Table II. Treatment-free interval (TFI) of patients who relapsed after achieving a complete response.

Histological type	No. of patients	Median TFI[a]
All types	107	11.5
Serous	73	11.5
Endometrioid	12	16.0
Clear cell	16	8.0[b]
Mucinous	6	11.0

[a]In months. [b]Serous vs. clear cell, P<0.02.

Table III. Progression-free survival (PFS) according to the interval from the end of first-line treatment to relapse.

	Interval from the end of first-line treatment to relapse (months)		
Variables	<6	6-12	>12
No. of patients	20	37	50
Median PFS (months)	3.0	5.5	13.0
Second-line treatment			
Platinum-based	6	23	41
Non-platinum-based	14	14	9

Table IV. Interval from the end of first-line treatment to relapse according to histological type.

		Interval from the end of first-line treatment to relapse (months)		
Histology	No. of patients	<6	6-12	>12
Serous	73	10 (14%)	27 (37%)	36 (49%)
Endometrioid	12	3 (25%)	3 (25%)	6 (50%)
Clear cell	16	5 (31%)	6 (38%)	5 (31%)
Mucinous	6	2 (33%)	1 (17%)	3 (50%)

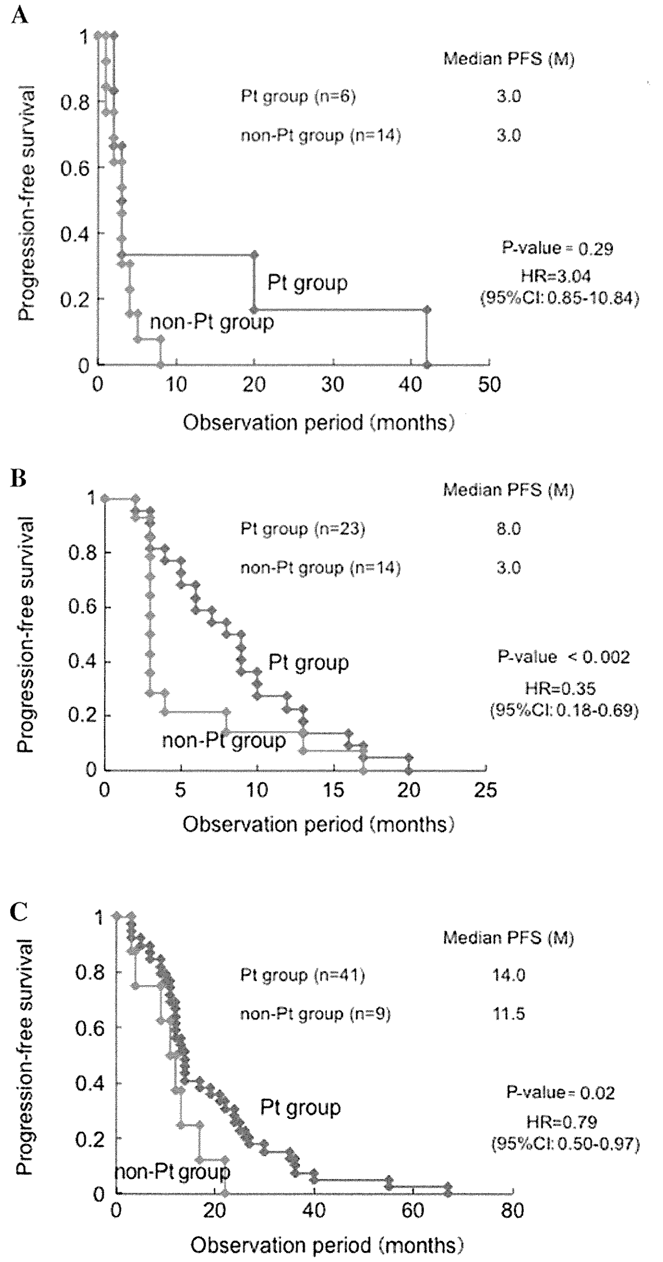

Figure 1. Comparison of progression-free survival (PFS) between the platinum (Pt) and non-Pt groups during the observation period of all histological types. Patients who relapsed (A) <6 months, (B) 6-12 months and (C) ≥12 months after the first-line treatment.

levels alone were not considered to reflect relapse. PFS was defined as the interval from the initiation of second-line treatment for relapsed lesions to confirmed disease progression.

Statistical analysis. The degree of platinum sensitivity was calculated by comparing the PFS values. PFS was estimated using the Kaplan-Meier method and compared using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated with the Cox proportional hazards regression model. P≤0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. The patient characteristics are summarized in Table I. The median age of the patients was 56 years. With regard to histological type, serous adenocarcinoma was diagnosed in 101 patients (65%) and clear cell adenocarcinoma, which was reported to have a measurable incidence in the USA and Europe (7), was identified in 26 patients (17%). The median number of first-line treatment cycles was 6 and the TC regimen was administered to 135 patients (87%), whereas docetaxel/carboplatin was selected for patients with paclitaxel hypersensitivity or peripheral neurotoxicity. As regards debulking surgery, complete or optimal outcomes were achieved in 70 patients (45%). A CR following administration of the first-line treatment was observed in 107 patients (69%). Although the prevalence of CR following administration of the first-line regimen varied by histological type from 72.3% in serous adenocarcinoma to 54.5% in mucinous

Table V. Progression-free survival (PFS) in patients with serous or endometrioid carcinoma and in those with clear cell or mucinous carcinoma treated with a platinum (Pt)-based regimen according to interval from the end of first-line treatment to relapse.

A, Serous/endometrioid group

Interval to relapse after CCR (months)	No. of patients (n=55) with Pt-based regimen		PFS (months)	
<6	4		4.5	
6-12	17		9.0	P=0.01; HR=0.14; 95% CI: 0.03-0.63
12-18	9		12.5	P<0.05; HR=0.56; 95% CI: 0.25-0.93
18-24	9	P<0.05; HR=0.49; 95% CI: 0.22-0.96	17.0	P=0.49; HR=1.43; 95% CI: 0.51-4.08
>24	16		19.0	P=0.51; HR=0.35; 95% CI: 0.54-3.34

B, Clear cell/mucinous group

Interval to relapse after CCR (months)	No. of patients (n=55) with Pt-based regimen	PFS (months)	
<6	2	2.5	
6-12	6	5.5	P=0.26; HR, 3.67; 95% CI: 0.38-9.34
>12	7	11.0	P<0.05; HR, 0.33; 95% CI: 0.10-0.97

CCR, clinical complete response; HR, hazard ratio; CI, confidence interval.

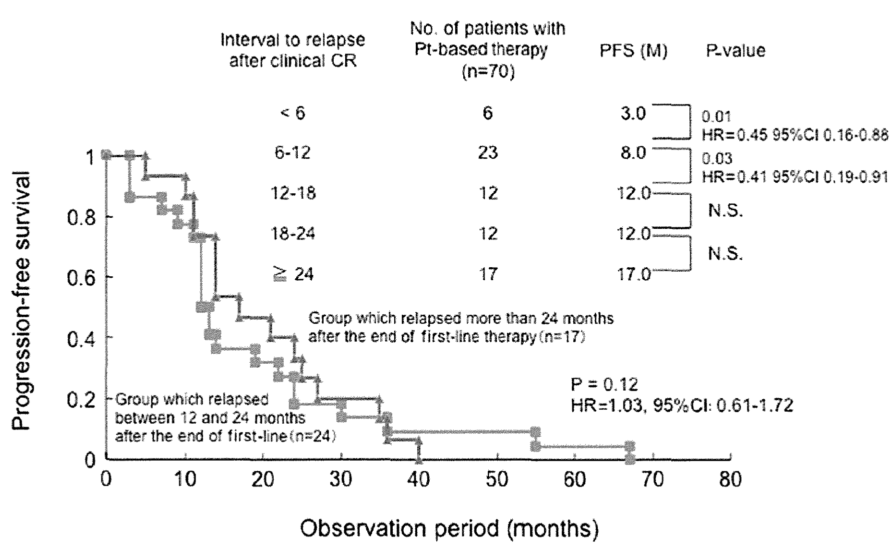

Figure 2. Comparison of the progression-free survival (PFS) by observation period in the platinum (Pt) group alone in all histological types. Patients who relapsed after 12 months were further classified every 6 months. There were no significant differences in the PFS between patients who relapsed between 12 and 24 months and those who relapsed after 24 months. N.S., not significant.

adenocarcinoma, there were no statistically significant differences in the prevalence of CR among the four histological types. The number of relapse sites was similar for abdominal and pelvic cavities. The majority of distant metastases were located in the lungs and in the mediastinal, supraclavicular or inguinal lymph nodes. In patients with a relapse following a CR (70 patients in the platinum and 37 in the non-platinum group), a second-line regimen was initiated.

TFI in relapsed patients following CR. The median TFI in relapsed patients was 11.5 months (Table II). Significant differences in the TFI by histological type were observed between cases with serous adenocarcinoma and those with clear cell adenocarcinoma (HR=0.53; 95% CI: 0.30-0.95; P<0.02) (Table II).

PFS following second-line treatment. A total of 20, 37 and 50 patients relapsed after a CR at <6, 6-12 and ≥12 months, respectively, and the median PFS following administration of a second-line regimen was 3.0, 5.5 and 13.0 months, respectively (Table III). There were no statistically significant differences in the distribution of the interval from the end of first-line treatment to relapse according to the histological type (Table IV). There were no significant differences in the median PFS (3.0 months) between the platinum- and non-platinum-based treatment groups who relapsed within 6 months after CR, when the PFS was compared based on the observation period for all histological types (Fig. 1A). In patients who relapsed between 6 and 12 months, the median PFS was 8.0 and 3.0 months in the platinum- and non-platinum based groups, respectively, with PFS being significantly longer in the platinum group (HR=0.35; 95% CI: 0.18-0.69; P<0.002) (Fig. 1B). In patients who relapsed after 12 months, the median PFS was 14.0 and 11.5 months in the platinum- and non-platinum-based groups, respectively, with the PFS being significantly longer in the platinum group (HR=0.79; 95% CI: 0.50-0.97; P=0.02) (Fig. 1C). Therefore, the platinum group alone was further investigated. Patients who relapsed after 12 months were further classified every 6 months (Fig. 2). There were significant differences in PFS between patients who relapsed within 6 months and those who relapsed between 6 and 12 months (HR=0.45; 95% CI: 0.16-0.88; P=0.01), as well as between those who relapsed between 6 and 12 months and those who relapsed between 12 and 18 months (HR=0.41; 95% CI: 0.19-0.91; P=0.03; Fig. 2). However, there were no significant differences in the PFS between patients who relapsed between 12 and 18 months and those who relapsed between 18 and 24 months, or between those who relapsed between 18 and 24 months and those who relapsed after 24 months (Fig. 2). The patients who relapsed were divided into those who relapsed between 12 and 24 months and those who relapsed after 24 months and the PFS was compared between the groups: no significant differences in PFS were observed between the two groups (HR=1.03; 95% CI: 0.61-1.72; P=0.12).

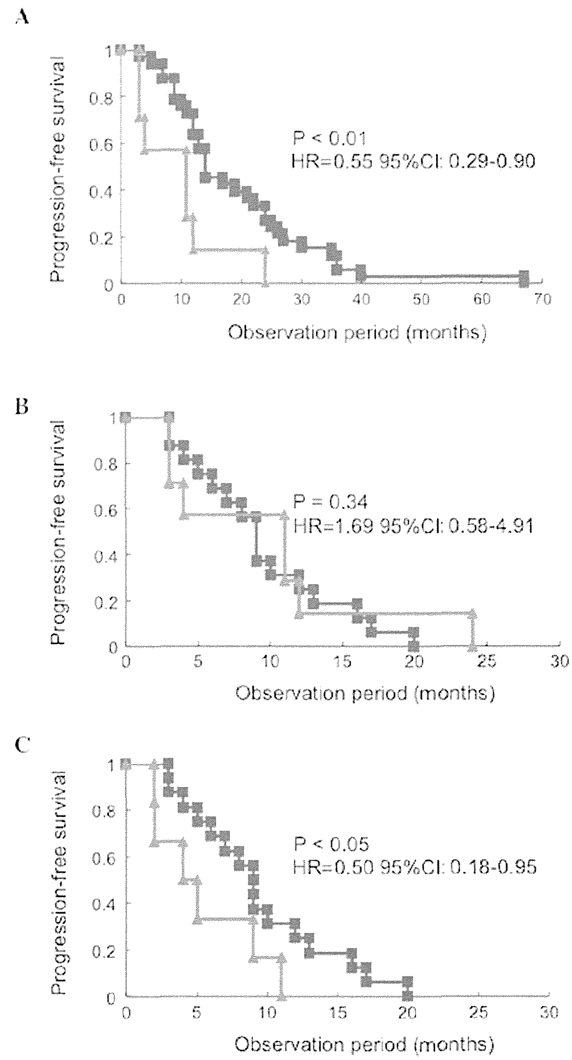

Figure 3. Evaluation of progression-free survival (PFS) of patients and redistribution of sensitivity to platinum according to the histological type. (A) Evaluation of PFS of patients with clear cell/mucinous adenocarcinoma who relapsed after 12 months (n=7, red line). The PFS was significantly shorter compared to that of patients with serous/endometrioid adenocarcinoma who relapsed after 12 months (n=34, blue line). (B) The PFS of patients with clear cell/mucinous adenocarcinoma who relapsed after 12 months (n=7, red line) was similar to that of patients with serous/endometrioid adenocarcinoma who relapsed between 6 and 12 months (n=17, blue line). (C) Comparison of PFS between patients with clear cell/mucinous adenocarcinoma (n=6, red line) and those with serous/endometrioid adenocarcinoma (n=17, blue line) who relapsed between 6 and 12 months.

PFS by histological type following second-line treatment. The differences in PFS by histological type were investigated. The PFS in the serous/endometrioid group treated with platinum after relapse was 4.5, 9.0, 12.5, 17.0 and 19.0 months in patients who relapsed at <6, 6-12, 12-18, 18-24 and ≥24 months, respectively (Table V). There were significant differences in the PFS between patients who relapsed within 6 months and those who relapsed between 6 and 12 months (HR=0.14; 95% CI: 0.03-0.63; P=0.01), as well as between those who relapsed between 6 and 12 months and those who relapsed between 12 and 18 months (HR=0.56; 95% CI: 0.25-0.93; P<0.05) (Table V). Although there were no significant differences in the PFS between those who relapsed between 12 and 18 and those who relapsed between 18 and 24 months, or between those who relapsed between 18 and 24 and those who relapsed after 24 months, there were significant differences in the PFS between patients who relapsed between 12 and 18 and those who relapsed after 18 months (HR=0.49; 95% CI: 0.22-0.96; P<0.05) (Table V). Furthermore, in the clear cell/mucinous adenocarcinoma group treated with platinum as a second-line regimen, there were no significant differences in the PFS between patients who relapsed within 6 months and those who relapsed between 6 and 12 months, while there were significant differences in the PFS between patients who relapsed between 6 and 12 months and those who relapsed after 12 months (HR=0.33; 95% CI: 0.10-0.97; P<0.05) (Table V). In patients who relapsed after 12 months, the PFS in the clear cell/mucinous adenocarcinoma group was significantly shorter compared to that in the serous/endometrioid

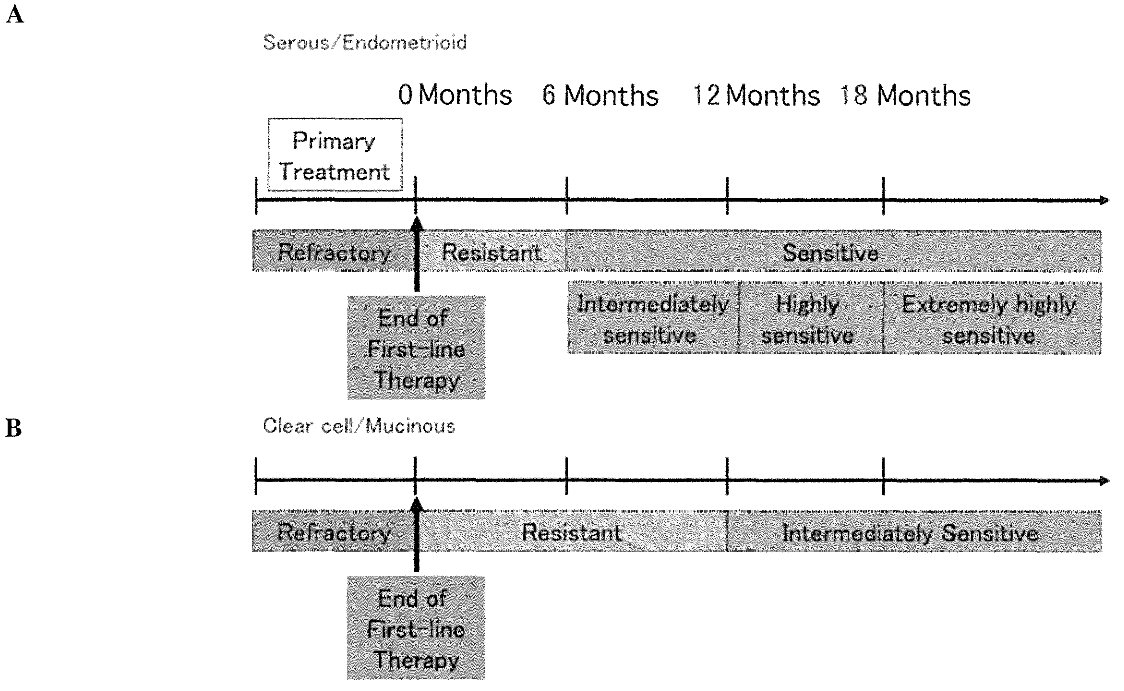

Figure 4. Redistribution of sensitivity to platinum according to the histological type. (A) Serous/endometrioid adenocarcinomas: Patients who relapsed within 6 months were considered to be 'platinum-resistant', those who relapsed between 6 and 12 months were 'intermediately sensitive', those who relapsed between 12 and 18 months were 'highly sensitive' and those who relapsed after 18 months were 'extremely highly sensitive'. (B) Clear cell/mucinous adenocarcinomas: Patients who relapsed within 12 months were considered to be 'platinum-resistant' and those who relapsed after 12 months were 'intermediately sensitive'.

adenocarcinoma group (HR=0.55; 95% CI: 0.29-0.90; P<0.01; Fig. 3A), but similar to that of patients who relapsed between 6 and 12 months in the serous/endometrioid adenocarcinoma group (HR=1.69; 95% CI: 0.58-4.91; P=0.34; Fig. 3B). Furthermore, in patients who relapsed between 6 and 12 months, the PFS of the clear cell/mucinous adenocarcinoma group was significantly shorter compared to that in the serous/endometrioid adenocarcinoma group (HR=0.50; 95% CI: 0.18-0.95; P<0.05; Fig. 3C).

Discussion

The aim of first-line treatment is to cure, whereas the primary goal of second-line treatment is palliation. Accordingly, less toxic and more convenient regimens should be selected, focusing on the balance between toxicity and effectiveness. Quality of life, including improving symptoms and preventing the onset of new symptoms is also preferentially maintained. Therefore, it is crucial to appropriately determine how the sensitivity or resistance to platinum is defined by TFI when selecting a regimen and TFI should also be individualized according to histological type.

Although the TFI of patients who relapsed within 6 months was suggested to indicate platinum sensitivity in this study, the sensitivity to platinum was similar between patients who relapsed between 12 and 24 months and those who relapsed after 24 months for all histological types. However, these results were inconsistent with previous findings reporting a significantly higher response rate in patients with a TFI of ≥24 months (6,8). In this study, the overall proportion of clear cell and mucinous adenocarcinomas, which are relatively refractory to treatment, accounted for ~20% of the cases of ovarian cancer and platinum sensitivity was evaluated according to histological type. In patients with serous/endometrioid adenocarcinoma, the PFS following platinum administration exhibited a significant increase in a stepwise manner depending on the TFI (Table V). These findings suggested a novel distribution of platinum sensitivity classification. The patients who relapsed between 6 and 12 months following the completion of first-line treatment (TFI of 6-12 months) may be classified as 'intermediately sensitive', those with a TFI of 12-18 months as 'highly sensitive' and those with a TFI of ≥18 months as 'extremely highly sensitive', whereas the patients with a TFI of <6 months were considered as platinum-resistant (Fig. 4A).

A significant difference in the PFS was only detected between patients with a TFI of 6-12 and those with a TFI of ≥12 months in the clear cell/mucinous adenocarcinoma group. There were no significant differences in the PFS between patients with a TFI of <6 months and those with a TFI of 6-12 months. However, the PFS of patients who relapsed after 12 months was significantly shorter in the clear cell/mucinous adenocarcinoma group compared to that in the serous/endometrioid adenocarcinoma group and was similar to the PFS of patients who relapsed between 6 and 12 months in the serous/endometrioid adenocarcinoma group. Furthermore, the PFS of patients who relapsed between 6 and 12 months was significantly shorter in the clear cell/mucinous adenocarcinoma group compared to that in the serous/endometrioid adenocarcinoma group. Therefore, it may be rational to classify patients with clear cell/mucinous adenocarcinoma who relapsed within12 months as 'platinum-resistant' and those who relapsed after 12 months as 'intermediately sensitive' (Fig. 4B).

In the 1990s, several studies focused on the identification and differentiation of platinum-sensitive from platinum-resistant relapse (6,8,9). Harries and Gore (10) suggested that sensitivity and resistance to platinum were separated by a PFS of 6 months. Furthermore, previous studies defined sensitivity and resistance to platinum according to the clinical response, such as the frequency of CR for agents administered to relapsed patients (6,8,9). However, in the present study, drug sensitivity was evaluated by the interval to disease progression (observation period), as well as the PFS of relapsed patients under platinum- and non-platinum-based treatment. It is widely accepted that the patients with a longer time interval between the completion of first-line treatment and the initiation of second-line treatment exhibit a higher response rate to the second-line regimen. In order to avoid ineffective treatment with resistant regimens, the length of the observation period should be considered on an individual basis. The results of the present study suggested that a TFI of <6 and ≥6 months after the completion of first-line treatment may be appropriate for patients with serous/endometrioid adenocarcinoma to determine sensitivity or resistance to platinum as second-line treatment, whereas a TFI of 6 months is too short to apply to patients with clear cell/mucinous adenocarcinoma.

Thus far, an observation period of ≥6 months following the end of first-line treatment has been defined as platinum-sensitive and phase III studies for patients with platinum-sensitive recurrent ovarian cancer have been designed. Although the incidence of relapsed patients with a TFI of ≥12 months was reported to be 60-70% in several randomized controlled studies (11-14), the proportion of patients who relapsed between 6 and 12 months was 30-40%, including those with platinum-resistant clear cell/mucinous adenocarcinoma. Furthermore, in the present study, although the TFI was ≥12 months in the serous/endometrioid adenocarcinoma group, there were significant differences in platinum sensitivity between patients who relapsed between 12 and 18 months and those who relapsed after 18 months. Thus, future clinical studies on the selection of chemotherapy for recurrent ovarian cancer must consider the histological type and platinum sensitivity with TFI.

With regard to taxane sensitivity in recurrent ovarian cancer, it was demonstrated that the number of intervention therapies following relapse, rather than the taxane-free interval, is associated with taxane sensitivity (15). Although there were no differences in the effects of taxanes on recurrent ovarian cancer, regardless of whether the interval between the first and subsequent use of taxanes was ≤12 or ≥24 months, additional intervention therapies resulted in a decreased response to taxanes (15). Similarly, it was previously reported that the taxane-free interval does not affect sensitivity to taxanes (16). Therefore, drug sensitivity to taxanes and platinum must be considered separately.

Novel biological therapies, including anti-angiogenic agents, signaling inhibitors, anti-CA125 antibody and dendritic cell immunotherapy, have been developed for the treatment of recurrent ovarian cancer. Bevacizumab was reported to prolong survival in subjects with recurrent ovarian cancer (17). Molecular-targeted agents are expected to exert additive effects and platinum sensitivity is considered to play a critical role in improving prognosis. Furthermore, maintenance therapy with biological agents may eventually alter the pattern of recurrence and novel characterizations of platinum sensitivity/resistance may emerge. Although TFI is a continuous variable with a wide boundary, it is crucial to determine a definitive criterion of the sensitivity and resistance to platinum in types of ovarian cancer with a prevalence of relapse of ≥60%, in order to enable the selection of the most efficient second-line regimen and design high-quality clinical studies.

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ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

Significance of Adenomyosis on Tumor Progression and Survival Outcome of Endometrial Cancer

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ABSTRACT

Background. To examine the effects of adenomyosis on tumor progression and survival outcome of endometrial cancer patients.

Methods. This is a retrospective study examining stage I–IV endometrial cancer patients who underwent hysterectomy-based surgical staging ($n = 571$), and endometrial hyperplasia patients who underwent hysterectomy ($n = 213$). Clinical demographics, histopathological factors, and survival outcomes were analyzed based on the presence or absence of adenomyosis.

Results. Among the endometrial cancer cohort, adenomyosis was observed in 47.5 % of cases and was significantly associated with lower grade (grade 1–2 tumors, 81.2 vs. 73.3 %; $p = 0.028$), earlier stage (stage I disease, 74.8 vs. 64.3 %; $p = 0.023$), and lower likelihood of deep myometrial invasion (19.2 vs. 28.2 %; $p = 0.039$) and cervical invasion (13.7 vs. 21.2 %; $p = 0.024$) than those without adenomyosis. In survival analysis, endometrial cancer coexisting with adenomyosis was associated with a significantly better disease-free survival (5-year rate, 89.2 vs. 78.2 %; $p < 0.001$) and overall survival (91.8 vs. 83.9 %; $p = 0.004$) after hysterectomy. In multivariate analysis, controlling for other significant variables in univariate analysis, presence of adenomyosis remained an independent prognostic factor associated with decreased risk of disease recurrence after surgery (hazard ratio [HR] 0.53; 95 % confidence interval [CI] 0.30–0.92; $p = 0.023$). Endometrial hyperplasia had a significantly increased incidence of adenomyosis when compared with type I endometrial cancer (grade 1–2 endometrioid adenocarcinoma, $n = 411$) on multivariate analysis (62.9 vs. 48.9 %; HR 1.88; 95 % CI 1.32–2.69; $p < 0.001$).

Conclusions. Adenomyosis appears to be associated with less aggressive tumor behavior of endometrial cancer, suggesting that it may have inhibitory effects on the progression of this disease.

Endometrial cancer is the most common gynecological cancer and the fourth most common cancer afflicting women overall in the US. In 2013, an estimated 49,560 women were diagnosed with endometrial cancer and 8,190 died of this disease.[1] A large portion of endometrial cancer patients are diagnosed at an early stage which is curable with surgical treatment alone. Surgical staging is the standard approach to endometrial cancer management unless the patient is not a candidate for surgery.[2] The standard procedure includes hysterectomy and bilateral salpingo-oophorectomy, with possible lymphadenectomy/omentectomy. Surgical specimens are valuable to identify the tumors that carry an increased risk of recurrence, and the necessity for postoperative adjuvant therapy with radiotherapy and/or chemotherapy is based on the histopathologic findings.[2]

Adenomyosis is histologically defined as the presence of endometrial tissue in uterine myometrial layers outside the endometrial lining.[3] Adenomyosis is a benign gynecologic

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condition which is commonly seen in women of reproductive age. Typical symptoms of adenomyosis include dysmenorrhea, chronic pelvic pain, and dysfunctional uterine bleeding.[3] Adenomyosis is one of the common histopathologic findings in surgical specimens in endometrial cancer patients.[4] In a review of the literature, there seems to be controversy as to whether or not adenomyosis is positively correlated to tumor progression of endometrial cancer. While there are multiple studies presenting endometrial cancer arising from adenomyosis or a positive correlation between adenomyosis and deep myometrial invasion,[5–28] other studies observed no relationship between adenomyosis and endometrial cancer occurrence [29] or concluded that the presence of adenomyosis in endometrial cancer is associated with a decreased risk of nodal metastasis, suggesting better prognosis (protective effect).[30–35] However, the majority of the previous literature was based on level III evidence with case reports, and the sample sizes of cohort studies were relatively small and limited to stage I disease, which made the conclusions of the studies difficult to adapt. The aim of this study was to evaluate the significance of the presence of adenomyosis on tumor progression and survival of endometrial cancer patients in a large-scale comprehensive analysis.

STUDY DESIGN

Eligibility

After Institutional Review Board approval was obtained at the University of Southern California, an institutional database for gynecologic malignancy was utilized to identify the cases. Inclusion criteria included endometrial cancer patients who underwent hysterectomy-based surgical staging at LAC + USC Medical Center between January 2000 and December 2012. Metastatic cancer to the endometrium from another organ site, uterine sarcoma (including carcinosarcoma), and synchronous double primary cancers were excluded from the study. In a separate cohort, consecutive patients of endometrial hyperplasia who underwent surgical treatment with hysterectomy between January 2003 and December 2013 were also collected.

Clinical Information

Among patients eligible for statistical analysis, medical records were further examined to abstract the following variables of interest: (i) patient demographics; (ii) histopathologic findings; (iii) treatment patterns; and (iv) survival outcomes. For patient demographics, variables were obtained from preoperative workup at the time of cancer diagnosis: patient age, ethnicity, parity, body mass index, and past medicosurgical history. For histopathology findings, information obtained from the pathology report included histologic subtype, tumor grade, uterine size, depth of invasion, presence of lymphovascular space invasion, cervical invasion, status of peritoneal washings, nodal metastasis, distant metastasis, presence of adenomyosis and uterine myoma in the myometrial layer, and presence of endometriosis. In our institution, evaluation of the myometrium is routinely performed in a synoptic report. Among tested cases, the results of estrogen and progesterone receptors were also collected. Treatment patterns abstracted from the medical record included type of surgery (type of hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, and omentectomy), type of postoperative chemotherapy (carboplatin, paclitaxel, or other), and type and location of postoperative radiotherapy (intracavitary vaginal brachytherapy, whole-pelvis radiotherapy, or whole-pelvic radiotherapy with extended field). Survival outcomes included disease-free survival (DFS), which was defined as the time interval between the date of surgery and the date of disease recurrence or the last date of follow-up, and overall survival (OS), which was defined as the time interval between the date of surgery and death or the last date of follow-up.

Statistical Analysis

Continuous variables were assessed for normality (Kolmogorov–Smirnov test) and expressed as appropriate [mean (standard deviation), or median (range)]. Student's t test or Mann–Whitney U test was performed for continuous variables as appropriate. Categorical variables were evaluated with Fisher's exact test or Chi-square test as appropriate, expressed with odds ratio (OR) and 95 % confidence interval (CI). Multivariate analysis with binary logistic regression test was further performed to determine independent risk factors in univariate analysis. Significance of adenomyosis on survival outcomes (DFS and OS) was examined with the log-rank test in univariate analysis. Cox's proportional hazard regression test (conditional backward method) was used to identify the independent prognostic factors of DFS and PS adjusted for all significant variables in univariate analysis. Survival curves were constructed with the Kaplan–Meier method. p values of less than 0.05 were considered statistically significant (all two-tailed). The Statistical Package for Social Science software (SPSS, version 12.0; SPSS Inc., Chicago, IL, USA) was used for all analyses.

RESULTS

Overall, 666 women with endometrial cancer underwent surgical staging during the study period. Of these women, myometrial findings for the hysterectomy specimens were available in 571 (85.7 %) patients who were evaluated for statistical analysis. Patient characteristics are shown in Table 1. Mean age of the study population was 52.7 years. The majority of endometrial cancer patients were hispanic (67.3 %), obese (67.7 %), multiparous (70.8 %), and underwent abdominal hysterectomy (60.6 %). Adenomyosis was diagnosed in nearly half of the endometrial cancer cases ($n = 271$, 47.5 %; 95 % CI 43.4–51.6), and was not associated with age ($p = 0.92$), ethnicity ($p = 0.65$), or body habitus ($p = 0.79$). Adenomyosis was more commonly seen in multigravidas (OR 1.77; 95 % CI 1.19–2.65; $p < 0.001$) and multiparous (OR 1.72; 95 % CI 1.18–2.51; $p < 0.001$) patients. Incidences of adenomyosis across the extent of parity were as follows: P0, 38.0 %; P1–2, 44.9 %; P3–4, 57.6 %; and $p \geq 5$, 56.4 %, respectively. Patients with adenomyosis were less likely to undergo total laparoscopic hysterectomy when compared with non-adenomyosis patients (24.0 vs. 29.0 %; $p = 0.025$).

Tumor characteristics of endometrial cancer were examined (Table 2). The majority of the study population had endometrioid histology (83.4 %), grade 1 tumors (52.5 %), and stage I disease (69.3 %). The presence of adenomyosis was significantly associated with a decreased risk of grade 3 tumors (18.8 vs. 26.7 %; $p = 0.028$) and a higher likelihood of stage I disease (74.8 vs. 64.3 %; $p = 0.023$) when compared with non-adenomyosis cases. When tumor details were compared, the presence of adenomyosis was significantly associated with a lower likelihood of outer-half myometrial invasion (19.2 vs. 28.2 %; $p = 0.039$) and a lower likelihood of cervical mucosal/stromal invasion (13.7 vs. 21.2 %; $p = 0.024$). Uterine myomas were seen in 260 (45.5 %; 95 % CI 41.4–49.6) cases but was not statistically associated with the presence of adenomyosis ($p = 0.078$). Endometriosis was infrequently seen in concert with endometrial cancer ($n = 29$, 5.1 %; 95 % CI 3.3–6.9), with the ovary and fallopian tube being the most common site of endometriosis (both 27.6 %). Endometriosis was significantly associated with the presence of adenomyosis in endometrial cancer (8.9 vs. 1.7 %; OR 5.73; 95 % CI 2.16–15.2; $p < 0.001$). Estrogen and progesterone receptors were examined in only 220 (38.5 %) cases; the majority of tested cases of endometrial cancer expressed estrogen receptor (88.6 %) and progesterone receptor (86.8 %) that were not statistically associated with the presence of adenomyosis ($p = 0.088$ and 0.11, respectively).

Survival outcomes of endometrial cancer were examined. Median follow-up time of all cases after hysterectomy was 26.9 months, and median follow-up time for the adenomyosis group was statistically longer than the non-adenomyosis group (37.3 vs. 23.9 months; $p = 0.008$). There were 67 events of disease recurrence and 47 events of death due to endometrial cancer. Risk factors for DFS are shown in Table 3. In univariate analysis, endometrial cancer patients with adenomyosis had a significantly improved DFS when compared with endometrial cancer patients with no adenomyosis (5-year DFS rate 89.2 vs. 78.2 %; hazard ratio [HR] 0.42; 95 % CI 0.25–0.70; $p < 0.001$) (Fig. 1a). The presence of uterine myomas ($p = 0.22$) or endometriosis ($p = 0.53$) was not associated with DFS. Significant prognosticators for decreased DFS included age $\geq$60 years ($p = 0.01$), CA-125 $\geq$ 35 IU/L ($p < 0.001$), non-endometrioid histology ($p < 0.001$), grade 3 tumors ($p < 0.001$), and stage III–IV disease ($p < 0.001$). Hispanic race ($p < 0.001$) and obesity ($p = 0.005$) were associated with improved DFS. On multivariate analysis, entering all the significant variables from univariate analysis, the presence of adenomyosis remained an independent significant predictor for improved DFS (HR 0.53; 95 % CI 0.30–0.92; $p = 0.023$). Other independent prognosticators for decreased DFS included CA-125 $\geq$ 35 IU/L ($p < 0.001$), grade 3 tumor ($p < 0.001$), and stage III–IV disease ($p < 0.001$). In a subanalysis of type II histology (grade 3 endometrioid, serous and clear cell histology, $n = 128$), adenomyosis remained an independent predictor for improved DFS (5-year rate 79.1 vs. 46.5 %; HR 0.42; 95 % CI 0.20–0.88; $p = 0.022$) in multivariate analysis (other independent variables, CA-125 $p = 0.007$, and stage $p = 0.013$).

Survival analysis for OS was performed (Table 4). On univariate analysis, endometrial cancer cases with adenomyosis was significantly associated with better OS when compared with non-adenomyosis cases (5-year OS rate 91.8 vs. 83.9 %; HR 0.42; 95 % CI 0.23–0.78; $p = 0.004$) (Fig. 1b). Variables associated with decreased OS included age $\geq$60 years ($p = 0.013$), CA-125 $\geq$35 IU/L ($p < 0.001$), non-endometrioid histology ($p < 0.001$), grade 3 tumor ($p < 0.001$), and stage III–IV disease ($p < 0.001$). In multivariate analysis, entering all the significant variables in univariate analysis, the presence of adenomyosis did not remain an independent predictor for OS. Similar to the results for DFS, CA-125 $\geq$ 35 IU/L ($p < 0.001$), grade 3 tumor ($p = 0.002$), and stage III–IV disease ($p < 0.001$) remained as significant prognostic factors for decreased OS.

To examine the impacts of adenomyosis in the paradigm of tumor genesis/progression in endometrial cancer, endometrial hyperplasia, a known precursor of type I endometrial cancer, was examined in the separate cohort. A total of 213 hysterectomy specimens for endometrial hyperplasia were evaluated for myometrial lesions. Mean

TABLE 1 Patient demographics of endometrial cancer

Subject	All $n = 571$	Adenomyosis (+) $n = 271$ (47.5 %)	Adenomyosis (−) $n = 300$ (52.5 %)	p value
Age, years				0.92
Mean (± SD)	52.7 (10.2)	52.7 (9.6)	52.7 (10.7)	
<60	432 (75.7)	206 (76.0)	226 (75.3)	
≥60	139 (24.3)	65 (24.0)	74 (24.7)	
Race				0.65
Caucasian	63 (11.0)	31 (11.4)	32 (10.7)	
African American	26 (4.6)	10 (3.7)	16 (5.3)	
Hispanic	384 (67.3)	187 (69.0)	197 (65.7)	
Asian	98 (17.2)	43 (15.9)	55 (18.3)	
BMI				0.79
Mean (± SD)	35.6 (10)	35.8 (9.1)	35.5 (10.7)	
<30	170 (32.3)	69 (28.4)	101 (35.6)	
≥30	357 (67.7)	174 (71.6)	183 (64.4)	
Gravidity				<0.001
Median (range)	2 (0–18)	3 (0–13)	2 (0–18)	
Null	133 (24.5)	49 (19.1)	84 (29.5)	
Multi	409 (75.5)	208 (80.9)	201 (70.5)	
Parity				<0.001
Median (range)	2 (0–17)	2 (0–12)	1 (0–17)	
Null	158 (29.2)	60 (23.3)	98 (34.4)	
Multi	384 (70.8)	197 (76.7)	187 (65.6)	
CA-125, IU/L				0.18
Median (range)	18 (2–7,192)	17 (3–7,192)	19 (2–4,068)	
<35	370 (72.4)	179 (75.2)	191 (70.0)	
≥35	141 (27.6)	59 (24.8)	82 (30.0)	
Hysterectomy type				0.025
TAH	346 (60.6)	166 (61.3)	180 (60.0)	
TLH	152 (26.6)	65 (24.0)	87 (29.0)	
LAVH	37 (6.5)	26 (9.6)	11 (3.7)	
TVH	17 (3.0)	9 (3.3)	8 (2.7)	
RH/MRH	16 (2.8)	4 (1.5)	12 (4.0)	
SCH	3 (0.5)	1 (0.4)	2 (0.7)	
Radiotherapy type				0.28
None	374 (65.5)	186 (68.6)	188 (62.7)	
WPRT alone	73 (12.8)	33 (12.2)	40 (13.3)	
WPRT + ICBT	66 (11.6)	31 (11.4)	35 (12.3)	
ICBT alone	58 (10.2)	21 (7.7)	37 (12.3)	
Chemotherapy type				0.14
None	427 (74.8)	213 (78.6)	214 (71.3)	
Carboplatin + paclitaxel	136 (23.8)	55 (20.3)	81 (27.0)	
Others	8 (1.4)	3 (1.1)	5 (1.7)	

Chi-square or Fisher's exact test were used to calculate p values

Data are expressed as n (%) unless specified otherwise

Total number may not equate to 571 due to missing variables

SD standard deviation, *BMI* body mass index, *CA-125* cancer antigen 125, *TAH* total abdominal hysterectomy, *TLH* total laparoscopic hysterectomy, *LAVH* laparoscopy-assisted vaginal hysterectomy, *TVH* total vaginal hysterectomy, *RH* radical hysterectomy, *MRH* modified radical hysterectomy, *SCH* supracervical hysterectomy, *WPRT* whole-pelvis radiotherapy, *ICBT* intracavitary brachytherapy

TABLE 2 Adenomyosis and tumoral factors in endometrial cancer

Subject	All $n = 571$	Adenomyosis (+) $n = 271$ (47.5 %)	Adenomyosis (−) $n = 300$ (52.5 %)	p value
Histology				0.13
Endometrioid	476 (83.4)	229 (84.5)	247 (82.3)	
Serous/clear cell	49 (8.6)	17 (6.3)	32 (10.7)	
Others	46 (8.1)	25 (9.2)	21 (7.0)	
Grade				0.028
1	300 (52.5)	150 (55.4)	150 (50.0)	
2	140 (24.5)	70 (25.8)	70 (23.3)	
3	131 (22.9)	51 (18.8)	80 (26.7)	
Stage				0.023
I	395 (69.3)	202 (74.8)	193 (64.3)	
II	50 (8.8)	18 (6.7)	32 (10.7)	
III	86 (15.1)	38 (14.1)	48 (16.0)	
IV	39 (6.8)	12 (4.4)	27 (9.0)	
Myometrial invasion, %				0.039
0	93 (16.6)	45 (16.9)	48 (16.3)	
1–49	333 (59.5)	170 (63.9)	163 (55.4)	
50–100	134 (23.9)	51 (19.2)	83 (28.2)	
Cervical invasion				0.024
None	443 (82.3)	221 (86.3)	222 (78.7)	
Mucosa	32 (5.9)	11 (4.3)	21 (7.4)	
Stroma	63 (11.7)	24 (9.4)	39 (13.8)	
LVSI				0.34
No	456 (80.4)	222 (82.2)	234 (78.8)	
Yes	111 (19.6)	48 (17.8)	63 (21.2)	
Adnexal/serosa				0.64
No	489 (91.4)	234 (92.1)	255 (90.7)	
Yes	46 (8.6)	20 (7.9)	26 (9.3)	
Peritoneal cytology				0.07
Negative	470 (90.7)	232 (93.2)	238 (88.5)	
Positive	48 (9.3)	17 (6.8)	31 (11.5)	
Nodal metastasis[a]				0.55
No	259 (82.7%)	113 (81.3)	146 (83.9)	
Yes	54 (17.3)	26 (18.7)	28 (16.1)	
Uterine myoma				0.078
No	311 (54.5)	137 (50.6)	174 (58.0)	
Yes	260 (45.5)	134 (49.4)	126 (42.0)	
Endometriosis				<0.001
No	542 (94.9)	247 (91.1)	295 (98.3)	
Yes	29 (5.1)	24 (8.9)	5 (1.7)	
ER				0.088
No	25 (11.4)	7 (7.1)	18 (14.9)	
Yes	195 (88.6)	92 (92.9)	103 (85.1)	
PR				0.11
No	29 (13.2)	9 (9.1)	20 (16.5)	

TABLE 2 continued

Subject	All $n = 571$	Adenomyosis (+) $n = 271$ (47.5 %)	Adenomyosis (−) $n = 300$ (52.5 %)	p value
Yes	191 (86.8)	90 (90.9)	101 (83.5)	

Chi-square or Fisher's exact test were used to calculate p values

Data are expressed as n (%)

Total number may not equate to 571 due to missing variables

LVSI lymphovascular space invasion, *ER* estrogen receptor, *PR* progesterone receptor

[a] Nodal metastasis for pelvic and/or para-aortic lymph nodes

TABLE 3 Risk factors for disease-free survival in endometrial cancer

	No. at risk	5-year survival proportion (%)	Univariate		Multivariate	
			HR (95 % CI)	p value	HR (95 % CI)	p value
Age, years				0.01		
<60	432	85.4	1			
≥60	139	77.2	1.92 (1.16–3.18)			
Race				<0.001		
Non-Hispanic	187	74.2	1			
Hispanic	384	87.6	0.45 (0.28–0.73)			
BMI				0.005		
<30	170	76.6	1			
≥30	357	85.2	0.51 (0.31–0.83)			
Parity				0.28		
Null	158	85.2	1			
Multi	384	83.1	1.38 (0.77–2.46)			
CA-125, IU/L				<0.001		<0.001
<35	370	92.4	1		1	
≥35	141	55.2	7.03 (4.14–11.9)		3.64 (2.06–6.42)	
Histology				<0.001		
Endometrioid	476	89.2	1			
Non-endometrioid	95	57.2	5.61 (3.47–9.06)			
Grade				<0.001		<0.001
1–2	440	91.5	1		1	
3	131	58.5	8.24 (4.94–13.7)		3.74 (2.11–6.62)	
Stage				<0.001		<0.001
I–II	445	94.7	1		1	
III–IV	125	48.7	13.3 (7.60–23.4)		4.38 (2.28–8.40)	
Adenomyosis				<0.001		0.023
No	300	78.2	1		1	
Yes	271	89.2	0.42 (0.25–0.70)		0.53 (0.30–0.92)	
Uterine myoma				0.22		
No	311	87.2	1			
Yes	260	80.3	1.35 (0.83–2.18)			
Endometriosis				0.53		
No	542	84.1	1			
Yes	29	74.6	1.34 (0.54–3.33)			

The log-rank test was used for univariate analysis and Cox's proportional hazard regression test (conditional backward method) was used for multivariate analysis

HR hazard ratio, *CI* confidence interval, *BMI* body mass index, *CA-125* cancer antigen 125

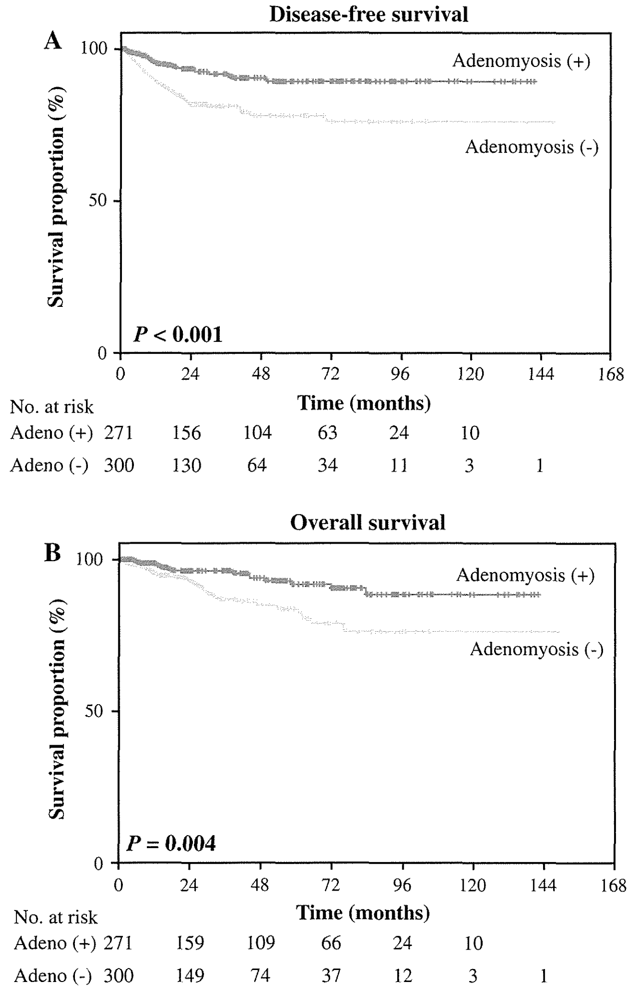

FIG. 1 Adenomyosis and survival outcomes of endometrial cancer. Log-rank test for p values. Survival outcomes are shown for **a** disease-free survival and **b** overall survival based on the presence or absence of adenomyosis in endometrial cancer patients. *Adeno* adenomyosis

age of the endometrial hyperplasia patients was 45.5 years (±9.2). Overall, 134 (62.9 %; 95 % CI 56.4–68.4) cases presenting with adenomyosis and 103 (48.4 %; 95 % CI 41.6–55.1) cases presenting with uterine myoma coexisted with endometrial hyperplasia. When endometrial hyperplasia cases were compared with type I endometrial cancer cases (grade 1–2 endometrioid adenocarcinoma, n = 411), endometrial hyperplasia was associated with a significantly younger age (mean age, endometrial hyperplasia vs. grade 1–2 endometrioid adenocarcinoma, 45.5 vs. 51.4; $p < 0.001$) and was associated with an increased risk of adenomyosis (62.9 vs. 48.9 %; OR 1.77; 95 % CI 1.26–2.49; $p = 0.001$). The incidence of uterine myoma did not differ between the two groups (48.4 vs. 43.6 %; $p = 0.27$). On multivariate analysis, controlling for age (≥50 vs. <50 years; 50.3 vs. 53.4 %; HR 1.22; 95 % CI 088–1.71; $p = 0.24$), endometrial hyperplasia remained a significant variable associated with increased incidence of adenomyosis when compared with type I endometrial cancer (HR 1.88; 95 % CI 1.32–2.69; $p < 0.001$).

DISCUSSION

Key findings of our results are that (i) the presence of adenomyosis in the myometrial layer of endometrial cancer patients was associated with less aggressive tumor behavior; and (ii) patients with endometrial cancer coexisting with adenomyosis were less likely to develop disease recurrence than those who did not have adenomyosis. In addition, an inverse correlation of adenomyosis occurrence was observed in the continuum of endometrial cancer progression from pre-cancer to cancer. Several key areas deserve further discussion.

The interaction among the triad of endometrial cancer, adenomyosis, and endometrial stromal cells is the important mechanism to understand our findings of adenomyosis in endometrial cancer. Adenomyosis, ectopic endometrium within the myometrium, is characterized by unique patterns of cytokine balance when compared with normal endometrium.[36] Adenomyosis is known to have increased secretions of interferon (IFN)-α, IFN-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-10.[36,37] Increased level of these cytokines may potentially augment the cancer-immune system (IFN-α and IFN-γ), anti-tumor effect via enhancing apoptosis (TNF-α), and anti-inflammatory cytokine production (IL-10), resulting in protective effects to endometrial cancer progression.[38–41] Adenomyosis is also known to have decreased secretions of various cytokines such as IL-1β, IL-8, and epidermal growth factor (EGF).[36] Because these cytokines play an important role in tumor progression in inflammasome (IL-1β), and in tumor microenviroment (IL-8) and tumor growth factor (TGF),[42,43] a decreased level of oncogenic cytokines/growth factor in adenomyosis may theoretically alleviate endometrial cancer progression.

Another possible link between adenomyosis and lack of endometrial cancer progression is the characteristics of the endometrial stroma of adenomyosis.[44] Previous studies have shown that the endometrial stroma of adenomyosis is associated with rapid cell proliferation under stimulation of estrogen or inflammatory cytokines. As a consequence, it is speculated that thickened endometrial stroma in adenomyosis may contribute to a mechanical block of endometrial cancer invasion in the myometrium. Even though the greatest thickening occurs at the foci of adenomyotic lesions in the deep myometrial tissue,[45] mild thickening of the subendothelial myometrial unit can be seen throughout.[46] Our findings of decreased deep myometrial invasion (≥50 %) strengthen this proposed theory.

TABLE 4 Risk factors for overall survival in endometrial cancer

	No. at risk	5-year survival proportion (%)	Univariate		Multivariate	
			HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Age, years				0.013		
<60	432	89.3	1			
≥60	139	84.0	2.13 (1.16–3.91)			
Race				0.003		
Non-Hispanic	187	80.8	1			
Hispanic	384	91.0	0.44 (0.25–0.77)			
BMI				0.12		
<30	170	83.5	1			
≥30	357	88.1	0.63 (0.35–1.13)			
Parity				0.26		
Null	158	90.6	1			
Multi	384	86.9	1.49 (0.74–3.01)			
CA-125, IU/L				<0.001		<0.001
<35	370	94.7	1		1	
≥35	141	67.6	7.24 (3.80–13.8)		3.49 (1.74–6.99)	
Histology				<0.001		
Endometrioid	476	92.1	1			
Non-endometrioid	95	68.6	4.97 (2.81–8.82)			
Grade				<0.001		0.002
1–2	440	93.9	1		1	
3	131	68.7	6.53 (3.60–11.8)		2.86 (1.48–5.53)	
Stage				<0.001		<0.001
I–II	445	95.8	1		1	
III–IV	125	64.2	14.9 (7.18–30.7)		5.48 (2.39–12.6)	
Adenomyosis				0.004		
No	300	83.9	1			
Yes	271	91.8	0.42 (0.23–0.78)			
Uterine myoma				0.63		
No	311	87.3	1			
Yes	260	88.8	0.87 (0.49–1.54)			
Endometriosis				0.87		
No	542	87.4	1			
Yes	29	96.4	1.10 (0.34–3.55)			

The log-rank test was used for univariate analysis and Cox's proportional hazard regression test (conditional backward method) was used for multivariate analysis

HR hazard ratio, *CI* confidence interval, *BMI* body mass index, *CA-125* cancer antigen 125

Collectively, these unique characteristics of cytokine parameters and local environments seen in adenomyosis may potentially contribute to block the tumor progression of endometrial cancer in a manner of molecular interactions (molecular blockage) or histological interaction (mechanical blockage). Further studies are warranted to elucidate the exact mechanism of the protective effects of adenomyosis in endometrial cancer.

While our data at least suggest there may be a possible protective effect of adenomyosis for endometrial cancer progression, oncogenesis related to adenomyosis is a different entity and needs to be discussed. It is important to note the high rate of adenomyosis seen in our population with endometrial cancer (47.5 %) and hyperplasia (62.5 %), which raises an insight into a possible positive correlation between endometrial cancer and adenomyosis, supporting previous literature proposing adenomyosis-linked endometrial cancer.[5–28] However, the true prevalence of adenomyosis in the general population is difficult to assess due to different criteria for diagnosing adenomyosis in previous studies or lack of autopsy studies in an unselected population. In a review of previous reported literature including 8,653 cases, a wide range of adenomyosis—from 18 % to 66 %—was noted.[47] Furthermore, our data do not have a control group for non-endometrial cancer in which to compare the incidence of adenomyosis. While it is speculated that a certain fraction of adenomyosis may be a precursor of endometrial cancer,[48] it remains understudied as to whether or not adenomyosis increases the risk of endometrial cancer, and the exact molecular mechanism of oncogenesis in adenomyosis remains unknown. Therefore, further studies are warranted to examine this link.

One of the strengths of our study is that this was one of the largest studies evaluating the significance of adenomyosis in endometrial cancer patients with multivariate analysis. The impact of adenomyosis was further validated in the endometrial hyperplasia cohort. A weakness of the study is that this was a retrospective study that may miss potential confounding factors. Another limitation is that histopathology slides were not reviewed and quantitative analysis based on the severity of adenomyosis was not performed in our study.

CONCLUSIONS

The presence of adenomyosis is a predictor of improved survival outcome of patients with endometrial cancer. Further clinical and pre-clinical studies will be needed to determine the exact mechanism of protective effects of adenomyosis on endometrial cancer progression.

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ORIGINAL ARTICLE

Evaluation of postoperative chemotherapy in patients with uterine carcinosarcoma: a retrospective survey of the Tohoku Gynecologic Cancer Unit

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Abstract
Background The aim of this study was to evaluate prognostic factors including efficacy of postoperative chemotherapy in Japanese patients with uterine carcinosarcoma.
Methods We conducted a retrospective survey of seven medical facilities in the Tohoku Gynecologic Cancer Unit.
Results A total of 45 patients who had undergone hysterectomy and bilateral salpingo-oophorectomy were enrolled. No significant difference was observed in overall survival according to patient age ($\leq$50 years vs >50 years) or retroperitoneal lymphadenectomy (performed vs. not performed). However, the International Federation of Gynecology and Obstetrics stage (stage I/II vs stage III/IV) and postoperative chemotherapy (provided vs not provided) were significant prognostic factors in both univariate and multivariate analyses for the 25-month median follow-up period.
Conclusions Our results revealed that postoperative chemotherapy should be considered for all uterine carcinosarcoma stages in Japanese patients.

Keywords Uterine carcinosarcoma · Prognostic factor · Chemotherapy · Retrospective study

Introduction

Carcinosarcoma is a rare, aggressive tumor with a poor prognosis and consists of both carcinoma and sarcoma components [1–3]. We previously completed a retrospective study on factors affecting the prognosis of carcinosarcoma, endometrial stromal sarcoma, and leiomyosarcoma [4], and reported that chemotherapy did not significantly predict overall survival for endometrial stromal sarcoma ($p = 0.0714$) or leiomyosarcoma ($p = 0.989$). However,

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the effect of postoperative chemotherapy on overall survival in carcinosarcoma remains unknown. Moreover, according to the results of phase III trials conducted by the Gynecologic Oncology Group (GOG), the National Comprehensive Cancer Network (NCCN) guidelines (version 1.2014) recommend postoperative chemotherapy using a combination of ifosfamide and cisplatin [5] or ifosfamide and paclitaxel [6] for all stages of carcinosarcoma.

Nevertheless, ifosfamide-based combination regimens are frequently accompanied by severe hematological toxicities; ifosfamide and cisplatin resulted in grade 3/4 hematological toxicities including leukopenia (87 %), granulocytopenia (60 %), and thrombocytopenia (58 %) [5], and ifosfamide and paclitaxel with granulocyte-colony stimulating factor led to leukopenia (31 %), granulocytopenia(38 %), and thrombocytopenia (3 %) [6]. Furthermore, death following ifosfamide and cisplatin treatment has been reported [7]. Therefore, we conducted a multicenter survey and analyzed treatment outcomes in Japanese uterine carcinosarcoma patients to evaluate different chemotherapy regimens and to determine if postoperative chemotherapy could predict prognosis even in early stage patients.

Materials and methods

The survey, with unlinkable anonymization, was conducted by mail between January 1995 and December 2005 at the following medical facilities—Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine; Department of Obstetrics and Gynecology, Hirosaki University School of Medicine; Department of Obstetrics and Gynecology, Iwate Medical University; Department of Obstetrics and Gynecology, Akita University Graduate School of Medicine; Department of Obstetrics and Gynecology, Yamagata University Faculty of Medicine; Department of Obstetrics and Gynecology, Fukushima Medical University; and Department of Gynecology, Miyagi Cancer Center. The survey collected information on patient age, whether the patient had undergone retroperitoneal lymphadenectomy, surgical staging determined by the International Federation of Gynecology and Obstetrics (FIGO; 1988), chemotherapy regimens, and prognosis following hysterectomy and bilateral salpingo-oophorectomy. The survey was approved by the ethics committee of each of the participating facilities. A standardized computer software package (JMP 9, SAS Institute Japan, Tokyo, Japan) was used for statistical analysis. The log-rank test and Cox hazard test were used to analyze data, and p values of <0.05 were considered significant.

Results

Patients

A total of 45 histopathologically confirmed uterine carcinosarcoma patients were enrolled into this survey. Patient characteristics are shown in Table 1. All patients underwent hysterectomy and bilateral salpingo-oophorectomy, and 27 (60.0 %) received postoperative chemotherapy. The postoperative chemotherapy regimens were ifosfamide, epirubicin, and cisplatin in 13 patients; cyclophosphamide, doxorubicin, and cisplatin in 6 patients; paclitaxel, doxorubicin, and carboplatin in 4 patients; paclitaxel and carboplatin in 3 patients; and doxorubicin and cisplatin in 1 patient. The median follow-up period was 25 months (1–166 months). However, confirmation of the detailed histopathological component of the carcinosarcomas (homologous or heterologous) remained at 25 (55.6 %) patients.

Survival analysis

Figure 1 shows the overall survival of all enrolled patients; the median survival time was 27.8 months. Furthermore,

Table 1 Patient characteristics

Number of patients	45
Median age (range)	60 (30–94)
Stage (FIGO, 1988)	
I	18
II	3
III	1
IV	8
Types of sarcoma component	
Homologous	10
Heterologous	15
Not obtained	20
Retroperitoneal lymphadenectomy	
Performed	30
Not performed	15
Chemotherapy	
Provided	27
IEP	13
CAP	6
PEC	4
TC	3
AP	1
Not provided	18

FIGO International Federation of Gynecology and Obstetrics, *IEP* ifosfamide, epirubicin, and cisplatin, *CAP* cyclophosphamide, doxorubicin, and cisplatin, *PEC* paclitaxel, doxorubicin and carboplatin, *TC* paclitaxel and carboplatin, *AP* doxorubicin and cisplatin

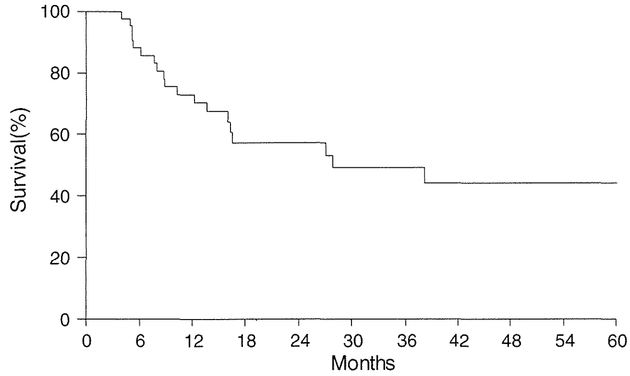

Fig. 1 Overall survival in patients with uterine carcinosarcoma. The median survival time was 27.8 months

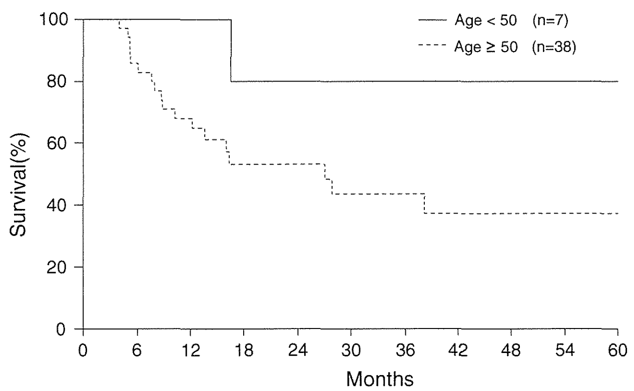

Fig. 2 Overall survival in patients with uterine carcinosarcoma subdivided by patient age. No significant survival difference was observed between <50 years and ≥50 years ($p = 0.091$)

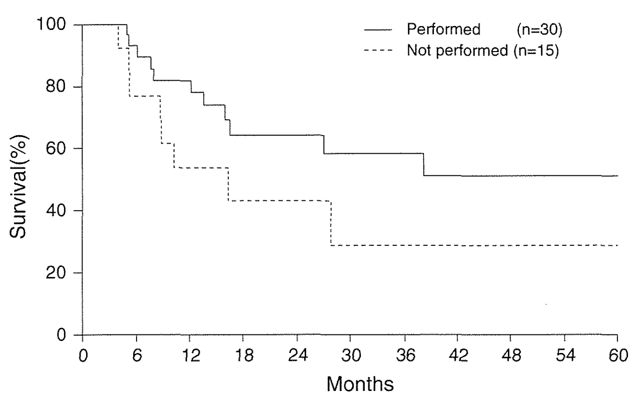

Fig. 3 Overall survival in all patients with uterine carcinosarcoma subdivided by retroperitoneal lymphadenectomy. No significant survival difference was observed with regard to retroperitoneal lymphadenectomy ($p = 0.123$)

no significant survival difference was observed with regard to patient age (<50 years vs ≥50 years, $p = 0.091$; Fig. 2) or retroperitoneal lymphadenectomy (performed vs not performed, $p = 0.123$; Fig. 3). Moreover, while the

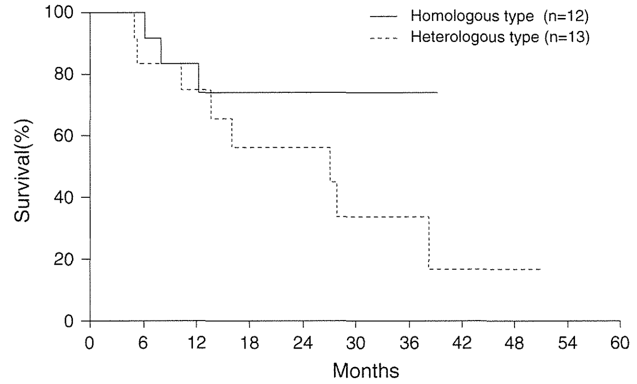

Fig. 4 Overall survival in patients with uterine carcinosarcoma subdivided by sarcoma component. No significant survival difference was observed between the homologous and heterologous types ($p = 0.248$)

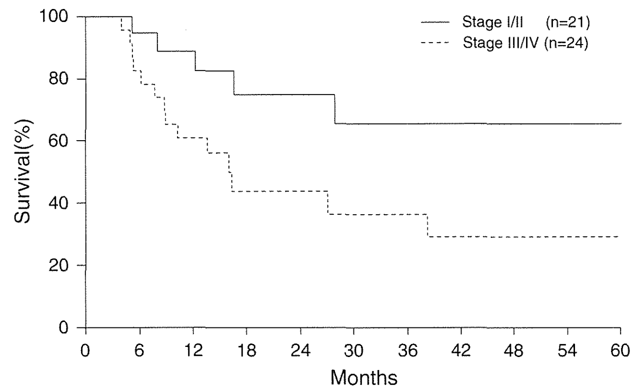

Fig. 5 Overall survival in patients with uterine carcinosarcoma subdivided by postoperative chemotherapy. Postoperative chemotherapy significantly predicted the survival of patients ($p = 0.049$)

number of patients with complete information was insufficient, no significant survival difference was observed according to the histological subtype of the sarcoma component (homologous vs heterologous, $p = 0.248$; Fig 4). However, the FIGO stage (I/II vs III/IV, $p = 0.034$; Fig. 5) and postoperative chemotherapy (provided vs not provided, $p = 0.049$; Fig. 6) significantly predicted survival. Moreover, multivariate analysis showed that both the FIGO stage ($p = 0.017$) and postoperative chemotherapy ($p = 0.018$) were significant prognostic factors for uterine carcinosarcoma patients who underwent hysterectomy and bilateral salpingo-oophorectomy (Table 2).

Discussion

Uterine carcinosarcoma has been classified as a type of endometrial carcinoma, and FIGO staging and recommendation for the primary treatment of uterine carcinosarcoma in the NCCN guidelines are also similar to those

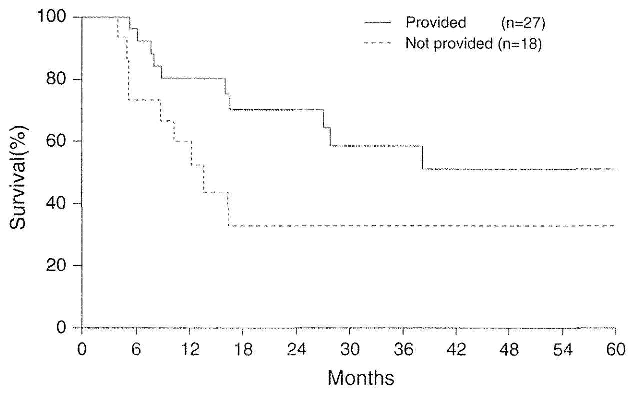

Fig. 6 Overall survival in patients with uterine carcinosarcoma subdivided by stage. The FIGO stage significantly predicted the survival of patients ($p = 0.034$)

Table 2 Prognostic significance

Factor	Hazard ratio	95 % CI	p value
Chemotherapy (performed vs not performed)	3.208	1.219–8.441	0.018
Stage (I/II vs III/IV)	3.620	1.254–10.451	0.017

CI confidential interval

for endometrial carcinoma. Although several studies have reported that patient age [8] and retroperitoneal lymphadenectomy including para-aortic lymph nodes for patients with intermediate and high risk of recurrence [9] were significant prognostic factors in endometrial carcinoma, these factors showed no significant effect on uterine carcinosarcoma. These results suggest a more aggressive biological behavior of uterine carcinosarcoma than of endometrial endometrioid adenocarcinoma. Several studies [10, 11] have also reported that although stage I/II was more frequently observed in uterine carcinosarcoma cases, the clinical outcome of this disease was significantly worse than grade 3 endometrioid endometrial carcinoma and non-endometrioid endometrial carcinoma. The most significant prognostic factor for predicting poor survival is the extension of the tumor beyond the uterus [12–15]. However, even in stage I/II disease, 32 % of patients exhibited extra-uterine disease spread [16] and 20–31 % [17, 18] had retroperitoneal lymph node metastasis in uterine carcinosarcoma. These results suggest that, in addition to optimal surgery, postoperative adjuvant therapy is key to improving the prognosis for carcinosarcoma patients. Although several chemotherapy regimens were included, the present results clearly demonstrated that postoperative chemotherapy is a significant independent prognostic factor for all FIGO stage patients who underwent hysterectomy and bilateral salpingo-oophorectomy.

The European Organization for Research and Treatment of Cancer evaluated the role of adjuvant pelvic radiotherapy for patients with stage I/II uterine sarcomas [19] and reported that although patients with carcinosarcoma displayed a trend for better local disease control, no significant overall survival improvement was observed. Furthermore, results from a phase III trial [7] showed no significant advantage of adjuvant chemotherapy over adjuvant radiotherapy for the recurrence rate or survival after adjusting for stage and age. These findings therefore suggest that postoperative chemotherapy in patients with early stage disease was not effective. However, a multi-institutional cohort study [20] has shown that adjuvant chemotherapy is associated with an improved progression-free survival compared with adjuvant radiation therapy and observation. Moreover, the Cochrane Review [21] analyzed three randomized trials of 579 women and reported that although abdominal radiotherapy was not associated with improved survival, combination chemotherapy had a lower risk of death and disease progression in the advanced stage for metastatic and recurrent disease. However, it remains unknown if postoperative adjuvant chemotherapy could also improve prognosis for FIGO stage I/II patients. Furthermore, a recent study has shown that adjuvant chemotherapy with doxorubicin and ifosfamide was not associated with a significant survival benefit for patients with stage I/II uterine leiomyosarcoma [22]. While several chemotherapy regimens were included in this survey, our results clearly show that postoperative chemotherapy is a significant independent prognostic factor for all FIGO stage patients who underwent hysterectomy and bilateral salpingo-oophorectomy. Although it is unknown why postoperative adjuvant chemotherapy contributed to a survival benefit for carcinosarcoma but not leiomyosarcoma, the presence of an epithelial component may be an important predictive factor. Moreover, even though both leiomyosarcomas and carcinosarcomas occur in the uterus and include a sarcomatous component, they are distinct tumor entities with different clinical features.

A current clinical problem is the improvement of treatment feasibility for uterine carcinosarcoma, especially for ifosfamide-based combination therapy. GOG has recently conducted a new phase III trial to compare paclitaxel plus carboplatin and paclitaxel plus ifosfamide in chemotherapy-naive patients with newly diagnosed stage I–IV persistent or recurrent carcinosarcoma (GOG 261). We have determined from our clinical experience with 6 Japanese patients with advanced or recurrent uterine carcinosarcoma that paclitaxel and carboplatin is a feasible and effective chemotherapy combination [23]. Moreover, although the number of enrolled patients did not reach the designed sample size, we recently reported results of a phase II study to evaluate the effects of paclitaxel and carboplatin therapy for advanced or recurrent uterine carcinosarcoma [24]. The study found that the overall response rate was 66.7 % and the progression-free survival was 9.1 months with acceptable toxicities. Our present survey has evaluated important information for the improvement of the long-term prognosis of patients with uterine carcinosarcoma. An additional well-designed clinical trial to evaluate paclitaxel and carboplatin as an adjuvant therapy for Japanese uterine carcinosarcoma patients is needed.

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

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