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ORIGINAL ARTICLE

Predictors of favorable survival after secondary cytoreductive surgery for recurrent endometrial cancer

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Abstract

Objective The selection criteria for secondary cytoreductive surgery (SCS) for recurrent endometrial cancer (EC) remain to be defined. The present study aimed to identify predictors for favorable survival after SCS for the disease.

Methods We retrospectively reviewed the medical records of 112 patients who relapsed by 2016 among 1052 who were diagnosed with primary EC between 1985 and 2014. Characteristics associated with overall survival (OS) after SCS were identified using univariate and multivariate analyses.

Results Twenty-nine of the 112 patients who relapsed underwent SCS. Complete resection was achieved in 18 (62%) patients, whose OS after SCS was significantly better than that of patients receiving incomplete resection (68 vs. 20 months; $p=0.001$). Endometrioid histology and performance status (PS) 0 were significant and independent factors for a favorable OS ($p=0.005$, and 0.049). The OS of patients with both factors was better than patients with one or no factors (median 75, 19 and 4 months; $p=0.001$ and 0.00001). The number of predictors was associated with the rate of complete resection ($p=0.001$).

Conclusions Patients with endometrioid histology and PS 0 should be offered SCS for recurrent EC. Prospective trials are warranted to verify this proposal.

Keywords Secondary cytoreductive surgery · Recurrent endometrial cancer · Survival

Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries [1]. Although most patients diagnosed with EC have early-stage disease and a good long-term prognosis, EC recurs in about 13% of them with a mortality rate of ~25% [2]. The management of recurrent EC has not been standardized. Depending on the distribution of recurrent disease, chemotherapy, radiotherapy, surgery, or hormonal therapy is selected.

The standard management for EC at initial diagnosis is surgery, because EC is considered to be rather refractory to chemotherapy or radiotherapy. However, the role of secondary cytoreductive surgery (SCS) has not been determined in the setting of recurrent disease. Patients with localized central pelvic recurrence in previously irradiated fields have benefited from pelvic exenteration [3, 4], but the reported mortality rate is 1–10% [5, 6]. Although several studies have identified an association between non-exenterative surgery for patients with recurrent EC and improved survival [7–11], the results are limited by small patient cohorts. Thus, predictors of favorable survival after SCS for recurrent EC remain to be clarified. The present study aimed to identify predictors of favorable survival after SCS for recurrent EC to identify patients who might benefit from SCS. The current findings provide useful information with which to formulate selection criteria and design prospective trials for SCS for recurrent EC.

Patients and methods

The study was approved by the Ethics Committee of University of Tsukuba Hospital. Among the 1052 patients

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diagnosed with primary endometrial carcinoma, who were treated at the University of Tsukuba Hospital between January 1985 and December 2014, we retrospectively reviewed the medical records of 112 who relapsed by December 2016. Patients with multiple cancers were excluded from further analysis. All patients with recurrent EC were diagnosed by computed tomography (CT), magnetic resonance (MRI), positron emission tomography (PET) imaging, or a combination of each modality. For the treatment of recurrent EC, we generally considered the patients as subjects for SCS, when complete resection was expected to be achieved. Overall survival (OS) after recurrence or SCS was determined from the date of diagnosis of recurrence or SCS to the date of death from any cause. TFI was calculated from the end of primary treatment to the date when recurrence was diagnosed. Kaplan–Meier survival curves were calculated and statistically compared using log-rank test. Prognostic factors selected by univariate and multivariate analyses were assessed using Cox proportional hazards model. Univariate and multivariate analyses of clinicopathological factors associated with SCS outcome were conducted by logistic regression analysis. Differences in proportions were evaluated using Fisher exact test. Values with $p < 0.05$ were considered statistically significant. All data were statistically analyzed using SPSS version 24.

Results

Survival of patients with recurrent EC

Between January 1985 and December 2016, 112 patients were diagnosed with recurrent EC. Table 1 summarizes the characteristics of the patients. The median follow-up of survivors after recurrence was 34 (range 3–296) months. Treatments for recurrence comprised chemotherapy, surgery, radiotherapy and best supportive care in 44 (39%), 29 (26%) 27 (24%) and 12 (11%), respectively. The median OS after recurrence was 21 months. The median OS of patients who were surgically treated for recurrence was significantly better than that of patients treated with chemotherapy or radiotherapy (45 vs. 16 and 26 months; $p = 0.002$ and 0.046, respectively; Fig. 1a). Five-year OS rates were 67, 28 and 25% after surgery, chemotherapy and radiotherapy for recurrence, respectively.

Characteristics of patients who underwent SCS

The median follow-up of 29 patients after SCS for EC survivors was 98 (range 19–295) months. The median age at recurrence was 59 (range 43–79) years and the median TFI was 28 (range 3–167) months.

Table 1 Patient characteristics ($n = 112$)

Characteristics	Patients
Age at recurrence, years (median; range)	64 (37–88)
TFI, months (median; range)	14 (1–167)
FIGO stage	
I	30 (27%)
II	15 (13%)
III	38 (34%)
IV	29 (26%)
Histology	
Endometrioid	78 (70%)
G1	36 (32%)
G2	27 (24%)
G3	15 (13%)
Serous	15 (13%)
Clear cell	7 (6%)
Mixed (endometrioid + serous)	6 (5%)
Others	6 (5%)
Primary treatment	
Surgery	98 (88%)
Chemotherapy	1 (0.9%)
Radiotherapy	3 (3%)
Adjuvant chemotherapy	64 (57%)
Adjuvant radiotherapy	27 (24%)
Secondary treatment	
Surgery	29 (26%)
Chemotherapy	44 (39%)
Radiotherapy	15 (13%)
Radiotherapy + chemotherapy	12 (11%)
Best supportive care	12 (11%)

TFI treatment-free interval, *FIGO* International Federation of Gynecology and Obstetrics

Surgical procedures and outcomes

The median OS of 29 patients after SCS was 43 (range 4–295) months. All visible tumors were completely resected in 18 (62%) patients, whereas 10 (34%) and 1 (3%) had residual tumors < 1 and ≥ 1 cm at the time of SCS. The OS was significantly better for patients with completely resected tumors after SCS than those with any size of residual tumor (median 68 vs. 20 months, $p = 0.001$; Fig. 1b). Among all patients who underwent therapy for recurrence, those treated by complete resection had significantly better OS after recurrence than those who underwent surgery with any size of

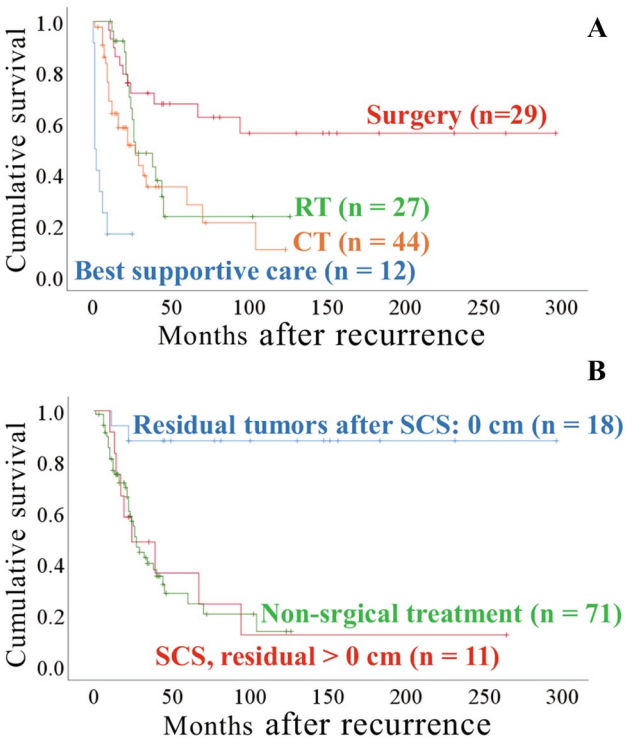

Fig. 1 Kaplan–Meier curves for overall survival after diagnosis of recurrence. **a** Overall survival after diagnosis of recurrence in patients who underwent chemotherapy (CT; $n=44$), surgery ($n=29$), radiotherapy (RT; $n=27$) and best supportive care ($n=12$). Surgery vs. CT; $p=0.002$. Surgery vs. RT; $p=0.046$. **b** Overall survival after recurrence according to treatment and residual disease. Survival of patients who underwent surgery with no visible tumor ($n=18$), surgery with any size of residual tumor ($n=11$) and non-surgical treatment ($n=71$). SCS 0 vs. > 0 cm; $p=0.001$. SCS 0 vs. non-SCS; $p=0.00005$. SCS > 0 cm vs. non-SCS $p=0.92$

residual tumor or non-surgical treatment (median 81, 23 and 21 months; $p=0.001$ and 0.00005, respectively; Fig. 1b). However, the difference in OS after recurrence between patients who were surgically treated for any size of residual tumor and those who were non-surgically treated did not reach significance ($p=0.92$; Fig. 1b). Supplementary Table 1 shows the surgical procedures.

The median blood loss was 130 (range 0–2518) mL (Supplementary Table 1). Two (7%) patients required blood transfusions and 6 (21%) developed perioperative complications, among which one had intestinal perforation and a pelvic abscess that required surgical management. None of the patients died during the perioperative period.

Predictors of survival

Clinicopathologic variables determined at primary cytoreductive surgery (PCS), and before and at SCS were analyzed using univariate and multivariate analyses. Univariate analysis for variables determined at PCS significantly associated FIGO stage (I/II vs. III/IV), pelvic and/or aortic node metastases (absent vs. present), and histology (endometrioid vs. non-endometrioid) with better OS after SCS ($p=0.005$, 0.002 and 0.047, respectively; Table 2). Univariate analysis of variables determined before SCS showed that TFI (≤ 24 vs. > 24 months), peritoneal dissemination (absent vs. present), and Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 vs. 1–2) were significantly associated with better OS after SCS ($p=0.025$, 0.027 and 0.0004, respectively; Table 2). We then entered factors that were significant in univariate analysis into multivariate analysis. Because pelvic and/or aortic node metastases (absent vs. present) correlate with FIGO stage (I/II vs. III/IV), we selected pelvic and/or aortic node metastases with lower p values. Subsequent multivariate analysis showed that PS 0 and endometrioid histology were significant and independent indicators of better OS after SCS ($p=0.005$ and 0.049; Table 2). Univariate analysis of variables determined at SCS significantly associated only residual tumors (none vs. any) with better OS after SCS ($p=0.001$; Table 3). Next, we correlated clinicopathological variables before SCS to complete resection at SCS. Univariate analysis revealed that pelvic and/or aortic node metastases at PCS, peritoneal dissemination, number of recurrent tumors, and PS at recurrence were significantly associated with the rate of complete resection at SCS ($p=0.012$, 0.011, 0.028 and 0.005; Table 4). However, the subsequent multivariate analysis found none of those factors to be significant for SCS outcome (Table 4).

The number of significant favorable prognostic factors determined before SCS, namely endometrioid histology and PS 0, was significantly associated with better OS after SCS (Fig. 2). Patients with both factors had significantly better OS after SCS than those with one or no factors (median 75, 19, and 4 months; $p=0.001$ and 0.00001, respectively; Fig. 2). Additionally, the number of predictors for favorable survival after SCS was significantly associated with the rate of complete resection during SCS: 16 (84%) of 19 patients with 2 factors, 2 (22%) of 9 with 1, and 0 (0%) of 1 of the patients with no factors underwent complete resection of all visible tumors ($p=0.001$; Table 5).

Eight (28%) patients underwent chemotherapy before SCS. One (3%) patient had no adjuvant therapy after SCS, 24 (83%) received platinum-based chemotherapy and one (3%) patient each underwent radiotherapy alone and both platinum-based chemotherapy and radiotherapy, respectively. Neither chemotherapy before or after SCS was significant for OS after SCS ($p=0.57$, Table 2 and 0.9; data not shown).

Table 2 Univariate and multivariate analyses for variables at PCS and at recurrence before SCS

Variables	Number ($n = 29$)	Median survival after SCS (months)	Univariate p	Multivariate	
				HR (95% CI)	p
At PCS					
Tumor spread					
Localized to the pelvis	23	60			
Extended beyond the pelvis	6	31	0.54		
FIGO stage					
I/II	11	98			
III/IV	18	27	0.005		
Pelvic and/or paraaortic lymph node metastasis					
Absent	22	64		3.86 (0.92–16.12)	
Present	7	19	0.002	1.00	0.06
Histology					
Endometrioid	26	54		1.00	
Non-endometrioid	3	10	0.047	9.07 (1.01–81.66)	0.049
Residual tumor at PCS					
None	26	54			
Any	3	19	0.89		
At recurrence before SCS					
Age at recurrence (years)					
< 60	15	47			
≥ 60	14	42	0.61		
TFI (months)					
< 24	13	19		3.10 (0.73–13.13)	
≥ 24	16	71	0.025	1.00	0.12
Pelvic and/or paraaortic lymph node metastasis (CT)					
No	23	47			
Yes	6	31	0.60		
Distant metastasis (CT)					
No	13	21			
Yes	15	64	0.22		
Lung metastasis alone (CT)					
No	21	33			
Yes	8	71	0.24		
Peritoneal dissemination (CT)					
No	17	67		1.00	
Yes	12	24	0.027	1.17 (0.23–6.02)	0.85
No. of recurrent tumors (CT)					
One	11	98			
Several	18	37	0.20		
Size of largest tumor on CT (mm)					
< 30	18	44			
≥ 30	11	43	0.35		
ECOG performance status					
0	21	60		6.96 (1.82–26.56)	
1–2	8	17	0.0004	1.00	0.005
Neoadjuvant chemotherapy					
No	21	47			
Yes	8	27	0.57		

CI confidence interval, *CT* computed tomography, *ECOG* Eastern Cooperative Oncology Group, *FIGO* International Federation of Gynecology and Obstetrics, *HR* hazard ratio, *PCS* primary cytoreductive surgery, *SCS* secondary cytoreductive surgery, *TFI* treatment-free interval

Table 3 Univariate analysis for variables at SCS

	Number ($n = 29$)	Median survival after SCS (months)	p
No. of recurrent tumors			
One	7	98	
Several	22	37	0.39
Pulmonary lobectomy			
No	21	33	
Yes	8	71	0.24
Bowel resection			
No	23	47	
Yes	6	16	0.07
Complications			
No	23	47	
Yes	6	28	0.41
Residual tumor at SCS			
None	18	68	
> 0 cm	11	20	0.001

SCS secondary cytoreductive surgery

Discussion

Our survival analysis showed that patients who were surgically treated had a significantly better OS after recurrence than those who received chemotherapy or radiotherapy (Fig. 1a). Among all patients with recurrent EC, the OS after recurrence was relatively favorable compared with that in a recent multicenter retrospective study from France (median OS after recurrence: 21 vs. 14.8 months) [12], indicating that SCS was effective. A recent study by Iwase et al. also found that the median OS after recurrence among patients undergoing surgery and/or radiotherapy was significantly better than that of patients who received chemotherapy alone or best supportive care (39, 22 and 8 months; $p = 0.0011$) [13]. These findings suggested that SCS improves survival among carefully selected patients. However, patients with recurrence treated by surgery might have more favorable prognostic factors such as less extensive tumors, a longer TFI and better PS than those who received other therapies. Further analyses and prospective trials are needed to clarify the survival benefit of SCS for patients with recurrent EC.

Our survival analysis significantly associated complete resection of all visible tumors during SCS with favorable survival (Fig. 1b). Furthermore, univariate analysis of variables determined at SCS significantly associated only the absence of residual tumors with better OS after SCS (Table 3). Seven non-randomized retrospective studies to date have investigated predictors of favorable survival after SCS for patients with recurrent EC [5–11] (Supplementary Table 2). Among these including the present study, the amount of residual tumor at SCS was consistently identified as an independent prognostic factor for survival after SCS. However, the definition of optimal surgery differed among studies. Five of eight studies defined optimal surgery as no visible residual tumor at SCS. Campagnutta et al. [6] and Ren et al. [9] defined optimal surgery as residual tumor < 1 cm, and Awtrey et al. [8] defined optimal surgery as residual tumor < 2 cm. A meta-analysis of a series of 14 patients with advanced or recurrent EC associated significantly improved survival with complete resection at surgery [14]. Moreover, we found no difference in OS after recurrence between patients who underwent surgery with any size of residual tumor and those who received non-surgical treatment (Fig. 1b). Therefore, complete resection should perhaps be the SCS goal for recurrent EC. Further large studies are needed to confirm this notion.

Our univariate and multivariate analyses of prognostic factors suggested that patients with endometrioid histology might benefit from SCS (Table 2). A recent retrospective cohort study by Papadia et al. [10] also identified endometrioid histology as an independent prognostic factor for favorable survival after SCS ($p < 0.009$) (Supplementary Table 2). Ren et al. [9] associated low-grade tumors with favorable survival after SCS in the largest single-center study to date ($p = 0.012$). Tumors are generally less aggressive when they have endometrioid, compared with non-endometrioid histology. Previous studies of primary EC have demonstrated that the prognosis is better for patients with endometrioid, than non-endometrioid histology [15]. Primary tumors with an indolent phenotype might affect survival after SCS depending on tumor extent, resectability and the chemosensitivity of recurrent disease. However, multivariate analysis in a retrospective cohort study by Odagiri et al. [16] did not associate histology with survival in patients with recurrent EC. The number of patients analyzed is relatively small in the present and in the published retrospective studies. Our findings should be validated in larger cohorts.

We also identified PS as an independent prognostic factor for favorable survival in the univariate and multivariate analyses. Only two studies have identified PS as a prognostic factor for survival after SCS [9, 10]. An observational cohort study by Papadia et al. significantly associated PS 0 with complete resection at SCS, but not with favorable survival [10]. With respect to recurrent ovarian cancer, several studies selected PS as an independent prognostic factor for favorable survival after SCS [17–19]. The prospective DESKTOP II study of recurrent ovarian cancer [20] validated the findings that the AGO score, (1) PS 0, (2) complete

Table 4 Univariate and multivariate analyses between clinicopathological variables before SCS and outcome of SCS

Variables	Outcome of SCS		Univariate *p*	Multivariate *p*
	Incomplete	Complete		
At PCS				
Tumor spread			0.78	
Localized to the pelvis	9 (39%)	14 (61%)		
Extended beyond the pelvis	2 (33%)	4 (67%)		
FIGO stage			0.56	
I/II	3 (27%)	8 (73%)		
III/IV	8 (44%)	10 (56%)		
Pelvic and/or paraaortic lymph node metastasis			0.012	0.99
Absent	5 (23%)	17 (77%)		
Present	6 (86%)	1 (14%)		
Histology			0.30	
Endometrioid	9 (35%)	17 (65%)		
Non-endometrioid	2 (67%)	1 (33%)		
Residual tumor at PCS			0.86	
None	10 (38%)	16 (62%)		
Any	1 (33%)	2 (67%)		
At recurrence before SCS				
Age at recurrence (y)			0.60	
< 60	5 (33%)	10 (67%)		
≥ 60	6 (43%)	8 (57%)		
TFI (months)			0.41	
< 24	6 (46%)	7 (54%)		
≥ 24	5 (31%)	11 (69%)		
Pelvic and/or paraaortic lymph node metastasis (CT)			0.86	
No	8 (35%)	15 (65%)		
Yes	3 (50%)	3 (50%)		
Distant metastasis (CT)			0.96	
No	5 (38%)	8 (62%)		
Yes	6 (37%)	10 (63%)		
Lung metastasis alone (CT)			0.38	
No	9 (43%)	12 (57%)		
Yes	2 (25%)	6 (75%)		
Peritoneal dissemination (CT)			0.011	0.99
No	3 (18%)	14 (82%)		
Yes	8 (67%)	4 (33%)		
No. of recurrent tumors (CT)			0.028	0.58
One	1 (9%)	10 (91%)		
Several	10 (56%)	8 (44%)		
Size of largest tumor on CT (mm)			0.89	
< 30	7 (39%)	11 (61%)		
≥ 30	4 (36%)	7 (64%)		
ECOG performance status			0.005	0.99
0	4 (19%)	17 (81%)		
1–2	7 (88%)	1 (13%)		
Neoadjuvant chemotherapy			0.98	
No	8 (38%)	13 (62%)		
Yes	3 (37%)	5 (63%)		

CT computed tomography, *ECOG* Eastern Cooperative Oncology Group, *FIGO* International Federation of Gynecology and Obstetrics, *HR* hazard ratio, *PCS* primary cytoreductive surgery, *SCS* secondary cytoreductive surgery, *TFI* treatment-free interval

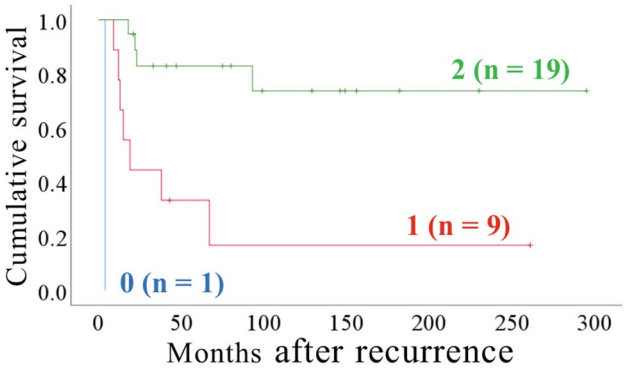

Fig. 2 Kaplan–Meier curves for overall survival after SCS based on a number of favorable prognostic factors. Overall survival of patients with two ($n=19$), one ($n=9$) and no ($n=1$) factors. 2 vs. 1; $p=0.001$. 2 vs. 0; $p=0.00005$. 1 vs. 0 $p=0.003$

resection at primary surgery and (3) the absence of ascites (< 500 mL) predict complete resection at SCS. The prospective randomized multicenter DESKTOP III trial is currently ongoing. As regards predictive factors for SCS outcome, our univariate and multivariate analyses failed to find any factors to be significant and independent for complete resection at SCS (Table 4). However, it is still important to take account of complete resectability when we select the patients for SCS, as complete resection at SCS significantly correlated with better OS (Fig. 1b, Table 3).

Among variables determined before SCS, endometrioid histology (1) and PS 0 (2) were identified as significant and independent factors for favorable survival after SCS in the present study (Table 2). Overall survival was significantly better for patients with both of these factors compared with having one or none of them (Fig. 2). Moreover, the number of predictors for favorable survival was significantly associated with the rate of complete resection at SCS (Table 2). Preoperative selection criteria might enable the identification of patients who are likely to achieve successful SCS. We propose that patients who have both factors should be offered the opportunity to undergo SCS.

The morbidity and mortality associated with SCS should be considered. None of our patients died during the perioperative period. Among the six (21%) patients who developed perioperative complications, only one required surgery (for intestinal perforation and a pelvic abscess). The rate of complications in our study was similar to those in previous studies (12–63%; Supplementary Table 2). According to Campagnutta et al., among 75 patients who received SCS for recurrent EC including 13 (18%) undergoing pelvic exenteration, 23 (30%) developed major surgical complications [6]. The mortality rate was 1.5% within 30 days after SCS, but this increased to 8% when considering all patients who died before discharge from hospital. The morbidity in our study was acceptable, suggesting that patient selection was adequate.

Some limitations of the present study should be acknowledged. The sample size was rather small for statistical analyses. The retrospective design might have led to selection bias. Prospective trials are necessary to confirm our selection criteria. The treatment strategies for patients with EC were not consistent throughout the study. We cannot exclude the possibility that these factors might have affected our findings.

In conclusion, we retrospectively analyzed patients with recurrent EC who underwent SCS to identify predictors of favorable survival. We found that complete resection at SCS was a significant prognostic factor for survival, suggesting that effort should be directed towards achieving complete resection by SCS. Endometrioid histology and PS 0 were identified as significant and independent favorable prognostic factors. Survival was significantly better for patients with endometrioid histology and PS 0 than either one or none. Accordingly, we propose that these patients should be offered the choice of SCS. A prospective trial is warranted to verify this notion.

Table 5 Survival based on number of predictors of favorable survival and SCS outcomes

Median survival after SCS (months)	Outcome of SCS	
	Incomplete resection	Complete resection
No. of predictors of favorable survival after SCS[a]		
0	4 ($n=1$)[b]	– ($n=0$)[b]
1	19 ($n=7$)[b]	26 ($n=2$)[b]
2	33 ($n=3$)[b]	87 ($n=16$)[b]

ECOG Eastern Cooperative Oncology Group, *SCS* secondary cytoreductive surgery

[a]Predictors of favorable survival after SCS: (1) endometrioid histology; (2) ECOG performance status 0

[b]$p=0.001$; Fisher exact test

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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