Disease-free Interval after Primary Treatment Predicts Prognosis of Recurrent Endometrial Carcinoma

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Abstract. *Aim: The aim of this study was to determine if the disease-free interval after initial surgical resection has any useful prognostic value for recurrent endometrial carcinoma patients. Patients and Methods: Between 1998 and 2007, complete resection of endometrial carcinoma was achieved in 536 cases at the Departments of Obstetrics and Gynecology of the Osaka University and Osaka Rosai Hospitals of Osaka, Japan. Clinical characteristics of these cases were retrospectively reviewed. Results: Recurrence was subsequently detected in 54 cases. Overall survival after recurrence in 27 patients with recurrences earlier than 12 months who received no postoperative therapy, radiation, and chemotherapy as an adjuvant therapy were significantly shorter than that of those with recurrences later than 12 months with similar treatments. Multivariate analysis demonstrated that the disease-free interval was an independent factor for prognosis. Conclusion: We demonstrate a significantly worse prognosis in cases with early versus late recurrence of resected endometrial carcinomas, irrespective of the type of adjuvant therapy.*

The incidence of uterine endometrial carcinoma, already the most common malignancy of the female pelvis and the fourth most common cancer of women in the United States, has increased steadily during the last three decades (1, 2). The prognostic factors for the disease include the tumor histological type and differentiation, disease stage, peritoneal cytology, myometrial invasion and extrauterine metastasis (1, 2). In the past, radiation therapy alone was performed for endometrial cancer; however, current treatment, even for early stage endometrial cancer without any risk factors, usually consists of hysterectomy and salpingo-oophorectomy, with or without retroperitoneal lymph node dissection. Patients with poor prognostic factors in the past often underwent postoperative irradiation therapy; however, a randomized study revealed that combined chemotherapy was superior to whole abdominal irradiation as the adjuvant therapy in advanced diseases (EORTC #55872) (3). Cytoreductive surgery for extrauterine disease followed by systemic chemotherapy is now performed as the suggested standard of care (4).

A previous systematic review showed that 13% of treated endometrial cancer cases went on to develop a recurrence (5). Unfortunately, 3 to 19 years after treatment for such recurrence, only 7.7% of the patients survived without evidence of the disease (2). Recurrences restricted to the vaginal vault have been shown to be relatively better treated with radiotherapy. However, in most cases of relapse, the disease has spread to other sites, including pelvic and para-aortic lymph nodes, the peritoneum of the pelvis and abdominal cavity, and the lungs. For these cases, systemic chemotherapy is usually superior.

Most recurrences are detected within the first two years after primary surgery (6-9). The prognostic significance of this disease-free interval (DFI) has been highly controversial (6, 7, 9-17). These studies included some patients who were treated by radiotherapy alone without surgery, and the majority of patients whose tumor was surgically resected either received no adjuvant therapy or underwent postoperative radiotherapy. Our own data (unpublished) provided us with evidence that the majority of refractory or

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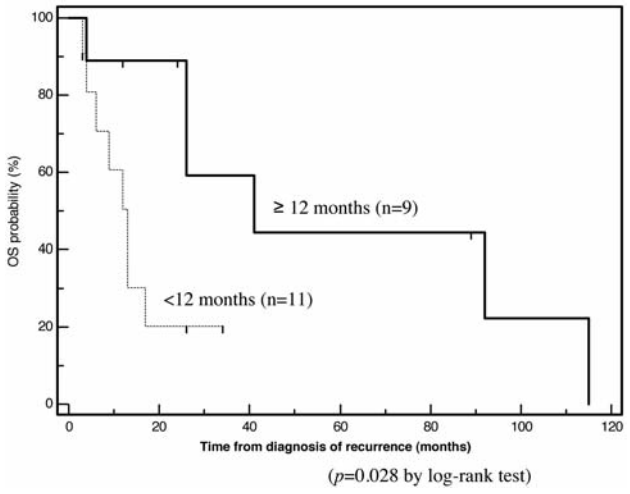

Figure 1. *Overall survival (OS) after recurrence by disease-free interval in those who did not undergo adjuvant therapy. The median OS after recurrence is shown in the cases where, at the initial treatment for endometrial cancer, any adjuvant therapy following surgery was performed. The OS of the early recurrent cases (<12 months from the initial surgery) was significantly shorter than that of the late ones (≥12 months) (p=0.028 by the log-rank test).*

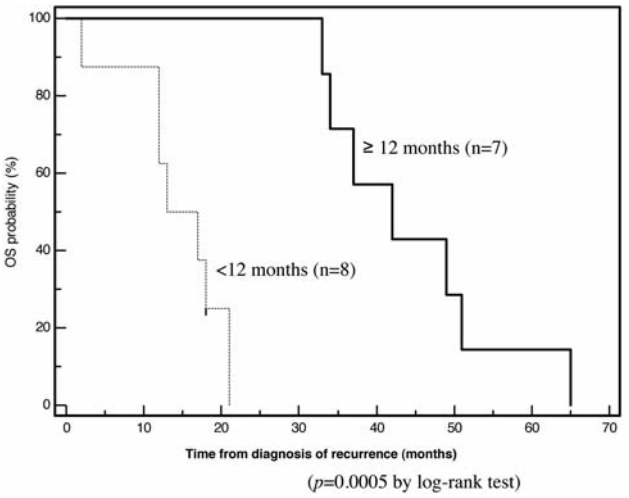

Figure 2. *Overall survival (OS) after recurrence by disease-free interval in those who underwent adjuvant radiotherapy. The median OS after recurrence is shown in the cases where adjuvant radiation was performed at the initial treatment for endometrial cancer. The OS of the early recurrent cases (<12 months from the initial surgery) was significantly shorter than that of the late ones (≥12 months) (p=0.0005 by the log-rank test).*

recurrent diseases occurring within 6 months of first-line chemotherapy are non-responsive to the current regimens of second-line chemotherapy. The recent widespread trend is to use chemotherapy as the preferred adjuvant therapy instead of radiotherapy for resected endometrial cancer.

We have now re-examined the prognostic significance of the time to recurrence in cases in which no adjuvant therapy was performed, those in which radiation was performed, and those which underwent adjuvant chemotherapy. We performed a comparison of the prognosis of the patients whose tumor recurred within 12 months from the primary surgical therapy and those detected after 12 months and we investigated the association of DFI with other factors, such as the type of adjuvant therapy, and its prognostic significance of recurrent endometrial carcinoma.

Patients and Methods

Patients. During the 10-year study period of 1998 to 2007, 555 endometrial carcinomas were diagnosed and treated within the Departments of Obstetrics and Gynecology of the Osaka University Hospital and of the Osaka Rosai Hospital of Osaka, Japan. The patients were all ethnically Asian. The diagnosis was histologically confirmed by pathologists within the respective Departments of Pathology. Complete surgical removal of the disease by total abdominal hysterectomy, bilateral salpingo-oophorectomy, staging, and a maximum cytoreduction, including a retroperitoneal lymph-node dissection, was provisionally achieved in 536 out of the 555 cases. Following surgery, adjuvant radiotherapy or chemotherapy was indicated in 284 cases having risk factors that included serous and clear cell adenocarcinomas, grade 3 endometrioid carcinoma with myometrial invasion, outer-wall myometrial invasion, remarkable lymph-vascular involvement, or development of tumors outside of the uterus. Fifty-one patients did not agree to receive any adjuvant therapy; 138 patients underwent adjuvant chemotherapy (paclitaxel, epirubicin and carboplatin (TEC) in 98 patients; paclitaxel and carboplatin (TC) in 29 patients; cisplatin, adriamycin and cyclophosphamide (CAP) in 8 patients; and some other regimen in 3 patients); 95 patients received adjuvant radiation therapy. Adjuvant therapy was not indicated for the 252 patients with low or no risk factors. After the initial tumor treatment, all patients received periodic intensive follow-up that included combinations of a pelvic-rectal examination, vaginal-vault cytology, and transvaginal ultrasonography (TV-USG), a computed tomography (CT) scan, chest X-ray and tumor marker analyses.

In the 45 cases in which recurrent diseases were detected, intensive rescue treatments, including surgical resection, radiation, and chemotherapy, were performed, except for those patients whose performance status was judged to be too poor for them to receive any therapy, or those who preferred watchful observation over intensive treatment.

Methods. We retrospectively reviewed the patients' characteristics and the clinicopathological features of all cases of endometrial carcinoma recurrence, utilizing their clinical records, which included physical examination notes, radiological reports, operation records and histology reports. Progression-free survival (PFS) after recurrence was measured from the date of diagnosis of the recurrence to the date of subsequent radiologic or pathologic relapse of the disease, or, in subsequently disease-free patients, to the date of their last known follow-up visit. Overall survival (OS) after recurrence was defined as the period from the diagnosis of the recurrence to the patient's disease-specific death, or to the date of their last known follow-up.

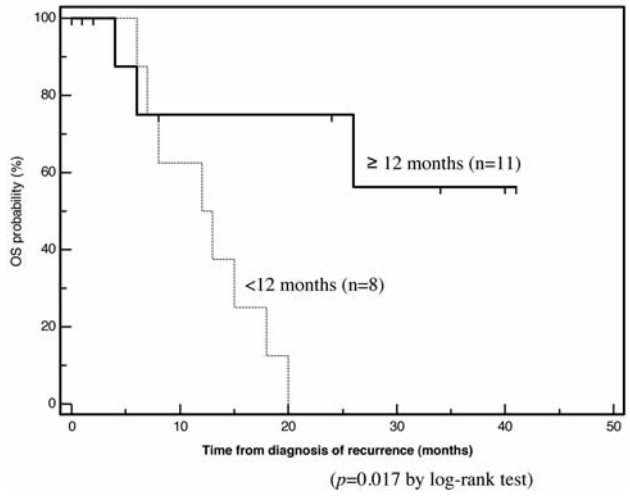

Figure 3. *Overall survival (OS) after recurrence by disease-free interval in those who underwent adjuvant chemotherapy. The median OS after recurrence is shown in the cases where adjuvant chemotherapy was performed at the initial treatment for endometrial cancer. The OS of the early recurrent cases (<12 months from the initial surgery) was significantly shorter than that of the late ones (≥12 months) (p=0.017 by the log-rank test).*

Statistical analysis. The clinicopathological characteristics of patients with recurrences that were diagnosed between early (<12 months from the initial treatment) and late (≥12 months) time periods were analyzed by Fisher's exact test, Pearson's chi-square (χ^2) test and the Mann-Whitney *U*-test. The patients with recurrence were divided into three groups according to the kind of adjuvant therapy they received: no adjuvant therapy group, radiation group, and chemotherapy group. Survival curves for the patients with early and late recurrences in each group were constructed using the Kaplan-Meier method and these results were evaluated for statistical significance by the log-rank test. A multivariate Cox proportional hazards model was used to determine the significantly important factors for survival of patients with recurrent endometrial cancer. The variables considered were: age of the patients, histology, the initial stage, adjuvant therapy, DFI, recurrent site, symptoms present at the time of detection of recurrence, and the treatment given for the recurrent disease. The results were considered to be significant when the *p*-value was less than 0.05.

Statements of ethics or conflicts of interest. Our Institutional Review Board and Ethics Committee approved this study. There were no known conflicts of interest.

Results

Clinical characteristics of the patients with recurrent endometrial cancer. During their post-surgical follow-up period (median 43 months, range 2-108 months), a recurrence was detected in 54 (10%) out of the 536 completely resected cases. The clinical characteristics of these cases are shown in Table I. Adjuvant therapy was performed in 34 of the 54 cases at initial treatment of their endometrial carcinoma. Fifteen patients received radiation and 19 patients underwent chemotherapy. Twenty-seven cases (50%) recurred in less than 12 months from the initial surgery and the other 27 cases (50%) recurred after 12 months.

Survival prognosis of the early and late recurrent cases. The OS of the early recurrent cases was significantly worse than that of the late ones ($p<0.0001$ by the log-rank test). Histology (endometrioid *versus* non-endometrioid), initial stage (I/II *versus* III/IV), adjuvant therapy (none *versus* radiation *versus* chemotherapy), symptom at recurrence (symptomatic *versus* asymptomatic), site of recurrence (localized *versus* metastatic) and treatment for recurrence (none *versus* performed) did not show any significant difference between early and late recurrent cases. However, the median ages of patient with early and late recurrences were 57 (33-83) and 62 (41-77) years, exhibiting a statistically significant difference ($p=0.021$ by the Mann-Whitney *U*-test) (data not shown).

The OS of the early and late recurrent cases were evaluated in each adjuvant therapy group. In those who did not undergo any adjuvant therapy, recurrence was detected early (<12 months) in 11 patients and late (≥12 months) in 9 patients. The median OS of the early and the late recurrent cases were 13 months and 41 months, respectively, demonstrating a statistically significant difference ($p=0.028$ by the log-rank test) (Figure 1). In those who received radiation as an adjuvant therapy, recurrence was detected early in 8 patients and late in 7 patients. The median OS of the early and the late recurrent cases were 15 months and 42 months, respectively, also demonstrating a statistically significant difference ($p=0.0005$ by the log-rank test) (Figure 2). In those who underwent adjuvant chemotherapy, recurrence was detected early in 8 patients and late in 11 patients. The median OS of the early recurrent cases was 12.5 months. On the other hand, it was not possible to calculate the OS of the late ones because more than the half (8 out of 11) of the patients were still alive at the time of our last analysis. However, OS curves for 8 early and 11 late recurrences were constructed using the Kaplan-Meier method, demonstrating a statistically significant difference between them ($p=0.017$ by the log-rank test) (Figure 3).

Multivariate Cox proportional hazards analysis for recurrent endometrial cancer. The prognostic significance of factors including the age of the patients, histology, the initial stage, adjuvant therapy, DFI, recurrent site, presence of symptoms at the time of the detection of recurrence and the treatment for recurrent diseases in the recurrent endometrial carcinoma cases were evaluated by a multivariate Cox proportional hazards model. The age of the patients (<60 *versus* ≥60 years), initial stage (stages I/II *versus* stages III/IV), symptoms at detection of recurrence (symptomatic *versus*

Table I. *Clinical characteristics of patients with recurrent endometrial cancer.*

	Characteristic
Number (cases)	54
Median age (year)	59 (33-83)
Histology (cases)	
Endometrioid	40
Non-endometrioid*	14
Initial stage (cases)	
I/II	17
III/IV	37
Adjuvant therapy (cases)	
None	20
Radiation	15
Chemotherapy	19
Symptoms at recurrence (cases)	
Asypmtomatic	29
Symptomatic	25
Site of recurrence (cases)	
Local alone	29
Distant**	25
DFI (cases)	
≥12 months	27
<12 months	27
Treatment for recurrence (cases)	
None	9
Performed	45

*Non-endometrioid: serous adenocarcinoma, clear cell adenocarcinoma, mucinous adenocarcinoma and other histological types. **Distant: recurrence out of the pelvis, with or without local vaginal vault recurrence.

Table II. *Multivariate Cox proportional hazards analysis for prognostic factors of recurrent endometrial carcinoma.*

Variable	Adjusted HR	95% CI	*p*-Value
Age (years)			
<60	1		
≥60	0.796	0.347-1.828	0.59
Histology			
Endometrioid	1		
Non-endometrioid*	2.773	1.221-6.300	0.015
Initial stage			
I/II	1		
III/IV	1.089	0.483-2.457	0.84
Adjuvant therapy			
None	1		
Radiation	1.572	0.678-3.646	0.29
Chemotherapy	1.151	0.395-3.348	0.55
Symptoms at recurrence			
Asyptomatic	1		
Symptomatic	1.214	0.575-2.564	0.61
Site of recurrence			
Local alone	1		
Distant**	0.917	0.449-1.869	0.81
DFI			
≥12 months	1		
<12 months	9.724	3.166-29.870	<0.0001
Treatment for recurrence			
Performed		1	
None	6.428	2.341-17.650	0.0003

*Non-endometrioid: serous adenocarcinoma, clear cell adenocarcinoma, mucinous adenocarcinoma and other histological types. ** Distant: recurrence out of the pelvis, with or without local vaginal vault recurrence.

asymptomatic) and site of recurrence (local alone *versus* distant) were not demonstrated to be significant predictors for prognosis of recurrent endometrial carcinoma cases (Table II). The type of adjuvant therapy (none *versus* radiation *versus* chemotherapy) also did not exhibit statistical significance for prognosis.

However, having a non-endometrioid type of histology showed an adjusted hazard ratio (HR) of 2.773 (95% confidence interval (CI)=1.221-6.300, p=0.015), and receiving no treatment for the recurrent disease also showed an adjusted HR of 6.428 (95% CI=2.341-17.650, p=0.0003). An adjusted HR for DFI <12 months was 9.724 (95% CI=3.166-29.870, p<0.0001), demonstrating that DFI was an independent predictor for prognosis of recurrent endometrial cancer cases.

Discussion

Endometrial adenocarcinoma, already the most common female pelvic malignancy in the United States, is increasing (1, 2). Although early endometrial cancer can sometimes be treated successfully by surgical resection alone, the current trend for initial treatment consists of surgical resection and postoperative chemotherapy. We have recently shown that even for advanced cases with distant metastasis, cytoreductive surgery for the metastases followed by postoperative chemotherapy can be effective (4).

Despite good initial intensive treatments, recurrences still develop in around 13% of patients (5). For these recurrences, combinations of surgery, radiation and chemotherapy are performed. However, in most cases of relapse the disease has spread to distant sites, and for these cases aggressive systemic chemotherapy is usually required (1,2).

The prognostic significance of the DFI following surgery has been highly controversial. A recent study demonstrated a significant impact of DFI (<24 *versus* >24 months) on the OS of patients with recurrent endometrial cancer (18). In their series, 7% of the patients were treated by radiation alone without surgery. Adjuvant radiation therapy following primary surgery was performed in 70.1% of the recurrent cases. Another recent study did not, however, demonstrate a significant impact of DFI (<12 months *versus* ≥12 months) on OS (17). In their study, 10% of the patients were treated

by radiation, not by surgery. The number of patients who received adjuvant therapy following primary surgery and the types of therapy were not described. Based on our own unpublished data, which show that the majority of refractory or recurrent diseases, occurring within 6 months of a first-line chemotherapy are non-responsive to the current regimens of second-line chemotherapy, DFI may be a possible predictor for prognosis of recurrent endometrial cancer cases, especially in those cases where adjuvant chemotherapy was performed.

In our present examination of the significance of DFI on the prognosis of patients with recurrent endometrial cancer, only the patients who were treated by surgery during the primary treatment were enrolled in the study. The recurrent cases were divided into three groups by kinds of adjuvant therapy: no adjuvant therapy group, radiation group, and chemotherapy group. Recurrence was detected in 54 (10%) out of the 536 completely resected cases, compatible with a previously described recurrence rate (5). The reason why the median age of 57 (33-83) years for early recurrence is somewhat younger than that of 62 (41-77) years for late recurrence is unclear. The OS of the early recurrent cases was significantly shorter than that of the late recurrences in all the adjuvant therapy groups: $p=0.028$ for those who did not receive any adjuvant therapy, $p=0.0005$ for those who underwent adjuvant radiation, and $p=0.017$ for those who received adjuvant chemotherapy. These results clearly show, for the first time, that DFI is an important predictor for prognosis of recurrent endometrial carcinoma, irrespective of the type of adjuvant therapy.

Moreover, a multivariate Cox proportional hazards model analysis reveals that having a non-endometrioid type of tumor histology, no treatment for recurrent disease, and DFI were each of independent significance for OS after recurrence. Especially significant was an adjusted HR for DFI <12 months, which was 9.724 (95% CI=3.166-29.870, $p<0.0001$), demonstrating that among those clinical factors studied, DFI was the most important predictor for prognosis of recurrent endometrial cancer cases (Table II). The type of adjuvant therapy (none *versus* radiation *versus* chemotherapy) also did not exhibit statistical significance for prognosis. On the other hand, symptoms at detection of recurrence, which our previous study had suggested to have a prognostic significance by univariate analysis, did not exhibit a significant impact on prognosis when examined by multivariate Cox analysis (19).

Our present study, for the first time, clearly demonstrates that DFI after recurrence is an extremely important predictor for prognosis of recurrent endometrial cancer cases. Recurrent endometrial cancer is usually highly difficult to cure completely, with the exception of when the recurrence is completely restricted, which can usually be successfully treated by surgery or radiation therapy (1, 2, 20). Especially, early recurrent tumors after previous chemotherapy was shown to exhibit extreme resistance to second-line chemotherapy (21).

In our studies, we have found that appropriate treatment for recurrent diseases does significantly improve the prognosis when compared to observation alone or palliative care. However, we have also found that the prognosis of cases which recur the earliest remains quite poor. Further investigations are required to find more useful predictors for recurrent endometrial cancer outcome and to establish better treatment plans for this disease.

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