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Prognostic factors for tumor recurrence in endometrioid endometrial cancer stages IA and IB

Kyung Hee Han, MD[a,b], Hee Seung Kim, MD[b,c], Maria Lee, MD[b], Hyun Hoon Chung, PhD[b], Yong Sang Song, PhD[b,c,d,*]

Abstract

Risk grouping for treatment and follow-up strategy of early stage endometrial cancer is confusing to apply in clinical conditions. We investigated the stage-based prognostic factors for tumor recurrence in stage I endometrial cancer with endometrioid histology (EEC).

The medical records of women diagnosed with endometrial adenocarcinoma between 1993 and 2013 were retrospectively reviewed. In 521 patients with International Federation of Gynecology and Obstetrics (FIGO) stage I EEC were included. The baseline patient characteristics were analyzed with the chi-square test and Fisher's exact tests. A multivariate analysis with a Cox proportional hazard model and logistic regression were performed to identify the prognostic factors for recurrence-free survival (RFS) in FIGO stage I EEC.

The median follow-up period for the included patients was 74.6 months (3.1–264.9 months). Tumor recurrence occurred in 30 patients (5.8%) with a median time span of 22.85 months (2.2–124.7 months). Only 2 factors among the conventional adverse risk factors, including myometrial invasion and histologic grade, affected tumor recurrence in stage I EEC ($P = .003$ and $P = .003$, respectively). Myometrial invasion was an independent prognostic factor for RFS in stage IA EEC via multivariate analysis ($P = .005$). In stage IB EEC, the histologic grade was an independent prognostic factor for RFS. The median RFS of stage IB EEC was 156.0 months in grade 1, 120.0 months in grade 2, and 105.9 months in grade 3 ($P = .006$).

Within stage I EEC, the prognostic factors for tumor recurrence were different between stages IA and IB. Myometrial invasion comprised the prognostic factor in stage IA, whereas the histologic grade comprised the prognostic factor in stage IB.

Abbreviations: CI = confidence interval, EEC = endometrial cancer with endometrioid histology, FIGO = International Federation of Gynecology and Obstetrics, HR = hazard ratio, LVSI = lymphovascular space invasion, RFS = recurrence-free survival.

Keywords: endometrial neoplasms, endometrioid carcinoma, prognosis, recurrence, survival

1. Introduction

Endometrial cancer is the fifth most common female cancer in western counties, and its incidence has doubled in a decade until 2013 in Korea, from 4.5 to 8.8 per 100,000.[1,2] Most endometrial cancers comprise endometrioid endometrial cancer (EEC), especially in the early stage.[3] Many previous studies have reported the survival of endometrial cancer; however, few studies have addressed the pure endometrioid histology in the International Federation of Gynecology and Obstetrics (FIGO) stage I endometrial cancer.

In previous reports, early stage endometrial cancer has typically been divided into low, intermediate, and high risk groups. However, these risk grouping did not implicate the staging system.[4] Although the FIGO system presents the tumor extent of early stage endometrial cancer, risk groups were classified using many possible factors that affect survival. Moreover, there was noticeable disparity in the criteria used for allocating patients into 3 risk groups among studies. Each study has applied its own criteria for risk group regarding patient age, histologic grade, myometrial invasion, and lymphovascular space invasion (LVSI).[3,5,6] Although many clinical trials tried to establish the evidence for adjuvant therapy in early stage endometrial cancer, there is yet a controversy whether to add adjuvant chemotherapy and/or adjuvant radiation therapy to the staging operation or not.[7]

The European Society for Medical Oncology-European Society of Gynaecological Oncology-European Society of Radiotherapy and Oncology guideline or the National Comprehensive Cancer Network guideline presents various options for adjuvant treatment in FIGO stage I EEC according to myometrial invasion, histologic grade, and adverse risk factors including age, LVSI, tumor size, and lower uterine segment or surface cervical glandular involvement.[8] However, there is limited evidence for the number and weight of these adverse risk factors.

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[a] Department of Obstetrics and Gynecology, Seoul National University Hospital Healthcare System Gangnam Center, [b] Department of Obstetrics and Gynecology, [c] Cancer Research Institute, Seoul National University College of Medicine, [d] Major in Biomodulation, World Class University, Seoul National University, Seoul, Republic of Korea.

[*] Correspondence: Yong Sang Song, Yong Sang Song, Department of Obstetrics and Gynecology, Seoul National University College of Medicine, 101 Daehak-Ro, Jongno-Gu, Seoul 110-744, Republic of Korea (e-mail: yssong@snu.ac.kr).

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To minimize confusion in clinical applications for postoperative treatment and to determine a staging-based simple guideline, we investigated the prognostic factors for tumor recurrence in stage I EEC.

2. Methods

2.1. Patients

We retrospectively reviewed the medical records of patients diagnosed with endometrial cancer at Seoul National University Hospital between 1993 and 2013 following Institutional Review Board approval. Women who had fatal comorbidity to affect survival, took hormone therapy for fertility sparing without surgery, or were diagnosed with uterine sarcoma were excluded. Of the 705 patients who undertook operation including total hysterectomy and bilateral salpingo-oophorectomy for endometrial cancer, 551 patients were stage I. Finally, 521 patients with pathologically proven endometrioid histology in stage I endometrial cancer were included. Pelvic or para-aortic lymph node dissection was omitted when there was no preoperative evidence of lymph node metastasis in serum CA 125 level and imaging test such as computed tomography or magnetic resonance imaging. When there were lymph nodes highly suspicious of metastasis on preoperative imaging studies, they were evaluated during operation. Adjuvant therapy was selected from brachytherapy, external-beam radiation therapy, chemotherapy, or concurrent chemoradiation based on the known risk factors by a gynecologic oncologist. Tumor recurrence was confirmed via clinical pelvic exam or imaging study during regular check-up or following the occurrence of symptoms, such as vaginal spotting or abdominal discomfort.

2.2. Statistical analysis

Clinical and pathologic characteristics were analyzed with Student's *t* test, chi-square test, or Fisher's exact test. To calculate the survival function as a hazard ratio (HR) and confidence interval (CI), we used univariate and multivariate Cox's proportional hazard models and the Kaplan–Meier method with the log-rank test. The recurrence-free survival (RFS) indicates the time from diagnosis date to recurrence or the last follow-up date without recurrence. Statistical analyses were performed with SPSS 21 software (SPSS, Inc., Chicago, IL). A *P*-value less than .05 was considered statistically significant.

3. Results

3.1. Patients' characteristics

The median age of the patients with stage I EEC was 52 years (19–84 years). The patient numbers in the age group less than 52 years were 255 in stage IA EEC and 15 in stage IB EEC (59.3% and 16.5%, respectively, $P < .001$). The known adverse risk factors were different between stages IA EEC and IB EEC (Table 1). More patients in stage IB EEC had at least 1 of the adverse risk factors, such as high histologic grade, large tumor size, positive LVSI, and positive lower uterine segment involvement or surface cervical glandular involvement, than patients in stage IA EEC (95.6% vs 55.7%; $P < .001$). Lymph node dissection was not related to subclassification within stage I EEC ($P = .64$).

Table 1

Clinical and pathologic characteristics of FIGO stage I endometrioid endometrial cancer.

Characteristics	Stage IA (n = 430, %)	Stage IB (n = 91, %)	*P*
Age, y			
< 65	396 (92.1)	66 (72.5)	<.001
≥ 65	34 (7.9)	25 (27.5)	
Grade			
1	301 (70.0)	39 (42.9)	
2	109 (25.3)	35 (38.5)	<.001
3	20 (4.7)	17 (18.7)	
Myometrial invasion			
No	220 (51.2)	0	
< 1/2 of myometrium	210 (48.8)	0	<.001
≥ 1/2 of myometrium	0	91 (100%)	
Size of tumor, cm			
< 2	217 (50.9)	15 (16.5)	<.001
≥ 2	209 (49.1)	76 (83.5)	
Lymphovascular space invasion			
Negative	399 (93.4)	56 (61.5)	<.001
Positive	28 (6.6)	35 (38.5)	
Lower uterine involvement			
Negative	402 (94.1)	79 (86.8)	.023
Positive	25 (5.9)	12 (13.2)	
Lymph node dissection			
No dissection	67 (15.6)	16 (17.6)	
Pelvic lymph node	311 (72.3)	51 (56.0)	.001
Pelvic and paraaortic node	52 (12.1)	24 (26.4)	
Adjuvant therapy			
No	374 (87.0)	31 (34.1)	
Radiation only	45 (10.5)	47 (51.6)	<.001
Concurrent chemoradiation	11 (2.6)	13 (14.3)	

FIGO = International Federation of Gynecology and Obstetrics.

3.2. Recurrence

The median follow-up period was 74.6 months (3.1–264.9 months), and 30 patients exhibited tumor recurrence in stage I EEC (5.7%). Of the recurrent cases, the median interval period between diagnosis and tumor recurrence was 22.9 months (2.2–124.7 months). Over 5 years after diagnosis, 4 patients experienced tumor recurrence (14.7%). In our study, they had no common characteristics with the exception of positive myometrial invasion. The presence or number of adverse risk factors including LVSI was not associated with tumor recurrence in stage I EEC ($P = .44$ or $P = .25$, respectively). The presence or absence of adjuvant therapy had no significant effect on tumor recurrence ($P = .17$). In addition, the method of adjuvant treatment was not a risk factor for tumor recurrence in stage I EEC ($P = .21$).

Recurrence that occurred in the pelvic lymph node, paraaortic lymph node, vagina, adnexa, or pelvic serosa was defined as locoregional recurrence, whereas distant metastasis included inguinal lymph node, intraperitoneal disease, lung, liver, and bone. The patients with stage IB exhibited a tendency for distant metastasis; however, the difference in the recurrence site between stages IA and IB was not significant ($P = .06$). Adjuvant therapy was not associated with the recurrence site in stages IA and IB ($P = .37$ and $P = .45$, respectively).

Two factors, myometrial invasion and histologic grade, were associated with tumor recurrence in stage I EEC ($P < .001$ and $P = .01$, respectively). The multivariate logistic regression analysis indicated the risk factors for tumor recurrence, including myometrial invasion in stage IA EEC ($P = .003$) and histologic grade in stage IB EEC ($P = .02$). LVSI was not associated with tumor recurrence in the multivariate analysis in stages IA or IB EEC ($P = .83$ and $P = .19$, respectively).

Table 2

Cox's proportional hazard models for prognostic factors of FIGO stage I endometrioid endometrial cancer.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	Adjusted HR	95% CI	P
Recurrence-free survival						
Age≥ 65 y	1.441	0.502–4.133	.497	0.603	0.201–1.807	.366
Grade 1	2.345	1.033–5.324	.042	5.101	1.711–15.209	.003
No myometrial invasion	7.651	1.749–33.467	.007	10.109	2.186–46.746	.003
Tumor size≥ 2cm	1.612	0.750–3.467	.222	0.702	0.302–1.629	.410
Positive LVSI	2.310	0.990–5.390	.053	0.570	0.204–1.595	.285
Lower uterine involvement	1.040	0.248–4.370	.957	0.621	0.135–2.857	.541
Lymph node dissection	1.031	0.381–2.790	.953	0.539	0.179–1.620	.271
Adjuvant therapy	2.422	0.720–8.152	.153	0.301	0.062–1.470	.138

CI = confidence interval, FIGO = International Federation of Gynecology and Obstetrics, HR = hazard ratio; LVSI = lymphovascular space invasion.

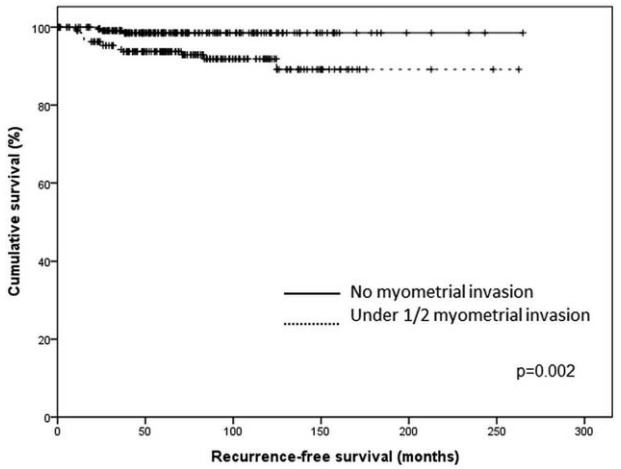

Figure 1. Kaplan–Meier curves of recurrence-free survival according to myometrial invasion in FIGO stage IA endometrioid endometrial cancer. Solid line: no myometrial invasion; dot line: under half of myometrial invasion. FIGO = International Federation of Gynecology and Obstetrics.

3.3. Predictors of survival

In the overall stage I EEC, myometrial invasion and histologic grade were prognostic factors for tumor recurrence in the multivariate analysis with Cox's proportional hazard model ($P = .003$ and $P = .003$, respectively, Table 2). LVSI exhibited a tendency to connect with RFS using the univariate analysis ($P = .05$). However, none of the conventional adverse risk factors including LVSI were associated with RFS using the multivariate analysis.

Figure 1 indicates the RFS of stage IA EEC according to myometrial invasion using the Kaplan–Meier method with the log rank test ($P = .002$). In stage IA EEC, 10 years of RFS occurred in 99% of the cases without myometrial invasion and 89% of the cases with less than half of myometrial invasion. In stage IA EEC, multivariate analysis demonstrated that no myometrial invasion prolonged RFS compared with less than half myometrial invasion ($P = .01$, Table 3).

Figure 2 indicates the RFS of stage IB EEC by histologic grade. The 5-year RFS of the patients with stage IB EEC was 94% in grade 1, 79% in grade 2, and 74% in grade 3 ($P = .01$). Of the patients with stage IB EEC, the histologic grade was the only prognostic factor of recurrence using multivariate analysis ($P = .01$, Table 4).

4. Discussion

The application of additional treatment, including adjuvant radiation, chemotherapy, or observation, followed by surgery has been a controversial issue in early stage endometrial cancer.[9,10] Current management guidelines have defined risk groups based on myometrial invasion, histologic grade, and LVSI. In addition, alleged adverse risk factors, including age, positive LVSI, large tumor size, and positive lower uterine segment or surface cervical glandular involvement, have been used to guide decisions regarding adjuvant therapy.

There was no uniformed criteria for classification among studies which suggested risk group in early stage endometrial

Table 3

Cox's proportional hazard models for prognostic factors in FIGO stage IA endometrioid endometrial cancer.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	Adjusted HR	95% CI	P
Recurrence-free survival						
Age ≥ 65 years	0.860	0.114–6.492	.883	0.436	0.052–3.654	.444
Grade 1	2.727	0.623–11.936	.183	2.764	0.423–18.054	.288
No myometrial invasion	7.552	1.726–33.044	.007	9.803	2.003–47.968	.005
Tumor size≥ 2cm	1.316	0.490–3.533	.586	0.767	0.271–2.169	.618
Positive LVSI	1.993	0.455–8.724	.360	0.960	0.175–4.975	.961
Lower uterine involvement	1.046	0.139–7.890	.965	1.024	0.131–7.987	.982
Lymph node dissection	0.428	0.129–1.427	.167	0.924	0.188–4.542	.922
Adjuvant therapy	1.128	0.256–4.972	.874	0.413	0.073–2.354	.320

CI = confidence interval, FIGO = International Federation of Gynecology and Obstetrics, HR = hazard ratio, LVSI = lymphovascular space invasion.

Table 4

Cox's proportional hazard models for prognostic factors of FIGO stage IB endometrioid endometrial cancer.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	Adjusted HR	95% CI	*P*
Recurrence-free survival						
Age ≥ 65 years	0.851	0.234–3.096	.807	0.824	0.188–3.614	.798
Grade 1	6.662	1.291–34.367	.023	11.231	1.988–63.434	.006
Tumor size ≥ 2 cm	0.728	0.200–2.652	.630	0.383	0.077–1.906	.241
Positive LVSI	0.787	0.257–2.411	.676	0.237	0.054–1.033	.055
Lower uterine involvement	0.668	0.086–5.180	.700	0.235	0.025–2.249	.209
Lymph node dissection	0.295	0.057–1.526	.145	0.290	0.072–1.171	.082
Adjuvant therapy	0.528	0.106–2.621	.435	0.591	0.094–3.714	.575

CI = confidence interval, FIGO = International Federation of Gynecology and Obstetrics, HR = hazard ratio, LVSI = lymphovascular space invasion.

cancer.[7] Moreover, a sorting system based on various factors may also induce confusion during disease management in clinical settings, because it did not correspond to FIGO staging. The individual preferences of gynecologic oncologists might affect the method of adjuvant therapy and the long-term plan, resulting in a different management in the same clinical condition.[11] Simple guidelines based on the staging system may help facilitate clear decision.

We followed patients over time for up to 10 years to evaluate the prognostic factors of stage I EEC. Only 2 factors, myometrial invasion and histologic grade, affected tumor recurrence in stage I EEC. The prognostic factors were different between stages IA and IB within stage I EEC. Our data demonstrated that myometrial invasion comprised the significant prognostic factor of stage IA EEC similar to the 1988 FIGO staging. The revised 2010 FIGO system, which covers the overall histology type of endometrial cancers, merged cases with no myometrial invasion and cases with less than half of myometrial invasion in stage IA. Studies that supported the previous system have reported the results from patients with endometrioid histology.[12] In stage IB EEC, which included more than half of myometrial invasion, the histologic grade comprised the prognostic factor of tumor recurrence. The presence, number, or type of alleged adverse risk factors did not significantly affect the RFS in our study. Our data suggested that the primary factor to predict tumor survival in stage IB EEC was the histologic grade.

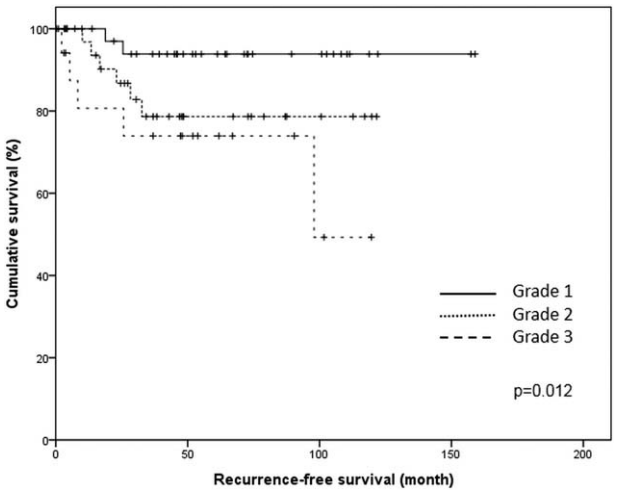

Figure 2. Kaplan–Meier curves of recurrence-free survival according to histologic grade in FIGO stage IB endometrioid endometrial cancer. Solid line: grade 2; narrow dot line: grade 2; wide dot line: grade 3. FIGO = International Federation of Gynecology and Obstetrics.

Some studies have indicated that lymphadenectomy influenced survival during the early stage of endometrial cancer.[13] However, a randomized trial determined that systematic pelvic lymphadenectomy of the early stage endometrial cancer only facilitated surgical staging, and it did not prolong survival.[14] Sentinel lymph node mapping and selective lymphadenectomy during the early stage of endometrial cancer comprised an effort to achieve a survival benefit and decrease adverse effects, such as lymphedema or delayed postoperative recovery.[15] In our study, whether pelvic or para-aortic lymph node dissection were performed or not had no effect on RFS of patients with stage I EEC.

A previous study reported that adjuvant therapy did not affect tumor survival in early stage endometrial cancer.[16] Adjuvant chemotherapy was performed on patients with intermediate to high risk stage I endometrial cancer. However, our multivariate analyses found that the application of adjuvant chemotherapy itself or its regimen was not associated with the rate of tumor recurrence of stage I EEC.

Although we investigated FIGO stage-specific prognostic factors of stage I EEC, this study had some limitations. Retrospective design of the current study might induce selection bias to include patients with stage I EEC. In addition, there were not sufficient death events to analyze overall survival or cancer-specific survival. Prospective evaluation with long-term follow-up is needed to draw the accurate conclusion.

There were no standard criteria of risk grouping in early stage endometrial cancer, and the methods stated in the previous reports were too complicated to be applied in clinical practice. Prognostic factors based on the FIGO stage would make it convenient for gynecologic oncologist to assess tumor prognosis and select appropriate postoperative management. Additional investigations regarding adjuvant treatment and follow-up according to the staging system would properly guide gynecologic oncologists without broad variation.

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