Multivariate survival analysis of the patients with recurrent endometrial cancer

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Objective: Few studies on the prognosticators of the patients with recurrent endometrial cancer after relapse have been reported in the literature. The aim of this study was to determine the prognosticators after relapse in patients with recurrent endometrial cancer who underwent primary complete cytoreductive surgery and adjuvant chemotherapy.

Methods: Thirty-five patients with recurrent endometrial cancer were included in this retrospective analysis. The prognostic significance of several clinicopathological factors including histologic type, risk for recurrence, time to relapse after primary surgery, number of relapse sites, site of relapse, treatment modality, and complete resection of recurrent tumors were evaluated. Survival analyses were performed by Kaplan-Meier curves and the log-rank test. Independent prognostic factors were determined by multivariate Cox regression analysis.

Results: Among the clinicopathological factors analyzed, histologic type (p=0.04), time to relapse after primary surgery (p=0.03), and the number of relapse sites (p=0.03) were significantly related to survival after relapse. Multivariate analysis revealed that time to relapse after primary surgery (hazard ratio, 6.8; p=0.004) and the number of relapse sites (hazard ratio, 11.1; p=0.002) were independent prognostic factors for survival after relapse. Survival after relapse could be stratified into three groups by the combination of two independent prognostic factors.

Conclusion: We conclude that time to relapse after primary surgery, and the number of relapse sites were independent prognostic factors for survival after relapse in patients with recurrent endometrial cancer.

Keywords: Endometrial cancer, Recurrence, Prognostic factor, Multivariate analysis

INTRODUCTION

The number of patients with endometrial cancer is increasing in Japan as well as in the United States and other countries [1]. A majority of endometrial cancer patients are diagnosed as being without clinical evidence of extrauterine spread (FIGO stage I and II) and have a 5-year survival of approximately 90%. Approximately 10% to 15% of patients with early stage endometrial cancer will experience recurrences [2,3]. To reduce the recurrence rate, adjuvant chemotherapy or radiotherapy has been applied. However, a definite standard therapy has not yet been established.

Recently, the number of patients with recurrent endometrial cancer and advanced-stage disease is also increasing. For stage III-IV endometrial cancer, Randall et al. [4] recently reported that platinum-doxorubicin (AP) chemotherapy showed significantly better survival effect than whole abdominal irradiation (WAI) as an adjuvant treatment for

advanced-stage endometrial cancer. Although cytotoxic chemotherapy has been used primarily as palliative therapy for patients with advanced endometrial cancer, there is relatively little experience with postoperative systemic chemotherapy used as an adjuvant treatment in western countries. However, with the introduction of routine surgical staging, we have performed extensive surgery including systematic pelvic and para-aortic lymphadenectomy and post-surgical cisplatin-based systemic chemotherapy for patients with intermediate or high risk of recurrence [5,6]. We have recently reported the prognosis and failure pattern of endometrial cancer patients treated with our treatment strategy, demonstrating better survival of node-positive patients with endometrial cancer compared to that reported in the literature [6]. We also revealed that distant failure was the most prevalent pattern of failure in spite of systemic adjuvant chemotherapy, suggesting that we need to optimize primary treatment and treatment after relapse to further improve survival of endometrial cancer [6].

While endometrial cancer is a highly curable malignancy when it presents as a uterine-confined disease, the prognosis for recurrent or metastatic disease is poor. The median survival of women enrolled in trials for recurrent or metastatic endometrial cancer hardly exceeds 12 months [7]. There is still no agreement in the literature regarding the most adequate treatment for those patients. Thus, it is important to establish a prognostic model to predict survival after relapse in endometrial cancer.

Therefore, the aim of this retrospective study was to determine the factors influencing survival of relapsing patients, and to assess an alternative strategy to routine adjuvant chemotherapy.

MATERIALS AND METHODS

1. Patients

A total of 316 patients with endometrial cancer underwent primary treatment with complete cytoreductive surgery and adjuvant chemotherapy from 1995 to 2008 at the Department of Obstetrics and Gynecology, Hokkaido University Hospital. All subjects underwent modified radical hysterectomy, bilateral salpingo-oophorectomy with systematic retroperitoneal lymphadenectomy [5,6]. Some patients did not receive lymphadenectomy because of their performance status or personal refusal. Thirty-five patients, whose complete follow-up information (especially exact date of relapse, treatment modality, and survival information) after relapse was available, were registered in this retrospective study. Stage IV disease with distant metastasis (liver or lung

metastasis) was excluded from this analysis. We therefore defined stage IV patients showing peritoneal metastasis. In this study, we defined the patients with high risk or low risk for recurrence as those having stage III/IV disease or stage IA/IB with no/minimal lymphovascular space invasion, respectively. The others are classified as the intermediate risk group. All patients with intermediate or high risk for recurrence were usually treated with platinum-based adjuvant chemotherapy (cyclophosphamide, 350 mg/m^2; adriamycin, 40 mg/m^2 and cisplatin, 50-70 mg/m^2 or paclitaxel, 175 mg/m^2; carboplatin, AUC5) every 3 weeks when necessary. We administered six cycles of chemotherapy after the initial surgery.

Disease-relapse was diagnosed when physical examination with cytological or pathological examination, and systemic enhanced CT indicated recurrent or metastatic tumors during the follow-up period. Patterns of failure were divided into two groups, intrapelvic failures (vaginal or pelvic failure) and extrapelvic failures (distant failure and peritoneal failure) in this study. In cases with both failures, they were included in the extrapelvic failure group.

The following clinicopathological factors were included in this survival analysis: risk for recurrence described above, histologic type (endometrioid vs. non-endometrioid), time to relapse after primary surgery (within one year vs. over one year), number of relapse sites (single vs. multiple), site of relapse (intrapelvic vs. extrapelvic), treatment modality (chemotherapy alone vs. multimodalities), complete resection of recurrent tumors. Extrapelvic failures also included simultaneous failures to intrapelvic and extrapelvic sites in this analysis. Multiple relapse sites included metastasis to multiple organs, multiple metastatic lesions in the same organ, and peritoneal dissemination in this study.

2. Statistics

Patient survival was calculated using the Kaplan-Meier method. The significance of the survival difference was examined by the log-rank test. A $p < 0.05$ was considered statistically significant. Statistical analyses were performed with the Statview (SAS Inc., Cary, NC, USA) as previously described [5,6].

RESULTS

1. Relapse site and treatment modality for recurrent endometrial cancer

Clinicopathological characteristics of thirty-five patients with recurrent endometrial cancer at initial treatment are listed in Table 1. The median age was fifty-seven years (range, 14 to 73

years). The median follow-up period after primary surgery was 41 months (range, 2 to 161 months). According to the results of surgical staging, we provided adjuvant therapy for patients with risk for disease recurrence, including twelve intermediate risk and twenty high risk patients. Three patients with low risk for recurrence did not receive any adjuvant therapy. Median duration for progression from primary surgery was 20 months (range, 1 to 79 months). Median survival after relapse was 19 months (range, 1 to 121 months).

Among thirty-five patients, eight patients resulted in intrapelvic failure (four, vaginal; four, pelvic), twenty-seven extrapelvic failure (twenty, distant; four, peritoneal; and three, both). Seventeen patients received systemic platinum-based chemotherapy alone, eighteen multimodalities consisting of combination of debulking surgery, chemotherapy, or radiotherapy. We administered mainly taxane/platinum (paclitaxel or docetaxel and carboplatin) for recurrent disease (21 cases). Some patients received AP (adriamycin/cisplatin) regimen (five cases), and others (two cases). Five patients received debulking surgery with complete resection of recurrent tumors followed by adjuvant therapy.

Table 1. Clinicopathological characteristics of recurrent endometrial cancer

Factor	No. (%)
FIGO stage	
I/II	15 (42.9)
III/IV	20 (57.1)
Histologic type	
Endometrioid	22 (62.9)
Non-endometrioid	13 (37.1)
Grade	
G1	3 (8.6)
G2	21 (60.0)
G3	11 (31.4)
Myoinvasion	
≤1/2	14 (40.0)
>1/2	21 (60.0)
Lymphovascular space invasion*	
(-)/(+)	24 (68.6)
(++)/(+++)	11 (31.4)
Cervical invasion	
(-)	28 (80.0)
(+)	7 (20.0)
Ovarian metastasis	
(-)	24 (68.6)
(+)	11 (31.4)
Lymph node metastasis	
(-)	22 (62.9)
(+)	8 (22.8)
Unknown	5 (14.3)
Risk of recurrence	
Low/intermediate	15 (42.9)
High	20 (57.1)

*Lymphovascular space invasion was graded as previously described by Nishiya et al. [8].

Table 2. Risk factors related to survival after recurrence

Factor	No. (%)
Histologic type	
Endometrioid	22 (62.9)
Non-endometrioid	13 (37.1)
Risk for recurrence	
Low/intermediate	15 (42.9)
High	20 (57.1)
Time to relapse	
Over one year	11 (31.4)
Within one year	24 (68.6)
No. of relapse sites	
Single	13 (37.1)
Multiple	22 (62.9)
Relapse site	
Intrapelvic	8 (22.9)
Extrapelvic	27 (77.1)
Complete surgical resection	
(+)	5 (14.3)
(-)	30 (85.7)
Treatment modality	
Multimodality	18 (51.4)
Chemotherapy alone	17 (48.6)

Table 3. Multivariate analysis on risk factors for recurrent endometrial cancer

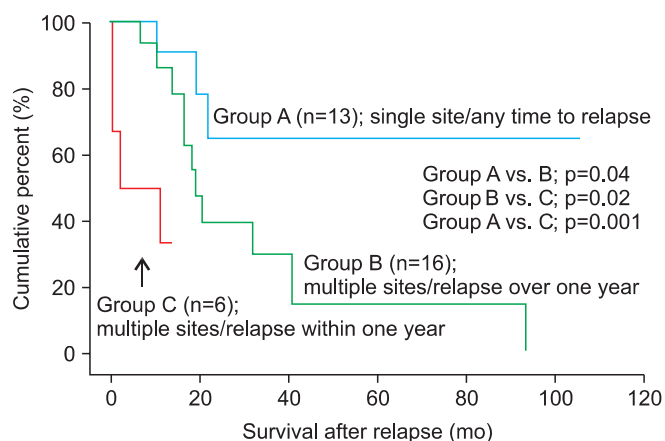|	Univariate	Multivariate		
Clinicopathologic factor	p-value	Risk ratio	95% CI	p-value
Histologic type	0.04	2.4	0.8-6.8	0.11
Risk for recurrence	0.07	-	-	-
Time to relapse	0.03	6.8	1.9-25.0	0.004
Number of relapse sites	0.03	11.1	2.3-52.6	0.002
Site of relapse	0.11	-	-	-
Complete surgical resection	0.22	-	-	-
Treatment modality	0.45	-	-	-

CI: confidence interval.

Fig. 1. Stratificatiion of survival of patients with recurrent endometrial cancer by the combination of two independent prognostic factors. Survival after relapse with recurrent endometrial cancer was stratified into three groups according to the combination of time to relapse after primary surgery and number of relapse sites. Survival after relapse was significantly different between each group.

Univariate and multivariate survival analysis for the patients with recurrent disease (Tables 2 and 3, Fig. 1).

Table 2 shows the result of distribution of seven clinico-pathological factors in thirty-five patients. Among the clinico-pathological factors analyzed, histologic type (p=0.04), time to relapse after primary surgery (p=0.03), and number of relapse sites (p=0.03) were related to survival after relapse. Risk for recurrence showed marginal significance for survival (p=0.07), while site of relapse (p=0.11), treatment modality (p=0.45), and complete resection of recurrent tumors (p=0.22) did not show prognostic significance for recurrent endometrial cancer in our patient cohort. Multivariate analysis revealed that time to relapse after primary surgery (hazard ratio, 6.8; p=0.004) and number of relapse sites (hazard ratio, 11.1; p=0.002) were independent prognostic factors for survival after relapse. Histologic type was found not to be an independent prognosticator (p=0.11) (Table 3).

Survival after relapse of patients with recurrent disease could be stratified into three groups by the combination of two independent prognosticators. An estimated 3-year survival rate for the patients with single relapse site, irrespective of time to relapse (group A, n=12), was 64.9 %, and for multiple relapse sites with relapse over one year (group B, n=17) was 39.2 %. The patients with multiple relapse sites who relapsed within one year (group C, n=6) did not reach 3 years after relapse (33.3 % at 16 months). There was statistically significant difference of survival among each group (p=0.001 for group A vs. group C, p=0.04 for group A vs. group B, p=0.02 for group B vs. group C) (Fig. 1).

DISCUSSION

In the present study, we analyzed the prognosticators for survival after relapse in patients with recurrent endometrial cancer who underwent primary complete cytoreductive surgery combined mainly with adjuvant chemotherapy. We first demonstrated that time to relapse after primary surgery and the number of relapse sites are independent prognostic factors for survival of recurrent endometrial cancer in this study.

In the literature, prognostic analyses have been reported for patients with recurrent endometrial cancer who received primary surgery and adjuvant radiotherapy. Previously reported studies had indicated histological grading of the tumor [9,10] and time to progression interval [10] as the most important prognostic factors in the recurrent and metastatic cancer setting. Sartori et al. [11] previously reported that site of relapse, the interval of time from original surgery to recurrence, and whether postoperative pelvic radiotherapy was administered were independent prognostic variables for survival by multivariate analysis in recurrent endometrial cancer. Sohaib et al. [12] reported that multivariate analysis identified multiple sites of disease, liver and splenic metastases to be independent predictors of poor outcome in recurrent endometrial cancer. Thus, this study may be the first report, as far as we know, on the prognostic analysis for patients with recurrent endometrial cancer treated with primary surgery and adjuvant chemotherapy.

Although the exact reason why two factors are independently related to survival after relapse remains to be determined, it is easy to speculate the possible reasons. Time to relapse within one year after primary surgery may largely depend on the aggressive phenotype and resistance to adjuvant chemotherapy of endometrial cancer cells, and multiple sites of recurrence may be related to the metastatic potential of endometrial cancer cells. Therefore, we need to establish a new treatment strategy to efficiently treat patients with recurrent endometrial cancer in addition to currently available treatment modalities including debulking surgery, chemotherapy, and radiotherapy. One of the promising molecular targeting agents is the vascular endothelial growth factor inhibitor, bevacizumab, which has been recently shown to improve progression-free survival of the patients with ovarian cancer [13]. To search for new molecular markers to predict survival after relapse and/or new molecular targets to improve survival, we need to further investigate the molecular mechanism of chemoresistance and radioresistance in endometrial cancer cells. Cyr61, a member of CCN family, may be a good target because Cyr61 predicts survival of patients

with endometrial cancer [14], and has been reported to induce resistance to carboplatin in ovarian cancer cells [15] and resistance to paclitaxel in breast cancer [16]. Additionally, we need to investigate the molecular mechanism on the metastasis and invasion process of endometrial cancer cells.

Complete resection of recurrent tumors has been reported to be a prognosticator for recurrent endometrial cancer in the literature [17], while this is not related to survival in our patient cohort. This may be due to the small number of analyzed cases. Another possibility is because debulking surgery is usually applied to selected patients with a single relapse site, which was independent prognostic factor for survival after relapse in this study. Histologic type was significantly related to survival after relapse in univariate analysis, whereas not after multivariate analysis in this study. This is probably because the patients with non-endometrioid histology tend to recur with shorter progression-free survival than those with endometrioid types, and time to relapse within one year after primary surgery was an independent prognostic factor in this study. Similar to all retrospective studies, the number of patients is fairly small and our findings need to be further validated in larger cohorts.

Since the prognosis of the patients with recurrent endometrial cancer generally remains poor, and risk for recurrence showed marginal significance for survival after relapse in this study as well as in our previous study [17], we need to reconsider the current best treatment strategy as a primary treatment. We have recently shown that para-aortic lymphadenectomy significantly improves recurrence-free survival and overall survival of endometrial cancer patients with intermediate or high risk for recurrence [18]. Therefore, we should offer a better treatment strategy consisting of extensive surgery including systematic para-aortic lymphadenectomy and systemic adjuvant chemotherapy to provide better survival benefit for patients with intermediate/high risk for recurrence. On the contrary, endometrial cancer patients with low risk for recurrence may not need to receive neither adjuvant treatment nor extensive lymphadenectomy including para-aortic nodes as previously reported by Mariani, et al. [19].

In summary, time to relapse after primary surgery and the number of relapse sites are independent prognosticators for survival after relapse in patients with recurrent endometrial cancer. We need to offer the opportunity to participate in clinical trials to establish new treatment strategies using molecular targeting drugs for recurrent endometrial cancer patients. We also need to further investigate the molecular mechanisms governing sensitivity to chemotherapy and radiotherapy, and the metastatic processes in endometrial cancer cells to establish new treatment strategy for recurrent cases.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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