Observational Study

Medicine®

OPEN

Stratification of risk groups according to survival after recurrence in endometrial cancer patients

Seung-Hyuk Shim, MD, PhD[a], Dae-Yeon Kim, MD, PhD[b,*], Hyun Jung Kim, MD[a], Shin-Wha Lee, MD, PhD[b], Jeong-Yeol Park, MD, PhD[b], Dae-Shik Suh, MD, PhD[b], Jong-Hyeok Kim, MD, PhD[b], Yong-Man Kim, MD, PhD[b], Young-Tak Kim, MD, PhD[b], Joo-Hyun Nam, MD, PhD[b]

Abstract

To identify prognostic factors for overall survival after recurrence (OSr) in endometrioid endometrial cancer (EC) patients and categorize patient subgroups that predict outcomes using these variables.

Consecutive patients with recurrent endometrioid EC seen in our institution from 1989 to 2013 were retrospectively reviewed. Cox regression models were used to identify the clinicopathological factors associated with OSr. By summing scores proportionate to the hazard ratio (HR) for each significant variable, we stratified patients into 3 risk groups.

Enrolled patients (n = 108) had a median time to recurrence of 15 (range, 3–163) months after initial treatment and a median OSr of 22 (range, 1–207) months. Twenty patients (18.5%) had locoregional recurrence, and 88 (81.5%) distant. One hundred three patients underwent salvage therapy; 51 (47.2%) received chemotherapy only, 22 (20.3%) received radiotherapy either alone or combined with chemotherapy, and 29 (26.9%) underwent salvage cytoreductive surgery. Multivariate regression analysis revealed that time to relapse after initial treatment, cancer antigen-125 level at recurrence, and the number of recurrent lesions were independent predictors of OSr. Incorporating these factors, we stratified patients into low-risk (n = 19), intermediate-risk (n = 43), and high-risk (n = 46) groups. The likelihood of cancer-specific death was higher in both the high-risk (HR = 8.948, 95% confidence interval [CI] = 3.498–22.893, $P < .001$) and the intermediate-risk (HR = 2.619, 95% CI = 1.002–6.850, $P = .05$) groups compared with the low-risk group.

Incorporating 3 variables, recurrent endometrioid EC patients with a broad spectrum of outcome could be stratified according to OSr. This model may help predict outcomes in recurrent EC patients.

Abbreviations: BMI = body mass index, CA-125 = cancer antigen-125, CI = confidence interval, EC = endometrial cancer, FIGO = International Federation of Gynecology and Obstetrics, HR = hazard ratio, OSr = overall survival after recurrence, PARP = poly ADP ribose polymerase, PORTEC-1 = Post Operative Radiation Therapy in Endometrial Cancer-1, TTR = time to relapse.

Keywords: prognosis, recurrence, uterine cancer

1. Introduction

An estimated 319,600 new cases of endometrial cancer (EC) occurred worldwide in 2012.[1] In developed countries, EC is the most commonly diagnosed gynecologic cancer with over 167,000 new cases in 2012.[1] The EC incidence rate has been increasing in Korea, where more than 1700 cases are diagnosed annually.[2]

Although most EC patients are diagnosed with early-stage disease and have a favorable prognosis, approximately 15% of these patients relapse.[3] Treatment for recurrence includes local treatment (radiotherapy or surgery), systemic chemotherapy, or relevant combinations. It differs according to the involved site, recurrent disease extent, and types of previous therapy.[4] The 3-year survival rate in recurrent EC patients is reported to be between 8% and 73%.[5] This broad range indicates that recurrent EC patients represent a heterogeneous group with different prognostic factors for survival. Thus, there is a need to better discriminate these patients depending on prognosis after relapse. Although a handful of studies have suggested several prognostic factors associated with survival after recurrence,[6–11] the individualized prediction model incorporating these risk factors has not been introduced.

Therefore, the present study aimed to develop a prediction model incorporating the prognostic factors for survival after recurrence in endometrioid EC patients and stratify the patients into subgroups according to survival outcomes.

2. Materials and methods

2.1. Patients

With approval from the institutional review board (S2015-1754-0001), records were retrieved retrospectively from a computerized database of patients diagnosed with primary EC in our

Editor: Yufang Ma.

The results of this manuscript were presented in part at the SGO 46th Annual Meeting on Women's Cancer, which was held from March 28 to 31, 2015, Chicago, IL.

This work was supported by Konkuk University Medical Center Research Grant 2017.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] Department of Obstetrics and Gynecology, Konkuk University School of Medicine, [b] Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea.

[*] Correspondence: Dae-Yeon Kim, Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, 88 Olympic-ro 43 gil, Songpa-gu, Seoul 05505, Korea (e-mail: nastassja@naver.com).

Medicine (2017) 96:21(e6920)

Received: 12 October 2016 / Received in final form: 17 April 2017 / Accepted: 25 April 2017

http://dx.doi.org/10.1097/MD.0000000000006920

institution between 1989 and 2013. Patients who received primary surgery (at least hysterectomy and/or bilateral salpingo-oophorectomy) for endometrioid EC were considered eligible for the study. Patients with non-endometrioid histologies (such as malignant mixed Müllerian tumors, papillary serous, clear cell, and undifferentiated carcinomas) were excluded from this study. Patients who received fertility-sparing treatment, lacked follow-up information, did not have a disease-free interval of at least 3 months, had concomitant ovarian or fallopian tube carcinoma, and/or had a history of another malignancy or underlying disease potentially affecting survival were also excluded. Recurrence was defined as the occurrence of disease after a disease-free interval of 3 months or more.[12]

The initial surgical procedures for EC used in our institution have been described previously.[13] In cases with deep myometrial invasion (≥50%), tumor size >2 cm in diameter, International Federation of Gynecology and Obstetrics (FIGO) stage II to IV, and grade 2 to 3, a comprehensive surgical staging procedure (including pelvic and/or para-aortic lymphadenectomy) was performed. All histologic specimens were microscopically evaluated by gynecologic pathologists for myometrial invasion, grade, histology, cervical invasion, and nodal metastasis. Adjuvant treatment was individualized depending on histology, stage, grade, and the discretion of the physician.[4]

After completion of the primary treatment, patients were evaluated by a gynecologic oncologist every 3 months for the first 2 years, every 6 months for the subsequent 3 years, and annually thereafter. Each follow-up visit included history-taking, physical examination, serum cancer antigen-125 (CA-125) measurements, and vaginal cytology. When recurrence was suspected clinically, it was confirmed using histopathological examination or radiological examinations, such as computed tomography. Local recurrence was defined as that confined to the vagina, regional recurrence was defined as disease limited to the false pelvis, and distant recurrence was defined as disease beyond the false pelvis.[11] Treatment modalities for recurrence were selected with consideration of the site of recurrence, and number and type of previous treatments. Radiotherapy was selected for local vaginal or regional lymph node recurrences. Salvage surgery was considered for patients with resectable isolated or a limited number of recurrent lesions. In cases where recurrence was not amenable to local treatment such as surgery or radiotherapy, chemotherapy was selected.

2.2. Variables and statistical analysis

The following clinicopathological variables were extracted from electronic medical records: age, body mass index (BMI), parity, menopause, primary surgical procedure, initial FIGO stage, initial pathological findings (including histology, grade, myometrial invasion, lymph node metastasis), information regarding adjuvant therapy, age at the time of recurrence, symptomatic recurrence,[10] time to relapse (TTR; from the completion date of initial treatment to the date of recurrence detected), location of recurrence, number of recurrent lesions, CA-125 level at the time of recurrence, and treatment modalities for recurrence. If the patient received multiple treatments for recurrence, the treatment of the first detected recurrence was evaluated. Initial surgical stage of patients with recurrence was determined using the 2009 FIGO staging system.[14] Of the variables that were tested, age at initial diagnosis, BMI, age at the time of recurrence, and CA-125 level at the time of recurrence were considered as continuous variables. Initial stage, grade (1, 2, and 3), location (local, regional, and distant), and number (single and multiple) of recurrent lesions, TTR (<6 and ≥6 months), symptomatic recurrence, and treatment type for recurrence (surgery, radiation, and chemotherapy) were considered as categorical variables. We chose 6 months as the cut-off value to test whether this variable is a prognostic factor for survival after recurrence given the results of previous studies.[8,15] A CA-125 level of ≥35 U/mL was considered to be elevated.[16]

The primary end point was overall survival after recurrence (OSr), which was calculated from the date of confirmed recurrence to the date of death, or the date of the last follow-up for surviving patients. Patients were censored if they were alive at last contact or died without disease. For 12 recurrent EC patients who were lost to regular follow-up, it was possible to obtain definitive survival data from the National Cancer Information Center database. Thus, definitive survival data were available for every recurrent endometrioid EC patient. Survival curves were plotted with the Kaplan–Meier method and compared using the log-rank test. A multivariate Cox regression mode was used to identify the independent prognostic factors for OSr. All significant variables after univariate analysis were entered into a multivariate Cox regression model, and nonsignificant variables were removed in a stepwise fashion. The risk of cancer-specific death was calculated using adjusted hazard ratios (HRs) from this multivariate model. The prognostic score generated for each significant factor was proportionate to the HR. Patients were categorized into 3 subgroups based on the sum of the scores. A P value $< .05$ according to 2-sided tests indicated significant difference. All analyses were performed using SPSS version 19.0 (SPSS, Chicago, IL).

3. Results

3.1. Patients

During the study period, 1302 patients with EC underwent primary surgery. Of these patients, 108 developed recurrence and were analyzed (Supplementary Fig. 1, http://links.lww.com/MD/B702). The characteristics of the patients with recurrence are summarized in Table 1. The median age at initial treatment and recurrence was 54 years (range, 24–79 years) and 56 years (range, 27–80 years), respectively. At initial diagnosis, 41 patients (38%) had FIGO stage I/II disease. For the initial surgical procedure, 93 patients underwent pelvic lymphadenectomy and 62 underwent para-aortic lymphadenectomy. Pelvic and para-aortic nodal metastases were found in 45 and 35 patients by pathological evaluation, respectively. Ninety-one patients (84%) received adjuvant therapy after primary surgery: 40 (37.0%) had chemotherapy (37 received a platinum-based combination regimen and 3 received paclitaxel only), 26 (24.1%) had radiotherapy, and 25 (23.1%) had a combination of both. Thirty-seven patients (34.3%) showed symptoms of recurrence. The main symptoms at recurrence were vaginal bleeding (n = 14), abdominal pain (n = 13), and respiratory symptoms (n = 8).

3.2. Treatment for relapse

The treatments given for recurrence are described in Table 2. Locoregional and distant recurrences were diagnosed in 20 and 88 patients, respectively. One hundred three patients underwent salvage therapy including radiotherapy, surgery, chemotherapy, or combined therapy. The other 5 patients received palliative treatment alone because their poor performance status contra-

Table 1

Clinicopathological characteristics of patients with recurrent endometrioid endometrial cancer.

Characteristics	Patients (n = 108)
Age at initial diagnosis, median (range), y	54 (24–79)
Age at recurrence, median (range), y	56 (27–80)
BMI, median (range), kg/m^2	24.5 (18.8–43.85)
CA-125 at initial diagnosis, median (range), U/mL	28.8 (3–14,900)
CA-125 at recurrence, median (range), U/mL	27.1 (3–4002)
Surgical procedures at initial diagnosis, n (%)	
Hysterectomy	108 (100.0)
BSO	96 (88.9)
PLND	93 (86.1)
PALND	62 (57.4)
FIGO stage at initial diagnosis, n (%)	
I	33 (30.6)
II	8 (7.4)
III	50 (46.3)
IV	17 (15.7)
Grade, n (%)	
1	27 (25.0)
2	29 (26.9)
3	38 (35.2)
Depth of myometrial invasion	
<1/2	45 (41.7)
≥1/2	55 (50.9)
Nodal metastasis at initial diagnosis, n (%)	
Unknown	14 (13.0)
No	46 (42.6)
Yes	48 (44.4)
Adjuvant treatment, n (%)	
No	17 (15.7)
Chemotherapy only	40 (37.0)
Radiotherapy only	26 (24.1)
Chemotherapy + radiotherapy	25 (23.1)
Time from initial treatment to recurrence, median (range), mo	15 (3–163)
Symptomatic at recurrence, n (%)	
Yes	37 (34.3)
Site of recurrence, n (%)	
Local	7 (6.5)
Regional	13 (12.0)
Distant	88 (81.5)
Number of recurrent lesions, n (%)	
Single	36 (33.3)
Multiple	72 (66.7)
Salvage cytoreductive surgery, n (%)	
Yes	29 (26.9)

BMI = body mass index, BSO = bilateral salpingo-oophorectomy, CA-125 = cancer antigen-125, FIGO = International Federation of Gynecology and Obstetrics, PALND = para-aortic lymph node dissection, PLND = pelvic lymph node dissection.

indicated salvage therapy. Forty-four (41%) received combined therapy. Those with distant recurrence tended to receive chemotherapy only (45/88; 51%), whereas those with locoregional recurrence were more likely to receive radiotherapy or surgery (14/20; 70%). Twenty-nine patients (27%) with solitary or a limited number of recurrent lesions underwent salvage surgery, and the specific sites of recurrence were as follows: lung (n = 9), pelvic (n = 6), retroperitoneal lymph node (n = 5), vagina (n = 4), intra-abdominal (n = 3), and brain (n = 2).

3.3. Univariate and multivariate analyses of prognostic factors for OSr

The median follow-up period for the 108 patients was 45 months (range, 4–301 months). The median time from initial treatment to recurrence was 15 months (range, 3–163 months). Forty-five (41.7%) and 76 (70.4%) recurred within 1 and 3 years after primary treatment, respectively. During follow-up, 24 patients lived without disease and 76 died of disease. The median OSr was 28 months (range, 1–226 months). The 3- and 5-year OSr rates were 39% and 30%, respectively (Supplementary Fig. 2, http://links.lww.com/MD/B702).

Univariate Cox regression analysis revealed that TTR ($P < .001$), CA-125 level at recurrence ($P < .001$), number of recurrent lesions ($P = .003$), and initial stage ($P = .007$) were associated with OSr. After performing multivariate analysis to control for these variables, TTR, CA-125 level at recurrence, and number of recurrent lesions remained as significant prognostic factors (Table 3).

3.4. Stratification of subgroups to predict OSr

Using 3 independent prognostic variables for OSr, we generated a scoring system and stratified 3 subgroups according to the scores. For TTR, we assigned a score of 0 for ≥6 months and 1 for <6 months. For number of recurrent lesions, we assigned a score of 0 for single and 1 for multiple. For CA-125 level at recurrence, we assigned a score of 0 for ≤35 U/mL and 1 for >35 U/mL (Table 3).

According to the sum of scores, we stratified patients into 3 risk groups; the low-risk group (n = 19) was defined as patients with a score of 0. The intermediate-risk group (n = 43) was defined as patients with a score of 1. The high-risk group (n = 46) was defined as patients with a score of 2 or 3. Figure 1 shows the OSr in the low-, intermediate-, and high-risk groups. The 3-year OSr rates in each group were 81%, 54%, and 14%, respectively, and the 5-year OSr rates in each group were 71%, 42%, and 9%, respectively. The OSr differed significantly among the risk groups

Table 2

Numbers of patients who received a spectrum of treatments after recurrence stratified by site of recurrence.

Modality	Patients (n = 108)	Site of recurrence		
		Local (n = 7)	Regional (n = 13)	Distant (n = 88)
Chemotherapy, n	51	1	5	45
Chemotherapy + radiotherapy, n	16	2	2	12
Chemotherapy + surgery, n	15	2	2	11
Chemotherapy + radiotherapy + surgery, n	10	0	3	7
Radiotherapy + surgery, n	3	1	1	1
Radiotherapy, n	6	1	0	5
Surgery, n	1	0	0	1
Hormonal, n	1	0	0	1
No treatment, n	5	0	0	5

Table 3

Univariate and multivariate Cox regression analyses of the prognostic factors associated with overall survival after recurrence.

	Univariate		Multivariate		
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**Score**
Age at initial diagnosis*, y	1.009 (0.985–1.033)	.481			
Age at recurrence*, y	1.000 (0.975–1.025)	.984			
BMI*, kg/m^2	1.023 (0.963–1.087)	.461			
Time to relapse, mo					
≥6	1		1		0
<6	2.987 (1.863–4.790)	<.01	2.330 (1.389–3.909)	<.001	1
CA-125 at initial diagnosis*, U/mL	1.000 (1.000–1.000)	.245			
CA-125 at recurrence*, U/mL	1.000 (1.000–1.001)	.062			
CA-125 at recurrence, U/mL					
≤35	1		1		0
>35	2.712 (1.665–4.420)	<.001	2.291 (1.389–3.779)	.0012	1
Initial FIGO stage					
I	1	.007			
II	1.450 (0.543–3.876)				
III	1.512 (0.871–2.622)				
IV	3.276 (1.666–6.439)				
Grade					
1, 2	1				
3	1.574 (0.963–2.573)	.070			
Depth of myometrial invasion					
<1/2	1				
≥1/2	1.301 (0.807–2.099)	.280			
Adjuvant treatment after initial surgery, yes	1.688 (0.841–3.388)	.140			
Number of recurrent lesions					
Single	1		1		0
Multiple	2.198 (1.306–3.700)	.003	1.750 (1.000–3.064)	.05	1
Site of recurrence					
Local	1	.723			
Regional	1.238 (0.381–4.025)				
Distant	1.445 (0.526–3.973)				
Treatment for recurrence					
Nonsurgical modalities	1				
Salvage surgery	0.653 (0.380–1.120)	.121			
Symptom at recurrence, yes	0.933 (0.578–1.507)	.778			

BMI = body mass index, CA-125 = cancer antigen-125, CI = confidence interval, FIGO = International Federation of Gynecology and Obstetrics, HR = hazard ratio.
* Considered as a continuous variable.

(low-risk group vs. intermediate-risk group, $P = .032$; intermediate-risk group vs. high-risk group, $P < .001$). The likelihood of cancer-specific death was significantly higher in the intermediate- and high-risk groups than the low-risk group (HR = 8.948, 95% confidence interval [CI] = 3.498–22.893, $P < .001$ for the high-risk group; HR = 2.619, 95% CI = 1.002–6.850, $P < .05$ for the intermediate-risk group; Table 4).

4. Discussion

Recurrent EC is a highly heterogeneous entity, with a broad spectrum of survival outcomes.[4] Although the prognosis for the vast majority is poor, a specific group shows long-term survival after recurrence. In the present study, TTR, CA-125 level at recurrence, and number of recurrent lesions were revealed as significant factors for OSr in recurrent endometrioid EC patients. When we stratified patients into 3 subgroups by combining weighted prognostic factors, the OSr differed significantly among the risk groups. Our risk stratification model was designed as a user-friendly and simple scoring system. Meanwhile, the traditional multivariate regression model suggests a mathematically complicated formula, which is difficult for both clinicians and patients to apply and interpret in clinical practice. Considering the heterogeneous characteristics of the recurrent EC population, our model would be clinically useful for predicting outcomes, counseling patients, and designing future clinical trials.

Previous studies reported that 70% to 86% of incidences of recurrence are detected within 3 years after primary treatment and that the 3-year OSr is 17% to 35%,[6,10,17] findings similar to our results. However, only a handful of studies addressed the prognostic factors associated with OSr in these patients and as yet there is no consensus. Table 5 summarizes the published studies reporting the prognostic factors for OSr in recurrent EC patients. Commonly suggested prognostic factors for OSr include TTR,[6,8,15–22] number of recurrent lesions,[21,23,24] site of recurrence,[5,6,9,16,22,25,26] CA-125 level at recurrence,[24,27] histology,[20] grade,[9,10,28] initial stage,[10] symptomatic recurrence,[10,17,18,29] performance status,[8] and use of pelvic radiation after initial surgery.[5,6,8,22,23] To build a reliable model, we tested all aforementioned variables for inclusion.

In the present study, multiple recurrent lesions were independent poor prognostic factors for OSr. A retrospective study by Sohaib et al[23] of 86 recurrent EC cases suggested that multiple recurrent lesions were independent prognostic factors. Similarly,

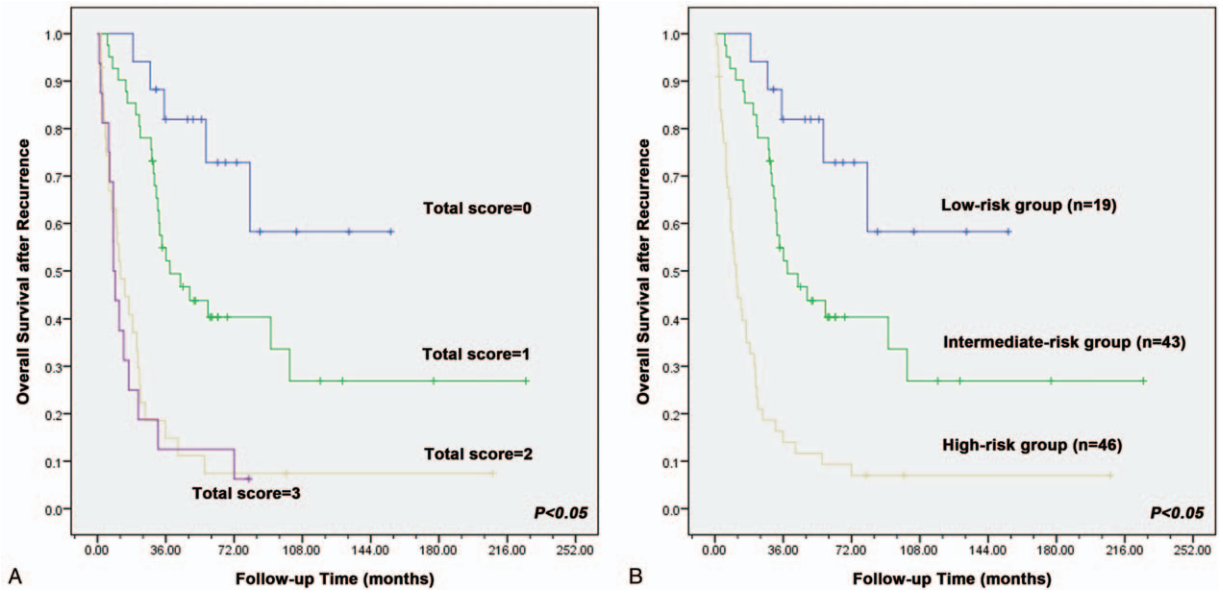

Figure 1. Overall survival after recurrence by the sum of prognostic scores (A) and risk groups (B). Patients with a total prognostic score of 0 were categorized as the low-risk group (n = 19), patients with a prognostic score of 1 were categorized as the intermediate-risk group (n = 43), and patients with a prognostic score of 2 or 3 were categorized as the high-risk group (n = 46).

Odagiri et al[21] reported that the number of recurrent lesions was an independent prognostic factor for OSr in 35 recurrent EC patients. In 2015, Turan et al[24] reported that multiplicity of recurrent lesions was associated with poor survival rates among 34 recurrent EC patients undergoing salvage cytoreductive surgery. One possible reason for this finding is that multiple recurrent lesions are indicative of the metastatic potential of EC cells and reflect inherent tumor aggressiveness.[5,21] Another possible explanation is that salvage surgery is generally performed in select cases with a single or limited number of recurrent lesions. In an analysis of 64 patients undergoing surgery for recurrent EC by Papadia et al,[30] multiplicity of the recurrent lesions was significantly associated with incomplete resection. Moreover, a meta-analysis indicated that, if complete cytoreduction of recurrent tumors is achieved, survival is improved in recurrent EC patients, regardless of the disease location.[31] In the present study, 16 patients with an isolated recurrent lesion underwent salvage surgery and none of them had any gross residual disease after salvage surgery. Of those patients, 8 had prolonged survival (>3 years).

In addition to the number of recurrent lesions, TTR also affected OSr in multivariate analysis, which is consistent with previous studies.[6,8,15–22] Although this variable may be indicative of a general prognostic factor in terms of tumor biology, it is still conflicting that this reflects tumor response to a second-line platinum-based chemotherapy, which means the concept of "platinum sensitivity" a term historically reserved for ovarian cancer. A retrospective study by Ueda et al[15] reported that patients with a TTR of >6 months had better response rates to salvage chemotherapy compared to those with a TTR of <6 months. Similarly, a multicenter retrospective study of 262 recurrent EC patients by Nagao et al showed that a platinum-free interval is a predictor of tumor response and survival after second-line platinum-based chemotherapy.[19] By contrast, such a time interval was not associated with tumor response to second-line chemotherapy in an ancillary analysis using pooled data from 5 phase III Gynecologic Oncology Group trials.[8] Interestingly, a time interval from primary treatment to recurrence of >6 months was still prognostic for survival after second-line chemotherapy in this analysis (HR = 0.70, 95% CI = 0.59–0.84, $P < .05$). Future studies are warranted to elucidate whether this variable has clinical utility in selection of the chemotherapy regimen for recurrent EC as is the case for ovarian cancer.

Assay of serum CA-125 may be useful for surveillance in EC patients after initial treatment, if levels were initially elevated.[32] Routine use of serum CA-125 varies across institutions, and furthermore the benefit of surveillance to detect asymptomatic disease is controversial. In our institution, serum CA-125

Table 4

Stratification of subgroups predicting overall survival after recurrence in patients with recurrent endometrioid endometrial cancer by the combination of independent prognostic factors.

Risk group	No. of patients	Sum of scores*	HR (95% CI)	P
Low	19	0	1	
Intermediate	43	1	2.619 (1.002–6.850)	<.05
High	46	≥2	8.948 (3.498–22.893)	<.001

CA-125 = cancer antigen-125, CI = confidence interval, HR = hazard ratio.

* Sums of risk factors including time to relapse (<6 mo), number of recurrent lesions (2 or more), and CA-125 level at recurrence (>35 U/mL). The presence of each risk factor above the cut-off, according to the Cox regression analysis, is represented by a score of 1.

Table 5

Published studies reporting the prognostic factors for survival after recurrence in recurrent endometrial cancer patients.

Study/design	Location/ study period	Total number of EC patients	Initial FIGO stage, %	Adjuvant radiotherapy, %	Recurrent patients, n (%)	Recurrence site		Median follow-up period, mo	Median time to recurrence, mo	Median survival after recurrence, mo	3-y OSr rate, %	Salvage rate, n (%)	Prognostic factor for OSr
						Locoregional, n (%)	Distant, n (%)						
Berchuck et al/NRS	USA/1978–1987	354	I 100	NR	44 (12)	24 (54)	20 (46)	>60	NR	NR	NR	NR	recurrence site, grade
Podczaski et al/NRS	USA/1977–1987	300	I/II 100	49	47 (16)	16 (34)	31 (66)	56	13	NR	17	5 (11)	recurrence site, time to relapse, use of adjuvant radiotherapy
Sartori et al/NRS	Italy/1980–1995	1606	I–IV 100	38	209 (13)	102 (49)	107 (51)	112	NR	NR	NR	NR	recurrence site, time to relapse, use of adjuvant radiotherapy
Gadducci et al/NRS	Italy/1988–1997	133	I 81; II 8; III/IV 11	64	24 (18)	6 (25)	18 (75)	53	18	NR	10	6 (25)	time to relapse
Salvesen et al/NRS	Norway/1981–1990	249	I 83; II 8; III/IV 9	73	47 (19)	15 (32)	32 (68)	108	NR	NR	NR	NR	recurrence site
Otsuka et al/NRS	Japan/1986–2007	NR	I–III 100	NR	51	17 (33)	34 (67)	NR	12 (3–119)	20	NR	NR	recurrence site, time to relapse
Creutzberg et al/RCT	The Netherlands/ 1990–1997	714	I 100	50	110 (15)	59 (54)	51 (46)	73	21 (3–108)	NR	51*	30 (27)	recurrence site, use of adjuvant radiotherapy
Smith et al/NRS	Australia/1990–2006	2637	I–IV 100	NR	280 (11)	100 (36)	169 (67)	109	19	36	32†	NR	initial FIGO stage, grade, symptomatic recurrence
Sohaib et al/NRS	UK/1996–2004	NR	NR	NR	86	30 (34)	56 (66)	NR	13	11	NR	13 (15)	number of recurrent lesions, use of adjuvant radiotherapy
Esselen et al/NRS	UK/1994–2007	1061	I–IV 100	25	77 (7)	22 (29)	55 (71)	NR	13	16	NR	NR	grade
Odagiri et al/NRS	Japan/1995–2008	316	I–III 100	NR	35 (11)	8 (23)	27 (77)	41	20	19	NR	NR	time to relapse, number of recurrent lesions
Ueda et al/NRS	Japan/1998–2007	536	I–IV 100	17	54 (10)	29 (54)	25 (46)	43	NR	NR	NR	NR	histology, time to relapse
Shimamoto et al/NRS	Japan/1997–2012	710	I–IV 100	NR	60 (8)	11 (18)	46 (82)	43	11	NR	40	NR	lymph node metastasis, time to relapse, symptomatic recurrence
Nagao et al/NRS	Japan/2005–2009	NR	I–IV 100	NR	262‡	NR	NR	17	9	NR	NR	NR	platinum-free interval, residual tumor after primary surgery
Present study/NRS	Korea/1989–2013	1302	I–IV 100	NR	108 (9)	20 (19)	88 (81)	45	15	28	39	24 (22)	time to relapse, CA-125 level at recurrence, number of recurrent lesions

CA-125 = cancer antigen-125, EC = endometrial cancer, FIGO = International Federation of Gynecology and Obstetrics, NR = not reported, NRS = nonrandomized study, OSr = overall survival after recurrence, RCT = randomized controlled trial.

* 3-y OSr rate was 51% and 19% for radiotherapy-naive group and previously irradiated group, respectively.

† 5-y OSr rate.

‡ Only received second-line platinum-based chemotherapy.

measurement is used for post-treatment surveillance in EC patients. In the present study, the CA-125 level at recurrence for all enrolled patients was available, and was revealed as a significant prognostic factor for OSr. In 2015, Turan et al[24] reported that CA-125 level at recurrence was prognostic in recurrent EC patients undergoing salvage cytoreductive surgery. In their series of 34 cases, the mean overall survival was 22 and 58 months in patients with levels of CA-125 at recurrence >27 and <27 IU/mL, respectively ($P < .05$). Elevated serum CA-125 levels at initial diagnosis correlated with extrauterine tumor extension and lymph node metastases.[33,34] Similarly, elevated serum CA-125 level at recurrence closely correlates with the peritoneal dissemination of cancer cells and an increased metastatic potential.[33]

Site of recurrence is a well-known prognostic factor for recurrent EC[5,6,9,16,22,25,26]; however, this was not observed in the present study. This may be due to the small number of cases with isolated vaginal recurrence (n = 7). The incidence of vaginal recurrence can be altered by administration of adjuvant radiation. In the Post Operative Radiation Therapy in Endometrial Cancer-1 (PORTEC-1) trial, isolated vaginal recurrence occurred in 2% of patients who received adjuvant radiotherapy, whereas it occurred in 8% of those who did not.[35] Another possible explanation is that the majority (5/7; 71%) of patients with local recurrence had received adjuvant radiotherapy previously. Although radiotherapy is the treatment of choice for radiotherapy-naive patients with vaginal recurrence, treatment for vaginal recurrence within a previously irradiated field may include surgery or additional radiotherapy.[36] However, if surgery or radiotherapy is not possible, the prognosis is worse since the treatment of choice becomes similar to that used for metastatic disease such as hormonal or cytotoxic agents.[37] As demonstrated in the PORTEC-1 trial, the 3-year OSr rate in patients with vaginal recurrence who received adjuvant radiotherapy was lower (43%) than that (65%) in radiotherapy-naive patients.[5]

Regarding the grade, published studies have shown conflicting results of whether this variable is a prognostic factor for survival after recurrence. As summarized in Table 5, 3 retrospective reviews showed that the grade is a prognostic indicator of survival after recurrence.[9,10,28] Of these reviews, the study by Berchuck et al was conducted at a time when the guidelines for postoperative radiation therapy for high- and intermediate-risk patients were not standardized.[9] In a study by Esselen et al, the controlling variables for multivariate analysis only included age, stage, and myometrial invasion.[28] They did not include CA-125 level, TTR, or number of recurrent lesions. These features may explain why our result is not consistent with those of other studies.

With advances in treatment modalities such as surgery and chemotherapy,[31,38] long-term survival of recurrent EC patients has improved. In the 1960 to 1976 cohort study by Aalders et al, the 5-year OSr rate for recurrent EC was 13%.[12] Radiotherapy was the most commonly used treatment for recurrence (64%), followed by hormone therapy (29%). However, in the 1990 to 2006 cohort study by Smith et al, recurrent EC patients had a 5-year OSr rate of 32%.[10] Salvage surgery and chemotherapy were more often prescribed for the 1990 to 2006 cohort. In the current study, the 5-year OSr rate of the 108 cases was 30%, which seems remarkably good considering the high proportion (82%) with distant recurrence. Nonetheless, the majority of recurrent EC cases still carry a poor prognosis. In cases of recurrence that develop after initial multimodal adjuvant treatment, salvage therapy can be challenging. Recently, data from the Cancer Genome Atlas suggest that in EC there are 4 genomic subtypes with different biology and prognosis, which presents the possibility of revealing druggable molecular aberrations.[39] To date, some molecular-targeted agents, such as anti-angiogenic therapies and poly ADP ribose polymerase inhibitors, and immunotherapies, appear to have clinical activity in the recurrent setting.[40,41]

Our study has several limitations inherent to its retrospective nature. First, the selection of patients for salvage treatment depended on previous adjuvant treatment, performance status, and the physician preferences. Second, the results of our study will require corroboration from other independent data sets to be applicable to the general population. It would be better if the scoring system could be validated using independent data from other sources. Further studies focusing on external validation by other institutions are needed. Third, this study covered a 20-year period, during which the adjuvant treatment for EC changed. The advancements in cancer care and treatment during this long period may have improved the survival rate. Therefore, such a long study period could potentially cause selection bias. Nonetheless, the number of enrolled patients was large compared with previous studies. Moreover, in the public healthcare system of Korea, which covers almost all the Korean population, it is mandatory to register the death with cause for cancer patients into the National Cancer Information Center database; definitive survival data were therefore available for all enrolled patients, including 12 (11%) who were lost to regular follow-up at our institution.

In conclusion, we found that TTR, CA-125 level at recurrence, and number of recurrent lesions were significant factors for OSr in recurrent endometrioid EC patients. When we stratified the patients into 3 subgroups considering these factors, their OSr differed among groups. After external validation, this model could be valuable in terms of predicting outcomes and planning clinical trials. Although individualized multimodal salvage therapy has led to an improvement in survival for a specific group, further efforts are necessary to facilitate new treatment strategies, such as molecular-targeted agents, for recurrent EC patients who still have poor prognosis.

References

[1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[2] Min KJ, Lee YJ, Suh M, et al. The Korean guideline for cervical cancer screening. J Gynecol Oncol 2015;26:232–9.
[3] Frandsen JE, Sause WT, Dodson MK, et al. Survival analysis of endometrial cancer patients with cervical stromal involvement. J Gynecol Oncol 2014;25:105–10.
[4] Wright JD, Barrena Medel NI, Sehouli J, et al. Contemporary management of endometrial cancer. Lancet 2012;379:1352–60.
[5] Creutzberg CL, van Putten WL, Koper PC, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol 2003;89:201–9.
[6] Podczaski E, Kaminski P, Gurski K, et al. Detection and patterns of treatment failure in 300 consecutive cases of "early" endometrial cancer after primary surgery. Gynecol Oncol 1992;47:323–7.
[7] Sears JD, Greven KM, Hoen HM, et al. Prognostic factors and treatment outcome for patients with locally recurrent endometrial cancer. Cancer 1994;74:1303–8.
[8] Moore KN, Tian C, McMeekin DS, et al. Does the progression-free interval after primary chemotherapy predict survival after salvage chemotherapy in advanced and recurrent endometrial cancer? A Gynecologic Oncology Group ancillary data analysis. Cancer 2010;116:5407–14.

[9] Berchuck A, Anspach C, Evans AC, et al. Postsurgical surveillance of patients with FIGO stage I/II endometrial adenocarcinoma. Gynecol Oncol 1995;59:20–4.
[10] Smith CJ, Heeren M, Nicklin JL, et al. Efficacy of routine follow-up in patients with recurrent uterine cancer. Gynecol Oncol 2007;107:124–9.
[11] Bristow RE, Santillan A, Zahurak ML, et al. Salvage cytoreductive surgery for recurrent endometrial cancer. Gynecol Oncol 2006;103:281–7.
[12] Aalders JG, Abeler V, Kolstad P. Recurrent adenocarcinoma of the endometrium: a clinical and histopathological study of 379 patients. Gynecol Oncol 1984;17:85–103.
[13] Shim SH, Kim DY, Lee DY, et al. Metabolic tumour volume and total lesion glycolysis, measured using preoperative 18F-FDG PET/CT, predict the recurrence of endometrial cancer. BJOG 2014;121:1097–106.
[14] Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 2009;105:103–4.
[15] Ueda Y, Miyake T, Egawa-Takata T, et al. Second-line chemotherapy for advanced or recurrent endometrial carcinoma previously treated with paclitaxel and carboplatin, with or without epirubicin. Cancer Chemother Pharmacol 2011;67:829–35.
[16] Otsuka I, Uno M, Wakabayashi A, et al. Predictive factors for prolonged survival in recurrent endometrial carcinoma: implications for follow-up protocol. Gynecol Oncol 2010;119:506–10.
[17] Shimamoto K, Saito T, Okadome M, et al. Prognostic significance of the treatment-free interval in patients with recurrent endometrial cancer. Eur J Obstet Gynecol Reprod Biol 2014;175:92–6.
[18] Gadducci A, Cosio S, Fanucchi A, et al. An intensive follow-up does not change survival of patients with clinical stage I endometrial cancer. Anticancer Res 2000;20:1977–84.
[19] Nagao S, Nishio S, Michimae H, et al. Applicability of the concept of "platinum sensitivity" to recurrent endometrial cancer: the SGSG-012/GOTIC-004/Intergroup study. Gynecol Oncol 2013;131:567–73.
[20] Ueda Y, Matsumura Y, Egawa-Takata T, et al. Disease-free interval after primary treatment predicts prognosis of recurrent endometrial carcinoma. Anticancer Res 2010;30:4347–52.
[21] Odagiri T, Watari H, Hosaka M, et al. Multivariate survival analysis of the patients with recurrent endometrial cancer. J Gynecol Oncol 2011;22:3–8.
[22] Sartori E, Laface B, Gadducci A, et al. Factors influencing survival in endometrial cancer relapsing patients: a Cooperation Task Force (CTF) study. Int J Gynecol Cancer 2003;13:458–65.
[23] Sohaib SA, Houghton SL, Meroni R, et al. Recurrent endometrial cancer: patterns of recurrent disease and assessment of prognosis. Clin Radiol 2007;62:28–34.
[24] Turan T, Tasci T, Karalok A, et al. Salvage cytoreductive surgery for recurrent endometrial cancer. Int J Gynecol Cancer 2015;25:1623–32.
[25] Agboola OO, Grunfeld E, Coyle D, et al. Costs and benefits of routine follow-up after curative treatment for endometrial cancer. CMAJ 1997;157:879–86.
[26] Salvesen HB, Akslen LA, Iversen T, et al. Recurrence of endometrial carcinoma and the value of routine follow up. Br J Obstet Gynaecol 1997;104:1302–7.
[27] Patsner B, Orr JWJr, Mann WJJr. Use of serum CA 125 measurement in posttreatment surveillance of early-stage endometrial carcinoma. Am J Obstet Gynecol 1990;162:427–9.
[28] Esselen KM, Boruta DM, del Carmen M, et al. Defining prognostic variables in recurrent endometrioid endometrial cancer: a 15-year single-institution review. Int J Gynecol Cancer 2011;21:1078–83.
[29] Gordon AF, Owen P, Chien PF, et al. A critical evaluation of follow-up of women treated for endometrial adenocarcinoma. J Obstet Gynaecol 1997;17:386–9.
[30] Papadia A, Bellati F, Ditto A, et al. Surgical treatment of recurrent endometrial cancer: time for a paradigm shift. Ann Surg Oncol 2015;22:4204–10.
[31] Barlin JN, Puri I, Bristow RE. Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis. Gynecol Oncol 2010;118:14–8.
[32] Salani R, Backes FJ, Fung MF, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. Am J Obstet Gynecol 2011;204:466–78.
[33] Yamazawa K, Hirashiki K, Usui H, et al. Discordance between serum level and tissue immunohistochemical staining of CA125 in endometrioid adenocarcinoma of the uterine corpus. Int J Gynecol Pathol 2005;24:254–9.
[34] Hsieh CH, Chang-Chien CC, Lin H, et al. Can a preoperative CA 125 level be a criterion for full pelvic lymphadenectomy in surgical staging of endometrial cancer? Gynecol Oncol 2002;86:28–33.
[35] Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000;355:1404–11.
[36] Del Carmen MG, Boruta DM II, Schorge JO. Recurrent endometrial cancer. Clin Obstet Gynecol 2011;54:266–77.
[37] Bradford LS, Rauh-Hain JA, Schorge J, et al. Advances in the management of recurrent endometrial cancer. Am J Clin Oncol 2015;38:206–12.
[38] Fleming GF. Systemic chemotherapy for uterine carcinoma: metastatic and adjuvant. J Clin Oncol 2007;25:2983–90.
[39] Kandoth C, Schultz N, et al. Cancer Genome Atlas Research NetworkIntegrated genomic characterization of endometrial carcinoma. Nature 2013;497:67–73.
[40] Rodriguez-Freixinos V, Karakasis K, Oza AM. New targeted agents in endometrial cancer: are we really making progress? Curr Oncol Rep 2016;18:23.
[41] Slomovitz BM, Jiang Y, Yates MS, et al. Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma. J Clin Oncol 2015;33:930–6.