type 1 endometrial cancer

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Abstract
Background Prognostic clinicopathological factors for type 1 endometrial cancer are unknown and the purpose of the current study was to determine the independent prognostic variables for type 1 endometrial cancer.
Methods We performed a retrospective study of 168 patients with type 1 endometrial cancer primarily treated with comprehensive staging surgery. The median follow-up time was 68 (12–100) months. Independent risk factors for disease-free survival (DFS) and overall survival (OS) were determined using multivariate Cox regression models. Sub-group analysis of stage I was also performed. We also assessed the patterns of failure among patients with recurrences and investigated the associations with the prognostic variables determined by multivariate analysis.
Results Twenty patients (11.9%) had recurrence and 13 patients (7.7%) died of the disease overall. Multivariate analysis revealed that grade 2 (G2) histology ($p = 0.008$) and positive peritoneal cytology ($p = 0.001$) predicted the recurrent event in type 1 endometrial cancer. G2 histology ($p = 0.007$) and positive peritoneal cytology ($p = 0.003$) were also found to be independent risk factors for tumor-related deaths. Among stage I patients, G2 histology and positive peritoneal cytology were also independent prognostic variables for DFS and OS. Patients with G2 histology and/or positive peritoneal cytology were more likely to have recurrence at distant sites.
Conclusions G2 histology and positive peritoneal cytology were independent prognostic factors for DFS and OS in type 1 endometrial cancer.

Keywords Endometrial cancer · Prognostic factor · Type1 · Peritoneal cytology · Tumor grade

Introduction

Endometrial cancer is the most common gynecologic cancer in developed countries and ~11,000 women are newly diagnosed every year in Japan [1]. Endometrial cancer can be classified into two distinct groups—type 1 and type 2—based on the histologic features. These two types differ in both pathological and clinical profiles. Type 1 endometrial cancer is an estrogen-dependent cancer with endometrioid histology and arises from endometrial hyperplasia. Type 1 endometrial cancer has a good prognosis with >90% 5-year survival rate [2, 3]. Grade 1 (G1) and grade 2 (G2) endometrioid adenocarcinomas are included in type 1 endometrial cancer according to WHO Histological Classification criteria. Type 2 endometrial cancer is non-estrogen-dependent cancer with higher grade histology, including grade 3 (G3) endometrioid adenocarcinomas, uterine papillary serous carcinoma (UPSC) and clear-cell carcinoma (CC). Type 2 cancer typically arises in an atrophic endometrial background and often shows more aggressive features including deep myometrial invasions and lymph node spread [4]. Therefore, it carries an adverse prognosis with a recurrence rate of 50% and overall survival (OS) rate of 35% [3, 5]. In addition, type 1 and type 2 endometrial cancers have differences in molecular backgrounds [2, 6]. While type 1

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cancers are characterized by microsatellite instability and mutations in PTEN, PIK3CA, KRAS, and β-catenin, type 2 cancers are associated with genetic alteration in p53, p16, and E-cadherin.

Several previous studies had identified various independent prognostic variables for endometrial cancer, including age [7, 8], grade of tumor [8, 9], cervical stromal invasion [8, 10], depth of myometrial invasion [8], peritoneal cytology [11–14], and lymphovascular space invasion [8, 15]. However, few studies have examined the subsets of type 1 endometrial cancer. Considering the differences in clinical, pathological, and even molecular profiles as described above, we believe that it is preferable to investigate the prognostic factors of type 1 and type 2 individually.

Type 1 endometrial cancer is likely to receive less attention compared to type 2 because of its relatively better prognosis. However, type 1 cancer accounts for 90% of endometrial cancers and the incidence of type 1 has been increasing over recent years [3]. Therefore, the absolute number of type 1 recurrent cancer patients is actually considerable even though the recurrence rate is somewhat lower than type 2. Therefore, we should not underestimate both clinical and socio-economical impacts brought by type 1 endometrial cancer and it is of great importance to identify the prognostic factors to predict recurrence and survival of type 1 cancer.

The objective of the current study was to evaluate the association between clinicopathological features and outcomes in type 1 endometrial cancer and to determine the independent prognostic variables for recurrence and survival.

Patients and methods

We conducted a retrospective observational study of surgically treated type 1 endometrial cancers at Kyorin University Hospital, the Japanese Red Cross Musashino Hospital, and the Tokyo Dental College Ichikawa General Hospital between January 2007 and December 2010. This study was approved by the institutional review boards and all subjects provided informed consent regarding research use of their medical information.

We reviewed each patient's demographic data and pathological features of the tumor from their medical records. Demographic data included age, body mass index (BMI), menopause, and parity at the time of initial surgery. The times of the initial surgery, the last follow-up, the first recurrence, and death from any cause were reviewed for each subject. Recurrence was determined when the relapse sites were documented radiographically, by physical examination, or histologically. We also collected information regarding the initial treatments including pelvic lymph node dissection and adjuvant chemotherapy.

The pathological features included tumor grade (G1 or G2), depth of myometrial invasion (MI), lymphovascular space invasion (LVSI), peritoneal (washing) cytology, pelvic lymph node metastasis, and extrauterine diseases. Histological types were evaluated according to the WHO International Histological Classification of Tumors criteria [16]. Depth of MI was categorized as superficial (<1/2) or deep (≥1/2). LVSI was defined as the presence of tumor cells within or attached to the wall of a blood vessel or lymphatic space. Extrauterine disease included metastasis or dissemination in uterine serosa and adnexa.

We included patients with endometrial cancers who were primarily treated with comprehensive staging surgery and diagnosed histologically as G1 or G2 endometrioid adenocarcinoma. Pathological diagnosis was confirmed at each institution by experienced pathologists certified by the Japanese Society of Pathology. We classified the stages of the subjects based on FIGO 2008 criteria [17], which staged patients with disease confined to the uterine corpus with positive peritoneal cytology as stage I.

Primary surgery consisted of total abdominal hysterectomy and bilateral salpingo-oophorectomy. A washing peritoneal cytology specimen was routinely obtained during surgery. Systematic pelvic lymph node dissection and postoperative adjuvant chemotherapy were indicated according to the risk assessment in the treatment guidelines of the Japan Society of Gynecologic Oncology (JSGO) [18]. We did not include cases with para-aortic lymph node dissection.

Patients with G3 endometrioid adenocarcinoma, UPSC and CC were excluded. According to previous articles reporting clinical and molecular similarities of G3 endometrioid adenocarcinoma with UPSC and CC [19, 20], we categorized G3 endometrioid adenocarcinoma as type 2. Patients with preoperative chemotherapy were not eligible. Patients who were lost-to-follow-up within 5 years from the initial surgery were not included in the study.

Disease-free survival (DFS) and OS referred to the date of the initial surgery and were calculated according to the Kaplan–Meier method. The relationship between each variable (age, BMI, menopause, parity, tumor grade, depth of MI, LVSI, peritoneal cytology, pelvic lymph node metastasis, extrauterine disease, pelvic lymph node dissection) and DFS or OS was evaluated univariately by log-rank tests. All variables with p values of <0.05 were include in the Cox proportional hazards model to determine the independent prognostic factors for DFS and OS in multivariate regression analysis. The estimated hazard ratios (HRs) for DFS and OS were calculated and reported with 95% confidence intervals (CI). We also conducted sub-group analysis

among stage I subjects to determine the prognostic factors in the patients with disease confined to the uterus.

We assessed the patterns of failure among the patients with recurrence and investigated the associations with the prognostic variables determined by multivariate analysis. Local recurrences include vaginal or pelvic recurrence (side wall or pelvic lymph nodes). Peritoneal, hematogenous, and lymph node recurrences outside the pelvis were considered as distant recurrences. We also examined the incidence of retroperitoneal lymph node metastasis. The relationships between each prognostic factor and the rate of recurrences were assessed using Fisher's exact test.

A value of $p < 0.05$ was taken to indicate a significant test result. Statistical evaluation was performed using a statistics program (SPSS Statistics ver21, IBM®, Japan).

Results

A total of 190 patients with type 1 endometrial cancers were surgically treated in three institutions during the study period. Twenty-two of these patients were lost-to-follow-up within 5 years from the initial surgery, leaving 168 patients for data analysis. Of those patients, 142 were classified as FIGO stage I disease according to FIGO 2008 criteria. The median follow-up time was 68 months (range 12–100 months). The demographic data and the pathological features of all subjects and stage I are described in Table 1. The treatments and the clinical outcomes are shown in Table 2.

Table 1 Patient demographics and tumor characteristics

		All stages $N = 168$	Stage I $N = 142$
Age (years)	<60	101 (60.1)	87 (61.2)
	≥60	67 (39.9)	55 (38.8)
Post-menopause		118 (70.2)	101 (71.1)
Nullipara		44 (26.1)	35 (24.6)
BMI (kg/m^2)	<25	112 (66.7)	94 (66.2)
	≥25	56 (33.3)	48 (33.8)
Stage	IA	106 (63.1)	
	IB	36 (21.4)	
	II	36 (8.3)	
	IIIA	3 (1.8)	
	IIIC	9 (5.4)	
Tumor grade	G1	125 (74.4)	107 (75.4)
	G2	43 (25.6)	35 (24.6)
Depth of MI	<1/2	113 (67.3)	105 (73.9)
	≥1/2	55 (32.7)	37 (26.1)
Peritoneal cytology	(−)	133 (79.2)	117 (82.3)
	(+)	28 (16.7)	18 (12.7)
LVSI	(−)	130 (77.4)	118 (83.1)
	(+)	36 (21.4)	24 (16.9)
Cervical involvement	(−)	153 (91.0)	
	(+)	35 (9.0)	
Pelvic lymph node metastasis	(−)	92 (54.2)	
	(+)	8 (4.8)	
Extrauterine disease	(−)	164 (97.6)	
	(+)	4 (2.4)	

Values are number (%)

BMI body mass index, *MI* myometrial invasion, *LVSI* lymphovascular space invasion

Recurrence

Twenty patients (11.9%) had recurrence overall during the follow-up period. The median time to recurrence was 16 (0–36) months. Among the variables, we found that peritoneal cytology ($p < 0.001$), tumor grade ($p = 0.004$), depth of MI ($p = 0.004$), and extrauterine disease ($p < 0.001$) were significantly related to recurrence in univariate analysis. In multivariate analysis using the Cox proportional hazards model, tumor grade G2 (HR 3.31; 95% CI 1.37–7.98) and positive peritoneal cytology (HR 4.80; 95% CI 1.98–11.6) were detected as independent predictors of recurrent events (Table 3). Kaplan–Meier estimated survival curves of DFS with respect to peritoneal cytology and tumor grade are described in Fig. 1a, b. Of the patients with positive peritoneal cytology, 5-year DFS was 67.9% compared to 91.7% with negative peritoneal cytology. Of the patients with G2, 5-year DFS was 76.7% while that of G1 was 92.0%.

Of 142 patients with stage I endometrial cancer, 13 (9.2%) had recurrence and the median time to recurrence was 19 (0–32) months. In the sub-group analysis of stage I patients, peritoneal cytology ($p = 0.003$), tumor grade ($p = 0.001$), and depth of MI ($p = 0.013$) were found to be significantly related to DFS in univariate analysis. In multivariate analysis, tumor grade G2 (HR 5.70; 95% CI 1.65–21.6) and positive peritoneal cytology (HR 7.58; 95% CI 2.19–26.2) were detected as independent risk factors for recurrence (Table 4). Of stage I patients with positive peritoneal cytology, 5-year DFS was 72.2% compared to 93.2% with negative peritoneal cytology. Of stage I patients with G2, 5-year DFS was 77.1% while that of G1 was 95.3%.

Survival

Fifteen patients (8.9%) died during the follow-up period. Of the patients who died during the follow-up, 13 died of disease and two patients died of other causes. The overall death rate from disease in the current study was 7.7% (13/166). The medium time to death after the initial surgery was 36 (12–100) months.

Table 2 Treatments and clinical outcomes

		All stages $N = 168$	Stage I $N = 142$
Treatment			
Pelvic lymph node dissection	(−)	68 (40.5)	60 (42.3)
	(+)	100 (59.5)	82 (58.7)
Adjuvant chemotherapy	(−)	106 (63.1)	101 (71.1)
	(+)	62 (36.9)	41 (28.9)
Outcomes			
Follow-up (months)		68 (12–100)	68 (12–100)
Overall recurrence		20 (11.9)	13 (9.2)
Death from disease		13 (7.7)	9 (6.3)
Death from any cause		15 (8.9)	11 (7.7)

Values are median (range) or number (%)

Table 3 Multivariate analysis of prognostic factors for DFS and OS (All stages)

Variable	DFS		OS	
	Hazard ratio	*p*	Hazard ratio	*p*
Positive peritoneal cytology	**4.80 (1.98–11.6)**	**0.001**	**7.80 (2.03–30.0)**	**0.003**
Grade 2 (vs Grade1)	**3.31 (1.37–7.98)**	**0.008**	**6.74 (1.70–26.8)**	**0.007**
Depth of MI ≥1/2 (vs <1/2)	1.99 (0.74–5.35)	0.18	2.06 (0.44–9.58)	0.36
Extrauterine disease	2.04 (0.48–8.64)	0.33	1.24 (0.22–6.96)	0.80
Positive LVSI			1.64 (0.44–6.20)	0.45

Values in bold setting are statistically significant

DFS disease-free survival, *OS* overall survival, *MI* myometrial invasion, *LVSI* lymphovascular space invasion

Among the variables, we found that peritoneal cytology ($p < 0.001$), tumor grade ($p < 0.001$), depth of MI ($p = 0.001$), LVSI ($p = 0.013$), and extrauterine disease ($p < 0.001$) were significantly related to death from disease in univariate analysis. In multivariate analysis using the Cox proportional hazards model, tumor grade G2 (HR 6.74; 95% CI 1.70–26.8) and positive peritoneal cytology (HR 7.80; 95% CI 2.03–30.0) were found to be independent risk factors of tumor-related death (Table 3). Kaplan–Meier estimated survival curves for OS with respect to peritoneal cytology and tumor grade are described in Fig. 1c, d. Of the patients with positive peritoneal cytology, 5-year DFS was 75.0% compared to 96.9% with negative peritoneal cytology. Of the patients with G2, 5-year DFS was 81.0 while that of G1 was 97.6%.

Among 142 patients with stage I endometrial cancer, 9 (6.3%) died of disease during the follow-up period. The medium time to death after the initial surgery was 43 (12–100) months. In the sub-group analysis of stage I endometrial cancers, peritoneal cytology ($p < 0.001$), tumor grade ($p < 0.001$), and depth of MI ($p = 0.002$) were found to be significantly related to OS in univariate analysis. In multivariate analysis, tumor grade G2 (HR 36.9; 95% CI 2.60–523.8) and positive peritoneal cytology (HR 37.0; 95% CI 3.60–381.3) were detected as independent risk factors for death from disease (Table 4). Of the patients with positive peritoneal cytology, 5-year DFS was 77.8% compared to 97.4% with negative peritoneal cytology. Of the patients with G2, 5-year DFS was 79.4% while that of G1 was 99.1%.

Patterns of recurrence

The relationships between prognostic variables (tumor grade and peritoneal cytology) and patterns of recurrence are described in Table 5. Although it did not reach statistical significances, positive peritoneal cytology is less associated with local recurrence and more likely to predict distant failures. Patients with G2 endometrioid cancer were more associated with distant failures and retroperitoneal lymph node metastasis, which were not statistically significant.

Discussion

In the current study, tumor grade and peritoneal cytology were determined as independent predictive factors for both DFS and OS in type 1 endometrial cancer. In sub-group analysis of stage I, tumor grade and peritoneal cytology also showed prognostic significance.

Tumor grade has been previously reported as a prognostic factor in several studies [8, 9, 14, 15, 21]; however, most of them included G1 and G2 patients together in the same group, in comparison with G3. G3 endometrioid cancer, categorized as type 2 cancer, has been known to have aggressive features and a much worse prognosis. On the other hand, the difference between G1 and G2 usually receives less attention because of the relatively better outcomes. However, compared with G1, it has been reported that G2 endometrioid cancer was actually more associated with other high-risk factors including myometrial and vessel invasions and had a worse prognosis, compared with G1 [9]. The results of our study confirmed the prognostic significance of tumor grade in type 1 cancer and we should therefore not underestimate the risk of G2 endometrioid cancer even in stage I cases.

The prognostic value of peritoneal cytology as an independent risk factor in endometrial cancer has been controversial. Positive peritoneal cytology is found in ~11% of endometrial cancer patients [20, 22]. The incidence

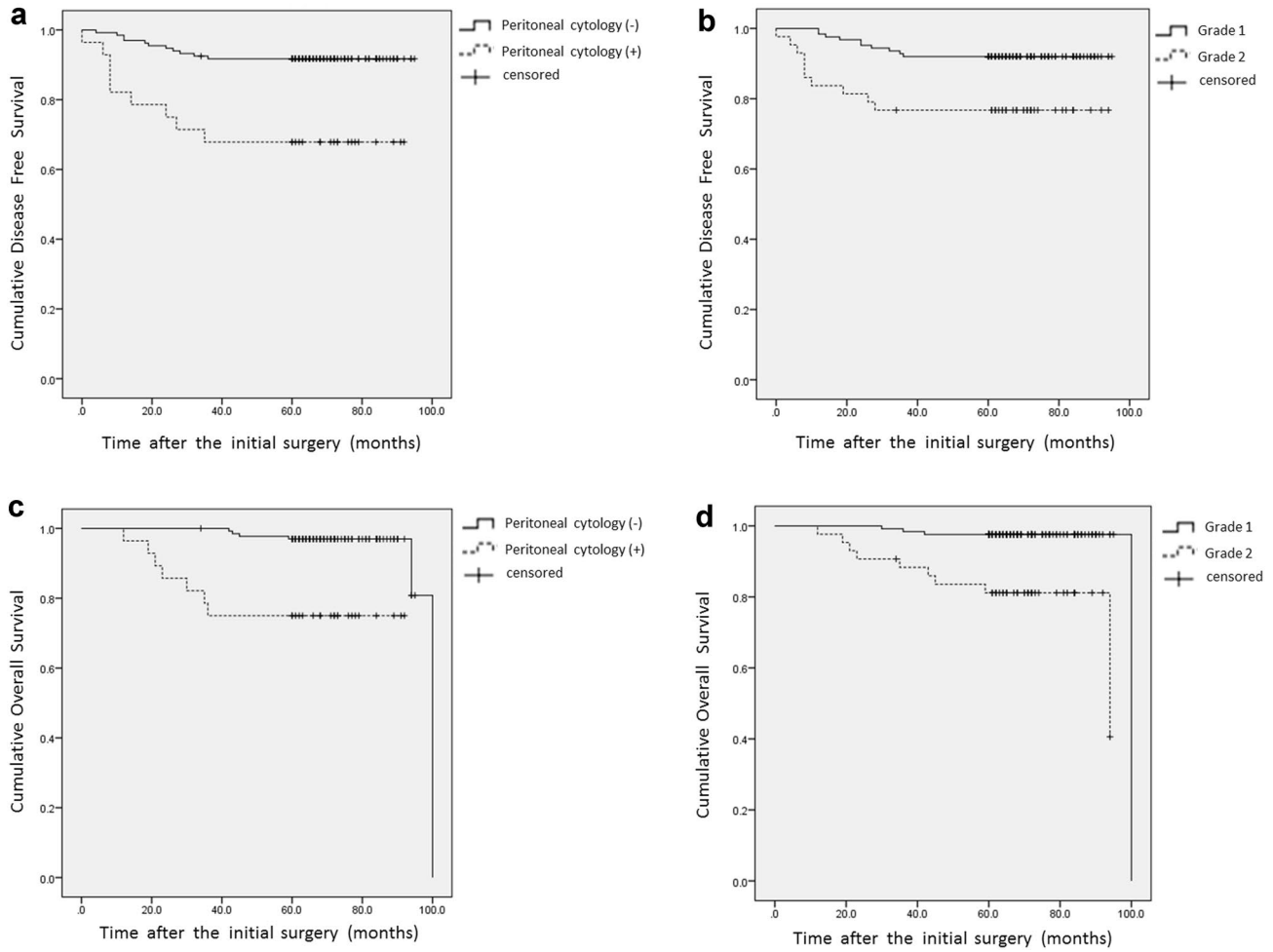

Fig. 1 Kaplan−Meier survival curves for prognostic factors. **a** Disease-free survival stratified by peritoneal cytology. **b** Disease-free survival stratified by tumor grade. **c** Overall survival stratified by peritoneal cytology. **d** Overall survival stratified by tumor grade

Table 4 Multivariate analysis of prognostic factors for DFS and OS (Stage I)

Variable	DFS		OS	
	Hazard ratio	*p*	Hazard ratio	*p*
Positive peritoneal cytology	**7.58 (2.19–26.2)**	**0.001**	**37.0 (3.60–381.3)**	**0.002**
Grade 2 (vs Grade1)	**5.70 (1.65–21.6)**	**0.006**	**36.9 (2.60–523.8)**	**0.008**
Depth of MI ≥1/2 (vs <1/2)	2.26 (0.63–8.10)	0.21	2.1 (0.37–11.7)	0.40

Values in bold setting are statistically significant

DFS Disease free survival, *OS* overall survival, *MI* myometrial invasion, *LVSI* lymphovascular space invasion

of positive cytology is highly increased (24–100%) in advanced cases with extrauterine disease [11, 23–25], and peritoneal cytology was found to be an independent adverse prognostic factor among those advanced patients.

However, with regard to patients with disease confined to the uterus, the significance of peritoneal cytology is still under discussion. Several studies have reported that peritoneal cytology does not serve as a prognosis factor for uterine-confined disease [19, 26–28]. Takeshima et al. concluded in their study that positive peritoneal cytology was not a negative prognostic indicator itself. They reported that positive cytology only potentiated other prognostic factors such as deep myometrial invasion and poorly differentiated tumor among stage I cancers [21]. Based on those reports, the result of peritoneal cytology was excluded from the variables of staging in uterine endometrial cancer in the revised FIGO 2008 criteria [17].

On the other hand, there have been some studies indicating the importance of peritoneal cytology as a prognostic factor in patients with disease confined to the uterus [12–14]. Saga et al. investigated the prognostic significance of peritoneal cytology among endometrioid cancer patients who underwent full surgical staging including

Table 5 Recurrence patterns and prognostic factors

Recurrence pattern	Peritoneal cytology			Tumor grade		
	(+) ($N = 9$)	(−) ($N = 11$)	p	Grade 2 ($N = 10$)	Grade 1 ($N = 10$)	p
Local	1 (11.1)	5 (45.6)	0.157	2 (20)	4 (40)	0.628
Distant	9 (100)	7 (62.7)	0.094	9 (90)	7 (70)	0.334
Retroperitoneal lymph node	3 (33.3)	2 (18.2)	0.617	4 (40)	1 (10)	0.303

Values are number (%)

retroperitoneal lymph node dissection [13]. They found positive peritoneal cytology and histologic grade as independent prognostic factors on multivariate analysis. Our study which included only type 1 endometrial cancer also revealed that positive peritoneal cytology, as well as tumor grade, was an independent prognostic factor for DFS and OS both in all stages and stage I.

We speculate that one of the reasons for the conflicting results among the studies evaluating prognostic significance of peritoneal cytology was the distribution of histologic types in the included subjects. As described above, the prognosis of type 2 endometrial cancer is extremely poor with a 5-year survival rate of <50% [3]. Therefore, the clinical outcomes might be strongly influenced by the aggressive features of type 2, when type 2 accounted for a certain portion of the study subjects, probably regardless of the positive peritoneal cytology. On the other hand, our study focused on type 1 endometrial cancer. Including the relatively homogenous subjects, we found the presence of malignant cells in peritoneal (washing) fluids played an important role in predicting the prognosis. The positivity rate of peritoneal cytology in our study was 12.7%, which is consistent with other previous reports [3]. We believe peritoneal cytology provides essential information in predicting the prognosis of type 1 endometrial cancer.

Although our study did not show statistical significances, positive peritoneal cytology and G2 histology were more related to recurrences at distant sites (Table 5). Previous studies have also reported an increased incidence of distant recurrences when the peritoneal cytology was positive [14, 26, 29]. Patients with G2 endometrioid cancer are more likely to relapse in the setting of retroperitoneal lymph nodes, which is consistent with a retrospective study by Gadducci et al. [8].

According to the JSGO treatment guidelines [18], pelvic lymph node dissection and adjuvant chemotherapy are optional for stage I endometrial cancer with type 1 histology without any other pathological risk factors. Indeed, systematic pelvic lymph node dissection was not performed in one-third (11/35) of G2 patients (stage I) in our study and two of the patients (18.2%) had recurrence. Sixteen patients (45.7%) did not receive adjuvant chemotherapy, but only one (6.3%) had relapse. Five of 18 patients (27.8%) with positive peritoneal cytology in stage I did not undergo pelvic lymph node dissection and one of them (20%) experienced recurrence. Of 6 patients without adjuvant chemotherapy in the positive peritoneal cytology group, none had a recurrent event. Although the number of the subjects is limited to draw a definitive conclusion, our results implied that the completion of systemic pelvic lymph node dissection may contribute to reducing the recurrence rate in type 1 endometrial cancer. Taskiran et al. reported that positive peritoneal cytology was an independent predictive factor for positive retroperitoneal nodal disease [30]. There have also been some studies reporting a significant association between omental metastasis and positive peritoneal cytology [31, 32]. Therefore, in the case of G2 histology and/or positive peritoneal cytology among type 1 endometrial cancers, we should consider performing comprehensive surgery in order to investigate the presence of extrauterine disease and to determine accurate surgical staging.

We acknowledge several limitations in the current study. First, due to the retrospective nature of the study, we could not completely eliminate some variations in therapeutic strategies between the institutions, including retroperitoneal lymph node dissection and adjuvant chemotherapy. However, the treatment decisions were made according to the JSGO treatment guidelines in all institutions. Second, the number of subjects included in the current study was relatively small compared with previous retrospective studies. However, we believe that the patients in our study sufficiently represented the type 1 endometrial cancer population since their background features and their prognosis did not differ from previously reported results. In addition, 42.3% of the patients classified as stage I in our study did not actually undergo lymph node dissection (Table 2), and they could have possibly been under-staged without lymph node assessment. However, among 82 patients without lymph node dissection, only one (1.2%) had recurrence in the retroperitoneal lymph node setting. Therefore, we believe that our subjects were sufficiently equivalent to complete surgical staging for stage I and that the completion rate of lymph node dissection did not affect the clinical outcomes. To confirm the clinical significance of the results of our retrospective study, a larger scale prospective study with designated therapeutic protocols should be conducted.

Subjects with risk factors (G2 and/or positive peritoneal cytology) should be randomized to observation or additional treatments (retroperitoneal lymph node dissection and/or adjuvant chemotherapy) after the initial surgeries, and progression-free survival and OS of the subjects should be evaluated as study outcomes.

In conclusion, tumor grade and peritoneal cytology were determined to be independent predictive factors for prognosis in type 1 endometrial cancers. Type 1 endometrial cancer shows comparatively good prognosis and we are likely to underestimate its potential risk of recurrence. However, 11 patients (55%) out of twenty with recurrence died within 5 years in our study. Even in stage I, 53.8% (7/13) did not survive 5 years after initial recurrence. Therefore, we should not be optimistic about the prognosis once the disease relapses, even in type 1 endometrial cancer. In the case of G2 histology and/or positive peritoneal cytology, we should be aware of an increased risk of adverse prognosis and determine the therapeutic strategy against type 1 endometrial cancers.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest, sources of financial support, corporate involvement, or patent holdings to disclose.

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