Table 3 Toxicities

Toxicity grade	Level 1 (n = 3)				Level 2 (n = 3)				Level 3 (n = 3)				Level 4 (n = 3)			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Hematological																
Leukopenia	0	3	0	0	0	2	1	0	0	2	1	0	0	2	1	0
Neutropenia	0	3	0	0	0	2	0	1	0	2	0	1	0	1	0	2
Thrombocytopenia	0	0	0	0	1	0	0	0	0	0	1	0	1	0	0	0
Anemia	3	0	0	0	2	1	0	0	1	1	0	0	2	0	0	0
Nonhematological																
Mucositis	1	0	0	0	1	0	0	0	0	0	0	0	3	0	0	0
Hand foot	1	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0
Diarrhea	2	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Nausea	2	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0
Vomiting	2	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Appetite loss	2	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0

was observed. The only grade 2 or higher nonhematological toxicity was grade 2 hand-and-foot syndrome, which occurred in one patient at level 4 (Table 3).

Administration status

In total, 43 treatment courses were administered. Table 4 shows the status of postponement of the next course, dose skipping, and dose reduction in each patient. The start of the next course was postponed due to the lack of recovery from neutropenia in one patient each at levels 1, 3, and 4 and in two patients at level 2. All of these patients started the next course within 7 days without using granulocyte colony-stimulating factor. Postponement of the next course

due to the lack of recovery from hand-and-foot syndrome occurred in one patient at level 4, but the next course was started within 7 days.

CPT-11 on day 15 was skipped in one patient each at level 1 and level 4, with the rate of skipping this treatment being 4.7 %. In the patient at level 1, CPT-11 administration in the second course was postponed because the neutrophil count on day 15 did not meet the criterion for administration, and the study was terminated during the second course at the discretion of the attending physician. In the patient at level 4, CPT-11 administration on day 15 in the third course was postponed, and due to the lack of recovery from leukopenia, the study was terminated at the discretion of the attending physician.

Table 4 Administration situation of CPT-11 and PLD

Patient no.	Level	CPT-11 (mg/m^2)	Stage	Cell type	Total cycles	Delay cycles (day 1)	Skip cycles (day 15)	Dose reduction
1	1	50	IIIc	SAC	4	2		
2	1	50	IIIc	SAC	4			
3	1	50	IIIc	SAC	2		1	
4	2	60	IIIc	EM	4	2		CPT-11 (−10mg/m^2), PLD (−7.5mg/m^2)
5	2	60	IIIb	SAC	4	1		
6	2	60	IIIc	CCC	4			
7	3	70	IV	SAC	4			
8	3	70	IIc	SAC	4			
9	3	70	Ic	CCC	2	1		CPT-11 (−10mg/m^2), PLD (−7.5mg/m^2)
10	4	80	Ic	CCC	4	1		
11	4	80	IIIc	SAC	3		1	CPT-11 (−10mg/m^2), PLD (−7.5mg/m^2)
12	4	80	IIIc	SAC	4			

SAC serous adenocarcinoma, *EMC* endometrioid adenocarcinoma, *CCC* clear cell carcinoma, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

CPT-11 and PLD doses were reduced in one patient each at levels 2, 3, and 4 because of grade 4 neutropenia in the previous course. The doses were reduced in the second course in the patients at levels 2 and 3, and in the third course in the patient at level 4.

Determination of recommended dose

Three patients were assigned to each dose level, and none of them experienced DLT during the first course, precluding the determination of MTD. Therefore, the individual cases were analyzed in detail. At level 4, grade 4 leukopenia was observed in two of three patients and grade 2 leukopenia in 1. The antitumor effect at level 4 was a PR in two of the three patients and stable disease (SD) in 1. The patient with SD had clear cell adenocarcinoma. At level 3, PR was observed in one of the three patients and SD in 2. As regards treatment postponement at level 4, CPT-11 administration on day 1 was postponed in the fourth course in 1 patient, and day-1 administration in the second course and day-15 administration in the third course were postponed in 1 patient (treatment in this patient was terminated due to the lack of recovery from adverse reactions). Thus, postponement of the next course occurred in two of the three patients. In addition, in one patient at level 4, CPT-11 and PLD doses were reduced in the third course because of grade 4 neutropenia in the previous course. These results suggested that more severe neutropenia would occur if CPT-11 is increased to level 5 (90 mg), although a greater antitumor effect could be achieved. Also, it was expected that the start of the next course would be postponed, and the dose would have to be reduced in a greater number of patients. Based on the above considerations, it was concluded that the recommended CPT-11 dose should be 80 mg/m^2.

Antitumor effect

Table 5 shows antitumor effects at each level. CR was observed in one patient (8.3 %), PR in six (50.0 %), SD in two (16.7 %), and PD in three (25.0 %), with the response rate being 58.3 % and the disease control rate 75.0 %.

Table 5 Treatment response

	CR	PR	SD	PD	Overall response (%)
Level 1 ($n=3$)	1	1	0	1	66.7
Level 2 ($n=3$)	0	2	1	0	66.7
Level 3 ($n=3$)	0	1	0	2	33.3
Level 4 ($n=3$)	0	2	1	0	66.7
Total ($n=12$)	1	6	2	3	58.3

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Discussion

The combined use of the topo-I inhibitor CPT-11 and the topo-II inhibitor PLD is expected to be effective, as suggested by their synergistic mechanisms of action. Also, this combination therapy allows dose reductions in each drug as compared with the monotherapy doses, thereby reducing the severity and frequency of adverse events without decreasing the antitumor effect. In light of the above, CPT-11/PLD is expected to be effective against recurrent or advanced ovarian cancer resistant to platinum or taxane agents. In the phase II clinical study on CPT-11 50 mg/m^2 (days 1, 8, 15) and doxorubicin (DXR) 40 mg/m^2 (day 3) combination therapy for recurrent ovarian cancer, Nishimura et al. [11] reported that the response rate was 23.5 % (CR, 1 patient; PR, 3 patients of 17 patients) and that the grade 3/4 adverse reactions observed were neutropenia (CPT-11, 52.9 %; DXR, 35.2 %), thrombocytopenia (5.9 %, 17.6 %), anemia (17.6 %, 0 %), and diarrhea (5.9 %, 0 %). In the present study, the rates of skipping CPT-11 on days 8 and 15 were 6.0 and 22.0 %, respectively, and that of DXR on day 3 was 4.0 %. In the phase II study on CPT-11/etoposide combination therapy for recurrent small-cell lung carcinoma, Masuda et al. [12] reported that 6 of 25 patients (24 %) received two doses of CPT-11(days 1 and 8 or days 1 or 15), and 3 of 25 patients (12 %) could receive only one dose of CPT-11. By referring to the results of the two aforementioned phase II clinical studies, we designed an administration schedule for CPT-11/PLD combination therapy. If CPT-11 was to be administered on a weekly basis, it was anticipated that the rates of skipping on days 8 and 15 would be high, resulting in 30–50 % of patients skipping day 15 administration. Therefore, it was decided to administer CPT-11 on a biweekly basis (day 1, day 15). Also, it was reported that, in giving combination therapy with a topo-I inhibiter and a topo-II inhibiter, these agents act competitively rather than synergistically if administered simultaneously [13]. By also taking account of the finding that CPT-11 is metabolized in 72 h [14], it was decided that PLD would be administered on day 3, as has been the case with combination therapy employing DXR. In past reports, the dose of PLD in the combination therapy for recurrent ovarian cancer was 25–30 mg/m^2 [15, 16]. While the recommended dose for PLD monotherapy is 50 mg/m^2, sufficient efficacy and reduced adverse reactions have also been reported at the dose of 40 mg/m^2 [17]. Therefore, in consideration of reduced adverse reactions such as hand-and-foot syndrome and mucositis, the PLD dose was fixed at 30 mg/m^2. As to CPT-11, no clinical study results are available for the combination with PLD or doxorubicin by the biweekly method and its optimal dose is unknown, and enormous variation in the dose response of CPT-11 among individuals, in general, is known [18]; therefore, the dose of CPT-11 alone was increased. A phase I clinical study was

planned to investigate the efficacy and safety of CPT-11/PLD combination therapy for recurrent ovarian cancer.

Adverse events were evaluated for each patient in the first course only. As shown in Table 3, although adverse events were observed, all were nonserious and manageable. Thus, the phase I clinical study could be conducted safely. Shoji et al. [19] reported that the rate of skipping CPT-11 on day 15 was 2.3 % with the combination therapy based on CPT-11 (60 mg/m^2) biweekly administration with etoposide oral administration for recurrent ovarian cancer. In our present study as well, CPT-11 was administered on a biweekly basis (days 1, 15), and as a result, day 15 administration was skipped in only 1 patient each at level 1 and level 4. Thus, CPT-11 on day 15 was skipped in only 2 of a total of 43 courses, with the rate of skipping treatment being just 4.7 %, suggesting biweekly administration of CPT-11 in CPT-11/PLD combination therapy to be appropriate. Since no DLT was observed at any of the levels tested, it would be feasible to increase the dose of CPT-11 to level 5 under ordinary circumstances. However, as mentioned above, as a result of detailed evaluation of grade 4 neutropenia in three patients at level 4, postponement to the next course, dose reduction, and antitumor effect, the recommended CPT-11 dose was determined to be 80 mg/m^2.

The response rate to combination therapy using CPT-11 or PLD for platinum-resistant recurrent ovarian cancer is 41.9 % with CPT-11/VP16 therapy according to Shoji et al. [19] and 44.4 % according to Nishio et al. [20], and 20 % with DTX/CPT-11 therapy according to Polyzos et al. [21]. The response rate was also reported to be 22 % with PLD/Gemcitabine therapy by Skarlos et al. [22] and 40 % [23] by Mirza et al. The response rate to CPT-11/PLD combination therapy was 58.3 %, a result not inferior to those reported previously. All 12 enrolled patients had previously been treated with taxane or platinum agents. In particular, eight of them had recurrence or recrudescence within 6 months after TC therapy. It is expected that CPT-11/PLD combination therapy will achieve a high response rate and that adverse reactions will be mild and manageable. This drug combination may thus be useful as an option for second-line chemotherapy for recurrent ovarian cancer within 6 months after TC therapy.

In the future, a phase II clinical study will be conducted to validate the usefulness of CPT-11/PLD combination therapy.

Conflict of interest The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Analysis of prognostic factors for patients with bulky squamous cell carcinoma of the uterine cervix who underwent neoadjuvant chemotherapy followed by radical hysterectomy

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Abstract

Background Neoadjuvant chemotherapy (NAC) is not yet widely recommended for the treatment of stage I/II cervical cancer. However, it may be possible to achieve a favorable outcome by selecting appropriate patients. In the present study, prognostic factors were retrospectively investigated to obtain data for devising individualized NAC.

Patients and methods The subjects were 33 patients with bulky stage Ib2–IIb squamous cell carcinoma (SCC) of the uterine cervix who gave consent and were scheduled to undergo radical hysterectomy. The patients intravenously received irinotecan 70 mg/m^2 on days 1 and 8 and cisplatin 70 mg/m^2 on day 1 of a 21-day course, and two courses were performed in principle. The potential prognostic factors investigated were age, performance status (PS), clinical stage, lymph node metastasis and tumor size before NAC, SCC antigen value, anti-tumor response, histological effect of NAC, lymph node metastasis in resected specimens, and postoperative adjuvant therapy after NAC. The impacts of these factors on overall survival (OS) were calculated with the Cox regression model.

Results According to the univariate analysis, lymph node metastasis before NAC, SCC antigen value after NAC, anti-tumor response, and histological effect of NAC significantly influenced OS. These factors were tested in a multivariate model, and significant prognostic factors were lymph node metastasis before NAC (hazard ratio 0.116, $P = 0.027$) and anti-tumor response (hazard ratio 0.025, $P = 0.003$).

Conclusion The presence or absence of lymph node metastasis by computed tomography imaging was the only significant prognostic factor identified during the pre-NAC period.

Keywords Prognostic analysis · Cervical cancer · Bulky tumor · Squamous cell carcinoma · Neoadjuvant chemotherapy

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Introduction

Treatment strategies for bulky stage Ib2–IIb cervical cancer differ between Western countries and Japan. In most Western countries, concurrent chemoradiation (CCRT) is recommended as a standard therapy based on results from multiple large randomized trials and meta-analyses [1–8]. In other countries, including Japan, South Korea, China, and Italy, approaches including neoadjuvant chemotherapy (NAC) have been widely introduced in clinical practice [9]. Irinotecan hydrochloride (CPT-11), one of the DNA topoisomerase-I inhibitors, is an anticancer agent and is drawing attention for its mechanism of action. The anti-tumor effect of CPT-11 is exerted through the systemic inhibition of nucleic acid synthesis by its active metabolite,

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SN-38. CPT-11, as monotherapy or in combination with cisplatin (CDDP), is reportedly useful for the treatment of recurrent cervical cancer [10, 11]. In CDDP/CPT-11 therapy, CDDP is administered on day 1 and CPT-11 is administered on days 1, 8, and 15 with a 2-week rest. This is a standard regimen [12].

Intending to shorten the time to surgery, the main treatment, we conducted a phase II clinical study of combined therapy with CDDP at increased dose intensity, with CPT-11 administered every 3 weeks, and reported the results of our interim analysis [13–15]. NAC has not yet come to be widely recommended for the treatment of cervical cancer. However, it may be possible to achieve a favorable outcome with NAC by selecting appropriate patients. In the present study, prognostic factors were retrospectively investigated to obtain data for devising individualized NAC and thereby improve the outcomes of individual patients.

Patients and methods

Subjects

Between June 2002 and March 2012, we enrolled in this study 33 patients with bulky clinical stage Ib2–IIb squamous cell carcinoma (SCC) of the uterine cervix who underwent two courses of NAC followed by radical hysterectomy with at least 6 months of follow-up.

Treatment

CDDP at 70 mg/m^2 was intravenously administered on day 1 and CPT-11 at 70 mg/m^2 was intravenously administered on days 1 and 8 of a 21-day course. In principle, two courses were administered followed by radical hysterectomy.

Postoperative adjuvant therapy

Patients with a positive vaginal margin, metastatic lymph nodes, infiltration to the parametrium, and/or vascular invasion, as demonstrated by pathological examination of the resected specimens, received postoperative irradiation, chemotherapy or concurrent chemoradiation therapy (CCRT). Before 2008, irradiation was performed as postoperative adjuvant therapy, while chemotherapy was performed from 2008 onward. However, CCRT was performed in patients who had multiple lymph node metastases.

Statistical analysis

Survival analysis was performed using the Kaplan–Meier method. The Cox regression model was used to conduct univariate and multivariate analyses of prognostic factors for overall surgical (OS). The tested factors were age, performance status (PS), clinical stage, histological subtype, lymph node metastasis and tumor size before NAC, SCC antigen value before and after NAC, anti-tumor response, histological effect of NAC, lymph node metastasis in the resected specimen, and postoperative adjuvant therapy. Pre-NAC lymph node metastases were identified on computed tomography (CT) images. We set a lymph node size of 10 mm or more measured by CT performed before NAC as the presence of lymph node metastases. Pre-NAC tumor size was measured on magnetic resonance images. Anti-tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), and the effects were evaluated according to the best overall response criteria. Histological effects of NAC were evaluated according to the "Histological evaluation criteria of tumor response after preoperative therapy" [16]. In this criteria, the histological effects of anti-cancer drugs are defined as follows: Grade 0; no evidence of effect, Grade 1a; viable tumor cells occupy >2/3 of the tumorous area, Grade 1b; viable tumor cells remain in >1/3 but <2/3 of the tumorous area, Grade 2; viable tumor cells remain in <1/3 of the tumorous area, Grade 3; no viable tumor cells remain. It is recommended that the finding is confirmed on additional sectioning.

Results

Patient characteristics

The median age was 42 years (range 25–63 years); the PS was 0 in 28 patients and 1 in 5; the clinical stage Ib2 in 8 patients, IIa in 2, and IIb in 23. The pre-NAC tumor size was <5 cm in 15 patients and ≥5 cm in 18. The presence of lymph node metastasis before NAC was identified in 12 patients and absence of lymph node metastasis in 21. The response rate was 84.8 % (complete response in 6 patients, partial response in 22, stable disease in 4, and progressive disease in 1). All patients received 2 courses of NAC and radical hysterectomy. The pathological results of the resected specimens were positive for lymph node metastasis in 11 patients and negative in 22. The results for the histological effect of NAC were grade Ia in 14 patients, Ib in 6, II in 10, and III in 3. After surgery, radiotherapy was performed in 13 patients, chemotherapy in 11, and concurrent chemoradiation therapy in 1. Postoperative therapies were not administered in 8 patients. The median follow-up time was 34 months (range 6–112 months), the median disease-free survival was 26 months (range 3–112 months), and the median OS was 34 months (range 6–112 months) (Table 1).

Table 1 Patient characteristics

Age, years	
Median (range)	42 (25–63)
PS	
0	28
1	5
FIGO stage	
Ib2	8
IIa	2
IIb	23
Histological subtype	
Keratinizing	11
Non-keratinizing	22
Tumor diameter	
<5 cm	15
≥5 cm	18
Lymph node metastasis by CT	
Absence	21
Presence	12
Anti-tumor response	
CR	6
PR	22
SD	4
PD	1
Histological effect of NAC (grade)	
Ia	14
Ib	6
II	10
III	3
SCC antigen value (ng/ml), median (range)	
Before NAC	9.4 (1.1–350)
After NAC	1.2 (0.5–49)
Histological lymph node metastasis	
Negative	22
Positive	11
Postoperative adjuvant therapy	
No therapy	8
Radiotherapy	13
Chemotherapy	11
CCRT	1
Follow-up period, months	
Median (range)	34 (6–112)
PFS, months	
Median (range)	26 (3–112)
OS, months	
Median (range)	34 (6–112)

PS performance status, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *CCRT* concurrent chemoradiation therapy, *PFS* progression-free survival, *OS* overall survival

Table 2 Univariate analysis of treatment-related factors

	Hazard ratio (95 % CI)	*P* value
Age (<40 years/≥40 years)	0.944 (0.848–1.030)	0.208
PS (0/1)	0.952 (0.050–5.596)	0.964
Stage (I/II)	0.937 (0.152–4.993)	0.938
Histological subtype (keratinizing/non-keratinizing)	0.766 (0.002–2.287)	0.723
TD (<5 cm/≤5 cm)	0.547 (0.105–2.551)	0.435
LM by pre-NAC CT imaging (presence/absence)	0.171 (0.024–0.799)	0.025
Postoperative adjuvant therapy (+/−)	0.315 (0.017–1.863)	0.227
SCC antigen value before NAC (<10 ng/ml /≤10 ng/ml)	0.605 (0.119–2.762)	0.510
SCC antigen value after NAC (<1.5 ng/ml /≤1.5 ng/ml)	0.093 (0.005–0.549)	0.007
Anti-tumor response (CR or PR vs. SD or PD)	0.025 (0.001–0.178)	0.001>
Histological effect of NAC (grade I/II vs. III)	0.161 (0.009–0.956)	0.044
Histopathological LM (positive/negative)	0.245 (0.048–1.133)	0.071

PS performance status, *TD* tumor diameter, *LM* lymph node metastasis, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Prognostic factors

According to the univariate analysis, lymph node metastasis before NAC, SCC antigen value after NAC, anti-tumor response, and histological effect of NAC significantly influenced OS (Table 2). Kaplan–Meier curves for OS of these factors are shown in Fig. 1. These factors were tested in a multivariate model, and lymph node metastasis before NAC [hazard ratio (HR) 0.116, $P = 0.027$] and anti-tumor response (HR 0.025, $P = 0.003$) were identified as significant prognostic factors (Table 3).

The median OS was 25.5 months (range 12–63 months) in 12 patients with and 41 months (range 6–112 months) in 21 without lymph node metastasis before NAC ($P = 0.025$).

Of the 12 patients with lymph node metastasis before NAC, 7 had a metastatic lymph node in the resected specimen on histological examination and the other 5 did not. The median OS was 22 months (range 12–50 months) in 7 patients with and 27 months (range 14–63 months) in 5 without lymph node metastasis on histological examination ($P = 0.232$). Thus, survival of patients with lymph
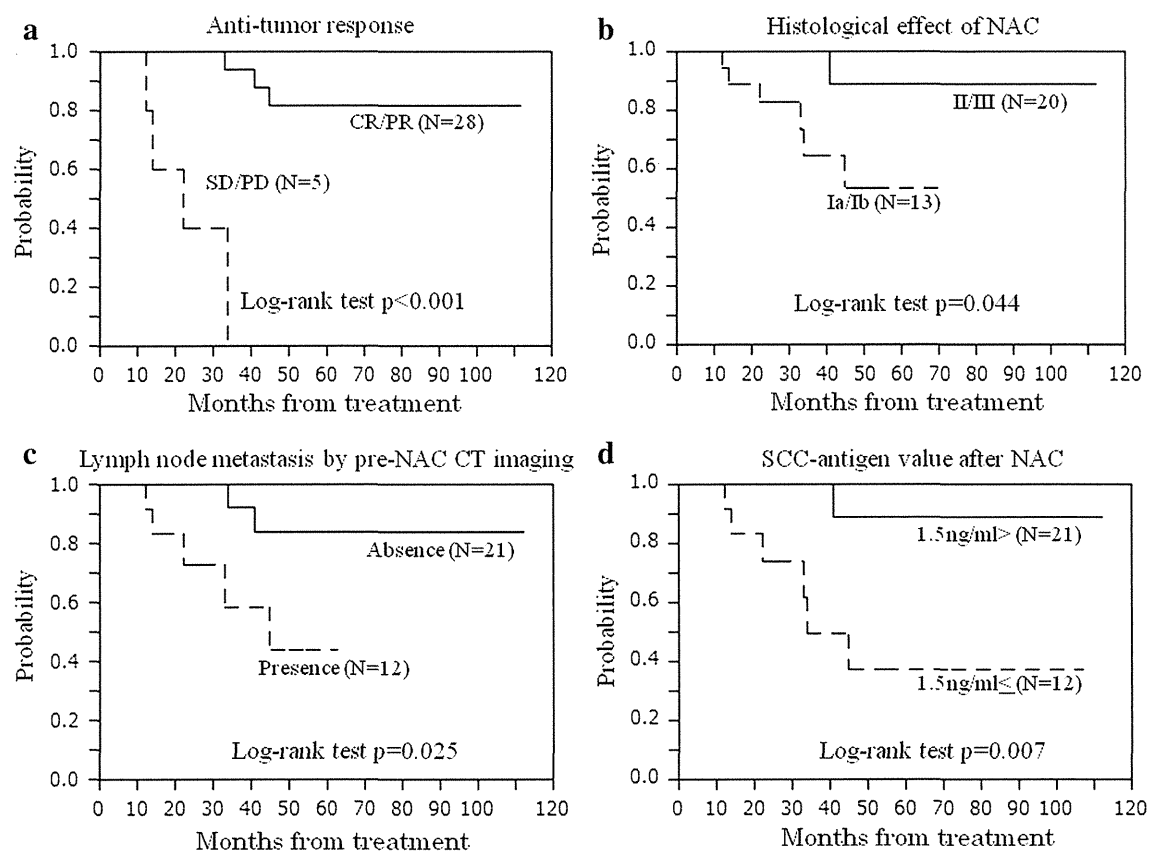
Fig. 1 Kaplan–Meier curves for overall survival. **a** Anti-tumor response: the median OS was 41 months (range 3–112 months) in 28 patients with complete response (*CR*)/ partial response (*PR*) and 22 months (range 12–34 months) in 5 with stable disease (*SD*)/ progressive disease (*PD*) (*P* < 0.001). **b** Histological effect of NAC: the median OS was 28 months (range 3–72 months) in 20 patients with grade I tumor and 63 months (range 12–34 months) in 13 with grade II/III (*P* = 0.044). **c** Lymph node metastasis by pre-NAC CT imaging: the median OS was 25.5 months (range 12–63 months) in 12 patients with presence and 41 months (range 3–112 months) in 21 with absence (*P* = 0.025). **d** SCC antigen value after NAC: the median OS was 41 months (range 3–112 months) in 21 patients with <1.5 ng/ml and 29.5 months (range 12–107 months) in 12 with ≥1.5 ng/ml (*P* = 0.007)

Table 3 Multivariate analysis of treatment-related factors

	Hazard ratio (95 % CI)	*P* value
LM by pre-NAC CT imaging (presence/absence)	0.116 (0.006–0.803)	0.027
SCC antigen value after NAC (<1.5 ng/ml /≤1.5 ng/ml)	0.424 (0.019–4.582)	0.476
Anti-tumor response (CR or PR vs. SD or PD)	0.025 (0.0006–0.329)	0.003
Histological effect of NAC (grade I/II vs. III)	0.545 (0.025–5.737)	0.612

LM lymph node metastasis, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

node metastasis before NAC may not change, even if the metastasis disappears with NAC, and the presence of lymph node metastasis before NAC thus appears to be a poor prognostic factor.

Discussion

The following two points are important for the clinical significance of NAC: (1) curability and safety with surgery can be increased by reducing tumor size, and the indications for surgery can be expanded to a wider range of patients; and (2) inhibition of distant metastasis can be expected due to the systemic effects on latent metastatic or micrometastatic lymph nodes. Meanwhile, the disadvantages of NAC include the following: (1) in nonresponsive cases, tumors may progress before the start of primary therapy; (2) although it is common to perform radiation therapy when it becomes difficult to perform surgery, NAC performed before radiation therapy may work disadvantageously in terms of local control and survival [17, 18]; (3) due to NAC-induced anemia, patients may become unable to preserve autologous blood or require blood transfusion during and after the operation; and (4) treatment is prone to

be extended over the long term and medical cost tends to be high.

The JCOG 0102, a representative randomized clinical trial of NAC for the treatment of cervical cancer conducted in Japan, involved subjects with bulky stage Ib–IIb tumors, comparing NAC + radical hysterectomy ± radiotherapy with radical hysterectomy ± radiotherapy. A BOMP (bleomycin, vincristine, mitomycin, and cisplatin) regimen was administered as NAC. However, the interim analysis results did not demonstrate the usefulness of NAC and the trial was thus terminated [19]. The JGOG 1065 was a phase II clinical trial of NAC with nedaplatin (NDP) and CPT-11 followed by radical hysterectomy in 66 patients with bulky stage Ib2–IIb cervical tumors. The response rate was 75.8 % and the 2-year relapse-free survival rate was 73.8 % [20]. However, since the response rate was not superior to that of NAC with CDDP and CPT-11, a plan for conducting a phase III clinical trial comparing NAC with NDP and CPT-11 + radical hysterectomy with CCRT did not go forward. Meanwhile, as to the comparisons between NAC and CCRT conducted overseas, Gonzalez et al. [21] compared NAC with cisplatin and gemcitabine plus surgery with CCRT using cisplatin, and reported the survival rates to be comparable. However, the KGOG1005 study retrospectively compared patients in the IB2 period who underwent surgery first, who received NAC, and who received CCRT, and reported that those undergoing the operation first had the most favorable outcomes [22].

Thus, there is no evidence that NAC + radical hysterectomy is better than radical hysterectomy alone or CCRT. In the treatment guidelines for cervical cancer of the Japan Society of Gynecologic Oncology, NAC for stage Ib and II disease is a category C1 recommendation and is not limited to indications for patients with bulky tumors. The present study was conducted to investigate whether factors associated with therapies impact outcomes and to determine whether outcomes were improved by appropriately selecting patients who would potentially benefit from NAC before administering NAC.

On multivariate analysis, lymph node metastasis before NAC and anti-tumor response were extracted as independent prognostic factors. However, prognostic factors measurable before NAC are necessary for the selection of patients who would benefit from NAC and to achieve improved outcomes. As a result, the only potential factor measurable before NAC which might be associated with improved outcomes was presence or absence of lymph node metastasis prior to NAC.

Lymph node metastasis was detected before NAC in 12 patients, and 7 (58.3 %) of these patients had also resected specimens positive for lymph node metastases. Sub-analysis was performed in these 12 patients according to the presence of lymph node metastases in the resected specimens (positive, 7 patients; negative, 5 patients). The median OS was 22 months in those with and 27 months in those without lymph node metastasis in resected specimens, indicating no significant difference.

Of 7 patients who had metastases in the removed lymph nodes, 2 had a metastasis at one site and 5 had metastases at multiple sites, whereas of 5 patients without lymph node metastasis, 3 had a metastasis at one site and 2 had metastases at multiple sites. No patients had para-aortic lymph node (PAN) metastasis before NAC and all of them had intrapelvic metastasis. Of 7 patients who had metastases in removed lymph nodes and 5 who had no lymph node metastasis, 4 and 1, respectively, died from the primary disease. Therefore, we consider OS to not differ significantly because this was a comparison between 7 and 5 patients, and a significant difference would be detectable only if the number of patients were to be increased.

Thus, survival of patients with lymph node metastasis before NAC may not change, even if the metastasis disappears with NAC, and the presence of lymph node metastasis before NAC may be a poor prognostic factor. In 21 patients without lymph node metastasis on CT before NAC who underwent NAC + radical hysterectomy, the median OS was 41 months, i.e., longer than the median OS of 25.5 months in 12 patients with lymph node metastasis. Thus, it was assumed that NAC + radical hysterectomy would prolong OS in those without lymph node metastasis on CT before treatment among patients with bulky stage I–II cervical cancers. There are no reports comparing outcomes of patients with a bulky mass at cervical cancer stage I–II according to the presence or absence of lymph node metastasis before NAC. In order to demonstrate the efficacy of this combination therapy, it is necessary to compare therapeutic outcomes between NAC + radical hysterectomy and radical hysterectomy alone in patients without lymph node metastasis on CT before treatment. Moreover, OS in those with lymph node metastasis was shorter than that in patients without metastasis. In order to investigate therapeutic approaches with the potential to prolong OS in patients with lymph node metastasis, it is necessary to compare therapeutic outcomes among NAC + radical hysterectomy, radical hysterectomy alone, and CCRT in patients confirmed to have lymph node metastasis. These comparisons would appear to be tasks that must be performed to demonstrate the usefulness of NAC for cervical cancer with a bulky mass.

Li et al. evaluated prognostic factors before NAC in 154 patients with stage Ib2 and stage IIa cervical cancer and reported disease stage to be a prognostic factor. However, they did not evaluate lymph node metastasis before NAC [23]. Ours is the first report, to our knowledge, indicating lymph node metastasis before NAC to be a prognostic factor, although the results were obtained retrospectively.

The value of this report is that our results raise the possibility of improving outcomes of patients with bulky stage Ib2–IIb cervical cancers.

Prognostic factors associated with obtaining benefits from NAC with CDDP/CPT-11 were analyzed in patients with bulky stage Ib2–IIb cervical cancers. The presence or absence of lymph node metastasis based on CT imaging was identified as the only prognostic factor that can be evaluated before NAC. The presence of lymph node metastasis before NAC by CT imaging is a risk factor in bulky stage Ib2–IIb squamous cell carcinoma of the uterine cervix.

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

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ORIGINAL ARTICLE

Outcomes of abdominal radical trachelectomy: results of a multicenter prospective cohort study in a Tohoku Gynecologic Cancer Unit

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Abstract

Background This study aimed to evaluate surgical, pregnancy, and prognostic outcomes of radical abdominal trachelectomy (RAT) for Japanese patients with early-stage cervical cancer.

Methods This was a multicenter prospective cohort study conducted in member facilities of Tohoku Gynecologic Cancer Unit. Patients with FIGO 1A–1B1 squamous cell carcinoma were included.

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Results A total of 42 patients were registered in this study, and all patients underwent planned RAT. The median stromal invasion and median horizontal spread of resected specimens were 4.6 (range 1.0–10.0) and 12.4 mm (range 3.0–28.0), respectively. The median surgical time and median blood loss were 304 min (range 233–611) and 848 mL (range 250–3984), respectively. Five patients (11.9 %) received blood transfusion. Five of 18 (27.8 %) patients who attempted to conceive achieved pregnancy, and 3 patients had healthy babies. However, all pregnancies required assisted reproductive technology with in-vitro fertilization and embryo transfer. Four patients (9.5 %) received postoperative adjuvant therapy, and 3 patients (7.1 %) developed disease recurrence.

Conclusions RAT may be safely performed for Japanese patients with FIGO 1A–1B1 squamous cell carcinoma of the cervix, even in educational medical facilities. However, less-invasive surgery should be considered more often to improve pregnancy outcomes.

Keywords Abdominal trachelectomy · Fertility-sparing surgery · Cervical cancer · Prospective cohort study · Outcome

Introduction

Since first reported as a fertility-sparing surgery in 1994 [1], radical trachelectomy has now become widely accepted as a standard treatment modality for patients with early-stage cervical cancer. The National Comprehensive Cancer Network Guidelines version 1.2014 [2] currently recommends performing radical trachelectomy with pelvic lymph node dissection +/− para-aortic lymph node sampling when patients wish to preserve fertility and have

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stage IA2–IB1 disease, tumor diameter ≤2 cm, and squamous histology. However, treatment outcomes of radical trachelectomy, including the laparoscopic approach, in Japanese patients with early stage cervical cancer have been reported only in retrospective studies at single institutions [3–5]. Therefore, to evaluate the surgical, prognostic, and pregnancy outcomes of radical abdominal trachelectomy (RAT), we conducted a prospective cohort study in Tohoku Gynecologic Cancer Unit.

Materials and methods

Study design

This prospective cohort study was conducted from August 2002 to May 2013 in the following member institutions of Tohoku Gynecology Cancer Unit: Tohoku University Graduate School of Medicine; Hirosaki University School of Medicine; Iwate Medical University; Akita University Graduate School of Medicine; Yamagata University Faculty of Medicine; and Fukushima Medical University. Patient eligibility criteria were as follows: (1) histologically confirmed cervical cancer; (2) FIGO stage IA2–IB1; (3) squamous cell carcinoma; (4) tumors less than 2 cm in diameter determined by preoperative magnetic resonance imaging; (5) patients desired fertility-sparing surgery; (6) and age ≤40 years. This study was conducted to evaluate the safety of surgery, pregnancy outcomes, and prognostic outcomes. All patients were registered pre-operatively, and we prospectively collected patient data, including surgical records, clinicopathological characteristics, pregnancy and fertility outcomes, and prognostic outcomes. This study was approved by the ethics committee at each participating facility.

Surgical procedures

All radical trachelectomies were performed via open laparotomy with a low abdominal incision, and all surgeons had received RAT education so that those performing the procedure in each facility were not fixed. The uterine cervix was resected by a nerve-sparing procedure with the bilateral cardinal ligament and vaginal wall ≥2 cm. In addition, pelvic lymphadenectomy was performed, including removal of the common iliac, external iliac, internal iliac, obturator, supra-inguinal, sacral, and cardinal lymph nodes.

Adjuvant therapy

If there was any risk factor, such as lymph vascular space involvement (LVSI) or pelvic lymph node metastasis (PLNM) was observed in resected specimens, postoperative

adjuvant therapy was recommended. Radiotherapy or concurrent chemoradiotherapy (CCRT) were adopted when patients had intermediate risk (only LVSI or deep stromal invasion) or high risk (PLNM and/or cardinal ligament invasion) of recurrence. Moreover, combination chemotherapy of taxan and platinum was permitted as an optional therapy for patients who had a strong wish to preserve ovarian function.

Results

Clinicopathological characteristics

A total of 42 patients were registered for this study. The clinicopathological characteristics of patients are shown in Table 1. Thirty-seven (88.1 %) patients received diagnostic cervical conization before undergoing RAT. One patient who was diagnosed with stage 1A2 disease by colposcopy-directed biopsy was ultimately diagnosed with stage 1A1 disease based on the surgically resected specimens after RAT. The median stromal invasion and median horizontal spread of resected specimens were 4.6 (range 1.0–10.0) and 12.4 mm (range 3.0–28.0), respectively. Four patients received postoperative adjuvant therapy. Two patients with PLNM received CCRT with paclitaxel and carboplatin chemotherapy; 1 patient with vaginal invasion received whole pelvic radiation therapy; and 1 patient with LVSI received paclitaxel and cisplatin chemotherapy.

Treatment outcomes

All patients underwent the planned surgery. Surgical outcomes are shown in Table 2. The following surgical complications were observed: uretheral injury in 1 patient, postoperative ileus in 1 patient, and pelvic lymphocyst in

Table 1 Clinicopathologic characteristics of patients

Total number of patients	42
Median age, years (range)	32 (22–39)
FIGO (2008) stage (%)	
1A1	1 (2.3)
1A2	4 (9.6)
1B1	37 (88.1)
Histological subtype	Squamous cell carcinoma
Median follow-up period, months (range)	29.9 (1–122)
Median stromal invasion, mm (range)	4.6 (1.0–10.0)
Median horizontal spread, mm (range)	12.4 (3.0–28.0)
Lymph vascular space involvement (%)	5 (11.9)
Pelvic lymph-node metastasis (%)	2 (4.8)

FIGO International Federation of Gynecology and Obstetrics

Table 2 Surgical outcomes

Median surgical time, min (range)	304 (233–611)
Median blood loss, ml (range)	848 (250–3984)
Median number of PLNs resected (range)	35 (7–68)
Blood transfusion (%)	5 (11.9)
Surgical complications (%)	
Ureteral injury	1 (2.4)
Ileus	1 (2.4)
Pelvic lymph cyst	4 (9.5)

PLN pelvic lymph-node

Table 3 Pregnancy outcomes

Attempted to conceive (%)	18/42 (42.9)
Fertility treatment (%)	9/18 (50.0)
AIH	1/18 (5.6)
IVF-ET	8/18 (44.4)
Pregnancy (%)	5/18 (27.8)
Spontaneous abortion	1/5 (20.0)
Artificial abortion	1/5 (20.0)
Spontaneous delivery[a]	1/5 (20.0)
Cesarean section[b]	2/2 (40.0)

AIH artificial insemination by husband, *IVF-ET* in-vitro fertilization and embryo transfer

[a] Delivery at 38 weeks' pregnancy

[b] Delivery at 33 and 36 weeks' pregnancy

Table 4 Clinical outcomes

Number of recurrences (%)	3 (7.1)
Recurrence sites (%)	
Vaginal stump	1 (2.4)
Retroperitoneal cavity	2 (4.8)
Survival	
Disease-free alive	39 (92.8)
Alive with disease	1 (2.4)
Died of disease	2 (4.8)

4 patients. Pregnancy outcomes are shown in Table 3. A total of 18 patients attempted to conceive, resulting in 5 pregnancies and 3 healthy babies. However, all pregnancies were achieved by in-vitro fertilization and embryo transfer (IVF-ET), and none of the women who achieved pregnancy received adjuvant treatment after RAT. Although all patients met the eligibility criteria, 3 patients (7.1 %) developed disease recurrence, and 2 patients died because of disease progression. Recurrences were observed in the vaginal stump in 1 patient and in the retroperitoneal cavity in 2 patients (Table 4). Among 3 patients with recurrence, 1 patient had LSVI and refused to undergo postoperative

adjuvant chemotherapy, but another 2 patients showed neither LSVI nor PLNM even after re-diagnosis of surgically resected specimens. However, considering the recurrence sites, the existence of an undetectable skip lesion in the preserved uterus cannot be ruled out.

Discussion

A systematic review of radical trachelectomy for cervical cancer [6] reported that among patients who were treated via a vaginal approach, 146 of 480 (30.4 %) patients achieved pregnancy, and 23 of 618 (3.7 %) patients developed disease recurrence. However, among those who underwent RAT, 30 of 147 (20.4 %) patients achieved pregnancy, and 7 (4.8 %) patients developed recurrence. Moreover, a more recent review of 485 RAT patients (stage 1A1 in 33, 1A2 in 90, 1B1 in 330, and ≥1B2 in 11) [7] reported that 47 (9.7 %) patients were converted to radical hysterectomy, 25 of 438 (5.7 %) patients received adjuvant treatment including hysterectomy, 75 of 413 (18.2 %) achieved pregnancy, and 16 of 438 (3.7 %) patients developed disease recurrence. With regard to surgical outcomes, operative times ranged from 110 to 586 min, and blood loss ranged from 50 to 5568 mL. The actual status of RAT in Japan was first revealed by a survey conducted between 2000 and 2008 [8]. This survey reported that among 26 institutions that responded to the survey, a total of 269 patients underwent radical trachelectomy, and 74.7 % of patients were treated via an abdominal approach. Moreover, although 46 % of institutions did not consider histological subtype, tumor size ≤2 cm and stage 1B1 disease were the indication criteria for RAT. Furthermore, 20 pregnancies and 13 deliveries were achieved, and, among the pregnant patients, 8 delivered later than the 29th gestational week. Compared with recent studies [4, 9–12] of RAT (Table 5), our present study showed lower median blood loss and a longer median operative time. However, because the median number of resected pelvic lymph nodes was greater in this study compared with previous studies, and because the present study was performed only in academic educational facilities, we believe RAT is a safe surgical procedure for fertility sparing in patients with early-stage cervical cancer. However, the 3 recurrent cases in the present study suggest that strict determination of surgical margin and LSVI by examination of a sufficient number of pathological specimens is necessary to prevent disease recurrence. Furthermore, our present study raised a problem regarding fertility treatment after RAT. Although 5 of 18 patients managed to achieve pregnancy, no spontaneous pregnancies were observed; all pregnancies were achieved by IVF-ET. In a study by Nishio et al. [4], although 31 pregnancies were achieved in 25 patients, natural conception was observed only in 9 (29.0 %) patients, and 20 (66.7 %) patients achieved pregnancy by IVF-ET. Although

Table 5 Results of recent studies

Factors	Reference					Present study
	[9]	[10]	[11]	[4]	[12]	
No. of patients	64	30	101	114	73	42
Age, years (range)	29.5[a] (11–41)	32.5[b] (23–41)	31[b] (19–43)	33[a] (25–40)	31[a] (22–39)	32[a] (22–39)
FIGO stage						
1A1	16	0	3	9	5	1
1A2	7	2	8	12	10	4
1B1	36	25	88	93	58	37
≤2 cm	22	20	–	–	29	34
>2 cm	14	5	–	–	24	3[c]
≥1B2	0	3	2	0	0	0
Histology						
SCC	50	15	40	99	64	42
Non-SCC	12	15	61	15	9	0
Median follow-up, months	22.8	24	–	33	20.6	29.9
Recurrences	0	2	0	–	0	3
Pregnancy	2	3	28	31	0	5
Median operation time, min	148	170	–	–	177[b]	304
Median blood loss, ml	–	813	–	–	322[b]	848
Blood transfusion, %	6.25	20	–	–	–	11.9
Median no. of PLN retrieved	25	24	24	–	26	35

FIGO International Federation of Gynecology and Obstetrics, *SCC* squamous cell carcinoma, *PLN* pelvic lymph node

[a] Median value

[b] Mean value

[c] Postoperative evaluation

cervical stenosis has been reported as a major complication of trachelectomy, the frequency of postoperative cervical problems has been reported to range from 7.8 [9] to 21 % [13]. Moreover, recent results of total laparoscopic radical trachelectomy [14] reported that 52 % of patients also needed assisted reproductive technology, though intra-pelvic inflammation was correlated with fertility problems. Although the detailed mechanisms are still unknown, less-invasive surgical procedures should be performed to prevent surgical complications, including fertility problems. A more recent review reported that less-radical surgical options, such as simple trachelectomy and cervical conization with or without sentinel lymph node biopsy and pelvic lymph node dissection, may be considered for cases of low-risk early-stage cervical cancer, including squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma; tumor size <2 cm; stromal invasion <10 mm [15]. Previously, we have reported the usefulness of sentinel lymph node detection in early-stage cervical cancer [16–18]. As the results of robot-assisted laparoscopic radical trachelectomy have been recently reported [19], radical trachelectomy using a robot-assisted laproscopic approach with sentinel lymph node sampling may be implemented in the near future.

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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.

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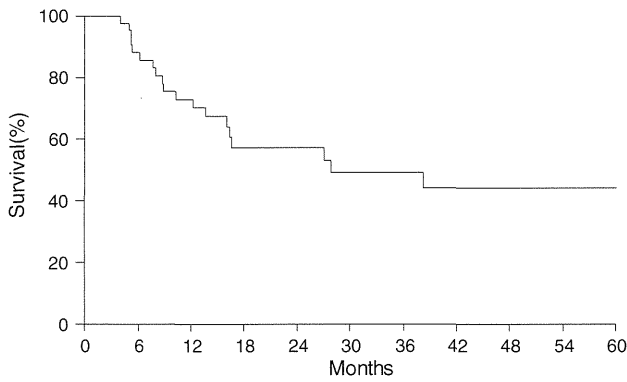
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Fig. 1 Overall survival in patients with uterine carcinosarcoma. The median survival time was 27.8 months
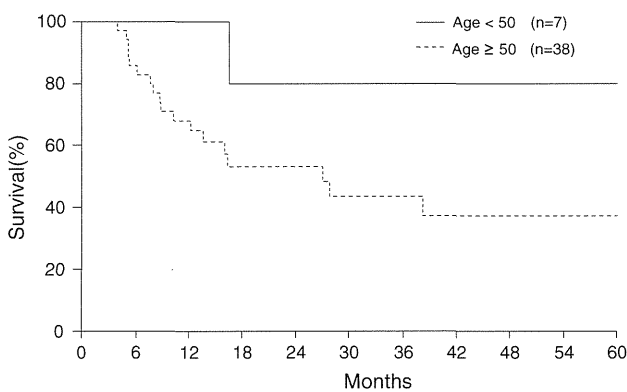

Fig. 2 Overall survival in patients with uterine carcinosarcoma subdivided by patient age. No significant survival difference was observed between <50 years and ≥50 years ($p = 0.091$)
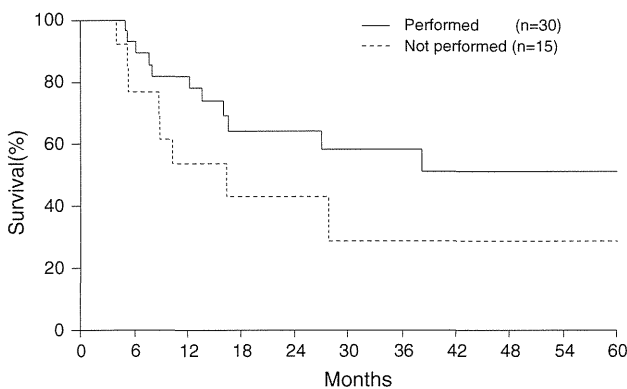

Fig. 3 Overall survival in all patients with uterine carcinosarcoma subdivided by retroperitoneal lymphadenectomy. No significant survival difference was observed with regard to retroperitoneal lymphadenectomy ($p = 0.123$)

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

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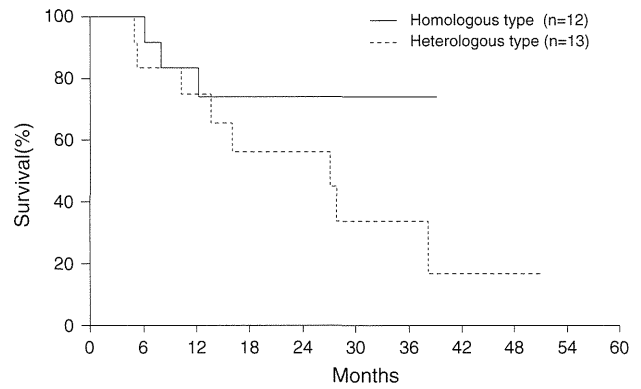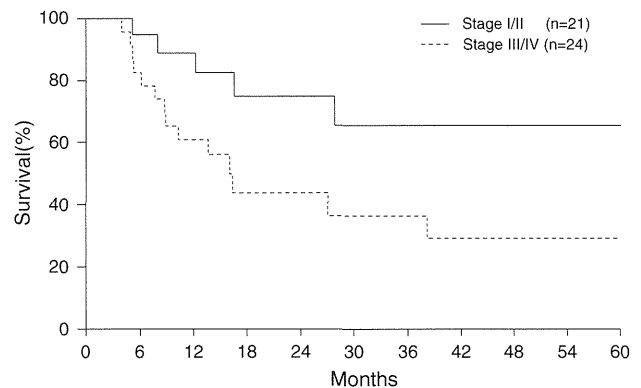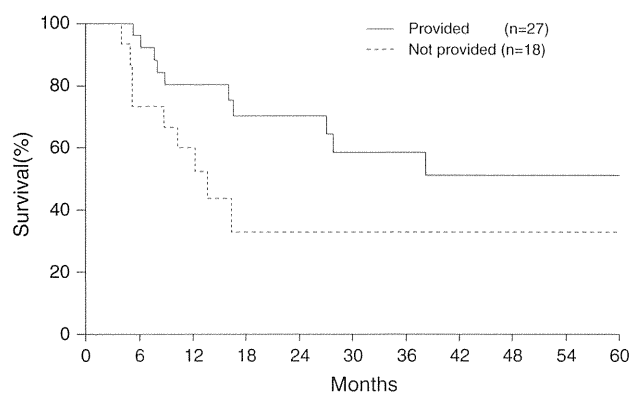
Fig. 6 Overall survival in patients with uterine carcinosarcoma subdivided by stage. The FIGO stage significantly predicted the survival of patients ($p = 0.034$)

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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