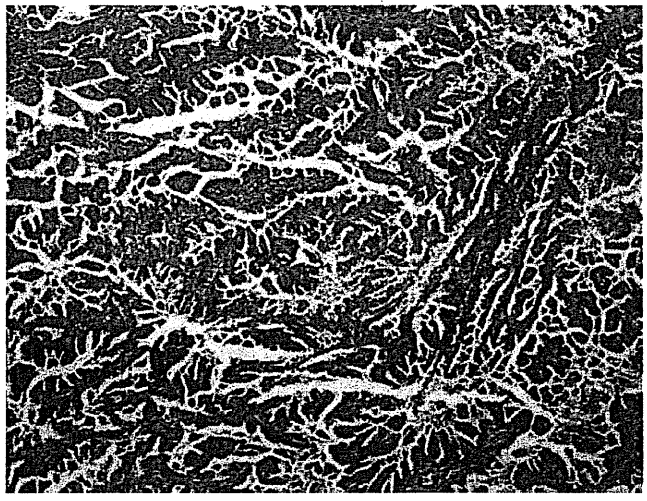

Fig. 1. Papillary serous adenocarcinoma. The tumor shows slender papillae with fibrovascular cores lined by small cells. HE stain, ×40.

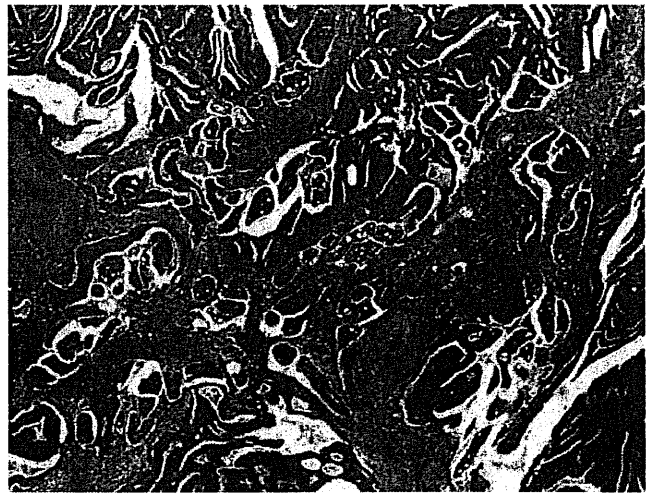

Fig. 2. Papillary serous adenocarcinoma invading cervical stroma, with clusters of tumor cells. HE stain, ×100.

mary hysterectomy. The diagnosis of serous adenocarcinoma was made only when an invasive cervical adenocarcinoma exhibited a prominent papillary structure and/or slit-like glandular spaces, and usually moderate to marked cytologic atypia (fig. 1, 2) without either intra- or extra-cytoplasmic mucin. At least 10% of the tumor area had to be of papillary serous type for inclusion in this study.

For this study, 2 gynecologic pathologists re-examined all surgically removed pathological specimens. Postoperative pathological classification was carried out according to the 2002 revision of the International Union against Cancer (UICC) TNM classification of malignant tumors.

Radical hysterectomy has long been a standard treatment option for the patients with FIGO stage IB–IIB disease in our institute. In patients with pelvic lymph node metastasis or parametrium involvement proven by pathological examination following surgery, adjuvant irradiation to the whole pelvis was administered.

Following primary treatment, asymptomatic patients underwent pelvic examination, Pap smear, ultrasound, and serial determination of tumor markers (CA125, CA19-9 and carcinoembryonic antigen) every 4–6 months. Symptomatic patients underwent the appropriate examination where indicated using chest radiography, computed tomography (CT) and magnetic resonance imaging (MRI).

Follow-up continued until January 2009. Recurrence-free and overall survival curves were calculated using the Kaplan-Meier method and were compared by non-parametric survival analysis (log-rank test). A p value of <0.05 was considered statistically significant. JMP software (version 5.0.1; SAS Institute Inc., Cary, N.C., USA) was used for statistical analysis.

Results

Patient Characteristics

Twelve patients met the study criteria. Their characteristics are summarized in table 1. Their median age was 52 years (range 30–74) and median follow-up time including death was 55 months (range 5–127). No patient was lost to follow-up. Baseline evaluation consisted of a complete gynecologic examination that included PAP smears, colposcopy and biopsy, laboratory studies inclusive of pretreatment CA125, CA19-9 and carcinoembryonic antigen as well as diagnostic imaging (CT, ultrasound, and MRI) at the initial visit. Eleven patients (92%) presented with abnormal genital bleeding as the primary symptom, with no other symptoms. The remaining patient (8%) was asymptomatic and was diagnosed based on abnormal cervical cytology. Nine patients had stage pT1b disease (seven with pT1b1 and two with pT1b2), and three had stage pT2b. All patients underwent radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. All tumors were completely removed. Adjuvant radiotherapy or chemotherapy was administered to the 4 patients in whom lymph node metastasis or parametrial invasion was proven by pathological examination of resected specimens. Three of these 4 patients received adjuvant radiotherapy to the whole pelvis, for a total dose of 50 Gy, and 1 patient was treated with chemotherapy (cisplatin, doxorubicin and cyclophosphamide). In this case, the primary care doctor selected not radio-

Table 1. Clinicopathological characteristics of the 12 patients with SACC

Patient No.	Age	Pathological stage	Growth pattern	Grade	Histologic type	Depth of invasion, mm (depth ratio)	Length mm	LVSI	Ovarian metastasis	Adjuvant therapy	Recurrent site	Recurrence months	Status (months)
1	44	pT1b1 N0	Endophytic	2	pure[a]	16 (<3/3)	25	+	–	none	NA	NA	NED (54)
2	46	pT1b1 N0	Exophytic	3	pure	5 (<1/3)	40	–	–	none	NA	NA	NED (106)
3	47	pT1b1 N0	Endophytic	3	mixed[b]	9 (<3/3)	21	–	–	none	NA	NA	NED (65)
4	30	pT1b1 N0	Endophytic	2	mixed	12 (<3/3)	35	+	–	none	NA	NA	NED (127)
5	61	pT1b1 N0	Exophytic	2	mixed	6 (<1/2)	31	+	–	none	NA	NA	NED (62)
6	51	pT1b1 N1	Exophytic	3	pure	10 (<1/3)	27	+	+	chemotherapy	lung	2	DOD (5)
7	53	pT1b1 N1	Exophytic	3	pure	15 (<2/3)	30	+	–	radiotherapy	NA	NA	NED (48)
8	68	pT1b2 N0	Exophytic	2	mixed	40 (<3/3)	55	+	–	none	NA	NA	NED (28)
9	50	pT1b2 N0	Endophytic	2	mixed	20 (<3/3)	40	–	–	none	NA	NA	NED (45)
10	51	pT2b N1	Endophytic	2	pure	21 (<3/3)	23	+	–	radiotherapy	peritoneum	43	DOD (51)
11	74	pT2b N1	Endophytic	3	pure	15 (3/>3)	80	+	+	radiotherapy	peritoneum	35	DOD (40)
12	52	pT2b N1	Endophytic	3	pure	17 (3/>3)	20	–	–	none	PALN	12	DOD (28)

SACC = Serous adenocarcinoma of the uterine cervix; LVSI = lymph-vascular space involvement; NA = not applicable; PALN = para-aortic lymph node; NED = no evidence of disease; DOD = dead of disease. + = positive; – = negative.

[a] Only serous adenocarcinoma was observed; [b] another pathological subtype (endocervical and endometrioid) was observed.

therapy but chemotherapy because he thought that chemotherapy was suitable for cervical serous adenocarcinoma at that time. For 7 patients without lymph node metastasis or parametrial invasion as evaluated histopathologically, no adjuvant therapy was performed. The remaining patient with pT2bN1 disease elected not to receive adjuvant therapy.

Pathological Features

There were large macroscopic tumors (20–80 mm), located in the uterine cervix. Five tumors showed an exophytic pattern and 7 an endophytic one. In 5, another pathological subtype of uterine cervical adenocarcinoma was observed. Three cases had endometrioid adenocarcinoma accounting for 30–60% of the tumor, whereas the other 2 had endocervical-type mucinous adenocarcinoma accounting for 50–70% of the tumor. These 12 cases were classified into 3 cytologic grades according to Zhou's criteria [3]. Six were grade 2, with moderate nuclear pleomorphism, small nucleoli, and moderate amounts of cytoplasm. The other 6 were grade 3, with marked nuclear pleomorphism and prominent nucleoli. All tumors, regardless of grade, had >10 mitotic figures per 10 high-power fields. Psammoma body was present in 1 of the grade 2 cases.

The patients were excluded if they had a history of previous primary serous carcinoma of the ovary, Fallopian tube, endometrium, or peritoneum. There were no serous adenocarcinoma lesions of the Fallopian tube or peritoneum. In 9 cases, tumor extent was confined to the uterine cervix, but 1 case had microscopic ovarian metastasis, and in 1 other, the primary tumor had started to invade the endometrium. Another case had both microscopic ovarian metastasis and myometrial invasion, but the size of the cervical tumor was 80 mm. These ovarian metastatic lesions were extremely small (1 and 6 mm) compared with the cervical mass and were present not in the parenchyma but on the surface of the ovary. In order to distinguish between primary cervical cancer and metastasis from serous ovarian cancer, 2 gynecologic pathologists re-examined all surgically removed pathological specimens.

Survival

Four (33%) patients suffered tumor recurrence after a median of 23 months following initial surgery (range 2–41 months). Two of these patients presented with symptoms of dyspnea caused by pleural effusions, and back problems related to peritoneal recurrence. All 4 of the patients with recurrent tumor died at a median of 9 months after the onset of recurrence despite intensive multimodal therapy (systemic chemotherapy, radiation and surgery).

For all 12 patients, the 5-year overall survival rate was 62% and 3-year recurrence-free survival (RFS) was 74%. The 5-year overall survival rate for patients with or without parametrial involvement (pT2b vs. pT1b) was 0 and 89%, respectively (fig. 3). This was statistically significant ($p = 0.01$). The 3-year RFS rate for patients with or without parametrial involvement was 33 and 89%, respectively, which was also statistically significant ($p = 0.01$).

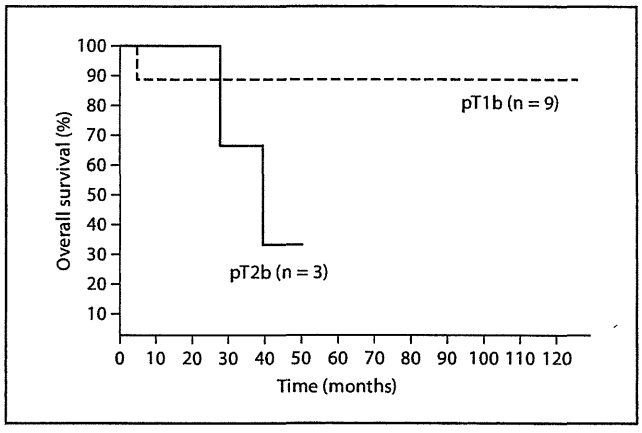

Fig. 3. Overall survival for 12 patients with SACC stratified by clinical stage.

Three-year RFS for patients with lymph node metastasis was 40 compared to 100% for those without. There was a significant difference in RFS between these 2 groups (p = 0.005).

The average number of resected lymph nodes was 28 (range 18–48). Pelvic lymph node metastasis was found in the surgically resected specimens from 1 (12.5 %) of the 8 patients with no recurrence, but in all 4 of those whose cancer recurred. All patients with 2 or more positive pelvic lymph node metastases suffered recurrence. Neither the one patient with only 1 positive pelvic lymph node metastasis nor any of the patients without metastasis suffered recurrence.

Recurrence Site

The initial sites of recurrence were located outside the pelvis in all 4 patients. The most frequent site of distant metastasis was the peritoneum (2/4, 50%), followed by the lung (1/4, 25%) and para-aortic lymph nodes (1/4, 25%).

Discussion

SACC is a very rare tumor. No large-scale multicenter study has been performed and the optimal primary therapeutic approach to SACC has not been determined. Several cases have been reported, but only very limited clinical data on SACC are available. The existing reports mostly provided information on the morphologic features and the behavior of this entity, but no accurate staging and assessment of lymph node metastasis based on reviewing surgical specimens for half the patients. Using 'serous adenocarcinoma' and 'uterine cervix' as key words, we conducted a Medline search of articles on SACC published in English from 1984 to 2008, and extracted papers describing accurate surgical staging, sites of recurrence and outcomes.

The literature provides information on a total of 25 patients including those in the present study. Twenty-one (84%) out of these 25 patients underwent radical hysterectomy [3–8]. The clinical characteristics of all 25 patients are summarized in table 2. The pathological stages were one case of pT1a, nineteen of pT1b, two of pT2a and three of pT2b. One patient with pT2a disease was categorized as advanced stage because of the presence of para-aortic lymph node metastasis. Recurrence occurred in 9 patients (three with pT1b disease, two with pT2a, three with pT2b, and one whose status was not mentioned), of whom 7 died of the disease. The recurrence rate in early (pT1 and pT2aM0) and advanced stage (pT2b and pT2aM1) was 23.8% (5/21) and 100% (4/4), respectively. Advanced stage was associated with poor prognosis.

Fregnani et al. [9] reported that the recurrence rate of patients with early-stage adenocarcinoma (FIGO stages IB and IIA) was 11.4% (4/35) and the 5-year RFS rate was 87.9%. Grisaru et al. [10] reported that the 5-year RFS rate of FIGO stage IA–IB patients with common-type adenocarcinoma (mucinous or endometrioid adenocarcinoma) was 90%. In both studies, all patients had undergone radical hysterectomy with or without adjuvant therapy. Kasamatsu et al. [11] reported that the recurrence rate for early-stage (pT1b–2a) patients with common-type adenocarcinoma (mucinous or endometrioid adenocarcinoma) was 16.7% (17/102) and their 3-year RFS rate was 91% and 100% for pT1b and pT1a, respectively. Although the recurrence rate in early-stage patients in the present review of the literature seems high (23.8%), 2 patients whose cancer recurred had not been treated with radical hysterectomy, but only with simple hysterectomy.

A radical hysterectomy with or without adjuvant therapy for early-stage SACC appeared to be associated with a favorable prognosis almost identical with common-type cervical adenocarcinoma. We suggest that the biological behavior of early-stage SACC is similar to common-type adenocarcinoma. On the other hand, all patients with advanced-stage SACC suffered recurrence, despite radical hysterectomy. In our institute, Kasamatsu et al. [11] reported that the 3-year RFS rate for patients with pT2b common-type adenocarcinoma (mucinous or endometrioid adenocarcinoma) who underwent radical

Table 2. Outcome and patterns of recurrence in 25 patients with SACC who underwent surgery: survey of the literature

	Postsurgical stage (n)	Age (mean)	Surgery (n)	Adjuvant therapy (n)	Lymph node metastasis (n)	Recurrence site (n)	Status (n)
Gilks et al. 1992 [4]	pT1b[a]	32	RH	Radiotherapy	Negative	None	NED
Shintaku et al. 1993 [5]	pT2a (1)	66	SH	Radiotherapy	Positive	Peritoneum	DOD
Rose et al. 1993 [6]	pT1a (1)	30	RH	None	Negative	None	NED
Zhou et al. 1998 [3]	pT1b (9)	Not mentioned	RH (8) SH (1)	Not mentioned	Not mentioned	Distant node (7) Peritoneum (3) Lung (2) Liver (1) Skin (1)	DOD (1) AWD (1) NED (7)
Kaplan et al. 1998 [7]	pT1b (1)	39	SH	Chemotherapy and radiotherapy	Positive	Peritoneum	DOD
Batistatou et al. 2000 [8]	pT2a[b] (1)	63	RH	Chemotherapy and radiotherapy	Positive	Lung, mediastinum and loco-regional	DOD
Present study	pT1b (9)	30–68 (50)	RH (9)	Chemotherapy (1) Radiotherapy (1)	Positive (2) Negative (7)	Lung (1)	DOD (1) NED (8)
	pT2b (3)	51–74 (57)	RH (3)	Radiotherapy (2)	Positive (3)	Peritoneum (2) PALN (1)	DOD (3)

SACC = Serous adenocarcinoma of the uterine cervix; RH = radical hysterectomy; SH = simple hysterectomy; PALN = para-aortic lymph node; NED = no evidence of disease; DOD = dead of disease; AWD = alive with disease.
[a] This patient is also included in the report by Zhou et al. [3]. [b] This patient has para-aortic lymph node metastasis.

hysterectomy was 38%. Patients with advanced-stage SACC may have more aggressive tumor behavior than those with common-type adenocarcinoma.

All patients whose tumor recurred had extra-pelvic metastasis in the present review of the literature. Of the 5 distant sites of recurrence, the most frequently reported was distant lymph node (8/21, 38%), followed by peritoneal spread (7/21, 33%), and then lung (4/21, 19%). In our institute, among the 123 patients with common-type adenocarcinoma who underwent radical hysterectomy, 27 (22%) suffered tumor recurrence [11]. Of these, the initial failure sites were inside the pelvis in 10 patients (38%), outside in 15 (58%) and both in 1 patient (4%). Of all distant failure sites, the most frequent were distant nodes (48%) and peritoneal spread (48%), followed by lung (8%). The spread pattern of the initial failure site in patients with SACC or common-type adenocarcinoma is therefore similar in that extra-pelvic metastasis is more frequent, in particular, peritoneal spread and distant node metastasis. Based on these findings, checking for extra-pelvic metastasis should be considered a priority issue for improving the survival of patients with SACC.

In patients with advanced-stage SACC, pelvic control alone usually does not lead to a favorable outcome because of the high incidence of distant metastasis. Whole-pelvic irradiation is generally selected in many institutes as a post-operative adjuvant therapy.

The largest single study of 17 cases, published by Zhou et al. in 1998 [3], revealed several key features. They reported that there was a bimodal age distribution, with 1 peak occurring before the age of 40 years and the second peak after the age of 65. In the present study, however, the mean age of all patients at the time of diagnosis was 52.2 years (range 30–74) and there are 9 cases in patients between the ages of 40 years and 65 years. From the literature review, the mean age of patients with common uterine cervical adenocarcinoma was 48.4 (±12.9) [12]. Thus, at 51 years (range 24–78) [11], the mean age of the

patients with SACC is similar to common-type adenocarcinoma.

Zhou et al. [3] reported that the presenting symptoms were abnormal vaginal bleeding or discharge (13 patients), and abnormal cervical cytology (4 patients). In the present study, 11 patients (92%) presented with abnormal genital bleeding and 1 (8%) with abnormal cervical cytology.

In summary, we have reported detailed clinicopathological features of 12 cases of SACC and reviewed the literature. Patients with pT1b disease may have a favorable outcome with radical surgery. In contrast, patients with more advanced-stage disease had a poor prognosis with established therapy, because of extra-pelvic recurrence. We need to seek effective systemic therapy for advanced-stage SACC.

Further study is warranted and is necessary to confirm the clinical behavior of SACC and to determine optimal therapy.

References

1 Young RH, Clement PB: Endocervical adenocarcinoma and its variants: their morphology and differential diagnosis. Histopathology 2002;41:185–207.
2 Young RH, Scully RE: Invasive adenocarcinoma and related tumors of the uterine cervix. Seminars in diagnostic pathology 1990; 7:205–227.
3 Zhou C, Gilks CB, Hayes M, Clement PB: Papillary serous carcinoma of the uterine cervix: a clinicopathologic study of 17 cases. American J Surg Pathol 1998;22:113–120.
4 Gilks CB, Clement PB: Papillary serous adenocarcinoma of the uterine cervix: a report of three cases. Mod Pathol 1992;5:426–431.
5 Shintaku M, Ueda H: Serous papillary adenocarcinoma of the uterine cervix. Histopathology 1993;22:506–507.
6 Rose PG, Reale FR: Serous papillary carcinoma of the cervix. Gynecol Oncol 1993;50: 361–364.
7 Kaplan EJ, Caputo TA, Shen PU, Sassoon RI, Soslow RA: Familial papillary serous carcinoma of the cervix, peritoneum, and ovary: a report of the first case. Gynecol Oncol 1998;70:289–294.
8 Batistatou A, Zolota V, Tzoracoleftherakis E, Scopa CD: Papillary serous adenocarcinoma of the endocervix: a rare neoplasm. Immunohistochemical profile. Int J Gynecol Cancer 2000;10:336–339.
9 Fregnani JH, Soares FA, Novik PR, Lopes A, Latorre MR: Comparison of biological behavior between early-stage adenocarcinoma and squamous cell carcinoma of the uterine cervix. Eur J Obstet Gynecol Reprod Biol 2008;136:215–223.
10 Grisaru D, Covens A, Chapman B, Shaw P, Colgan T, Murphy J, DePetrillo D, Lickrish G, Laframboise S, Rosen B: Does histology influence prognosis in patients with early-stage cervical carcinoma? Cancer 2001;92: 2999–3004.
11 Kasamatsu T, Onda T, Sawada M, Kato T, Ikeda S, Sasajima Y, Tsuda H: Radical hysterectomy for FIGO stage I-IIb adenocarcinoma of the uterine cervix. Br J Cancer 2009; 100:1400–1405.
12 Ayhan A, Al RA, Baykal C, Demirtas E, Yuce K, Ayhan A: A comparison of prognoses of FIGO stage Ib adenocarcinoma and squamous cell carcinoma. Int J Gynecol Cancer 2004;14:279–285.

Prognostic Impact of the History of Breast Cancer and of Hormone Therapy in Uterine Carcinosarcoma

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Objective: Recent studies reveal an association between hormone therapy for breast cancer (BC), such as tamoxifen (TAM) and toremifene (TOR), and uterine carcinosarcoma (UCS). The aim of this study was to investigate the characteristics and prognosis of patients with UCS after BC and hormone therapy.

Methods: Between January 1997 and December 2007, we treated 51 patients with UCS. The medical records of these patients were reviewed, and factors that influenced their survival were retrospectively analyzed using univariate and multivariate analyses.

Results: Ten (19.6%) of the 51 patients had a history of BC; 6 (11.8%) had received hormone therapy with TAM or TOR. The characteristics of the patients with UCS were similar regardless of whether they had a history of BC or hormone therapy. On univariate analysis, age greater than 56 years, elevated serum lactate dehydrogenase levels, residual tumors, FIGO (International Federation of Gynecology and Obstetrics) stage higher than stage IIIa, and non–endometrioid carcinomatous components were identified as prognostic factors. On multivariate analysis, in addition to residual tumors, FIGO stage higher than stage IIIa, and non–endometrioid carcinomatous components, a history of BC (relative risk, 0.14), a history of TAM use (relative risk, 15.9), and a history of TOR use (relative risk, 16.9) were also identified as independently significant prognostic factors.

Conclusions: Our data suggest that a history of BC and hormone therapy for BC is a risk factor for developing UCS without obvious impacts on the characteristics of UCS. Both of these factors had statistically significant impacts on the prognosis of patients with UCS. Further studies are necessary to clarify and validate these associations.

Key Words: Uterine carcinosarcoma, Breast cancer, Tamoxifen, Toremifene

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Tamoxifen (TAM) is a selective estrogen receptor modulator and is widely used as an adjuvant in patients with estrogen or progesterone receptor–positive breast cancer (BC). Toremifene (TOR), which has a similar structure to TAM, is now also used as hormone therapy for BC. Patients who receive long-term hormone therapy are well known to show an increased incidence of endometrial adenocarcinoma. Patients undergoing TAM therapy longer than 5 years are estimated to have an increased risk of endometrial adenocarcinoma by about 3- to 7-fold[1–3]; although its incidence is reported to be lower in patients undergoing TOR therapy.[4] In early studies, the prognosis of patients with endometrial adenocarcinoma related to TAM was thought to be worse than for those

unrelated to TAM.[3] However, later studies show a comparable prognosis between patients with diseases related to and unrelated to TAM[5,6]; however, this issue remains controversial.

Recently, the association between TAM and uterine carcinosarcoma (UCS) was demonstrated by a number of case reports and case-control studies.[3,7–14] Uterine carcinosarcoma is a tumor with carcinomatous and sarcomatous components and used to be classified as uterine sarcoma. Uterine carcinosarcoma is now considered one of the aggressive subtypes of endometrial adenocarcinoma, and its etiological features and symptoms are thought to be similar to those of endometrial adenocarcinoma. There are studies examining the prognosis of patients with UCS related to TAM.[5,11–13] However, there is still no consensus about the prognosis of patients with UCS related to TAM. Moreover, the prognosis of patients with UCS subsequent to BC without a history of hormone therapy is still unknown.

In the present study, we investigated the characteristics of patients with UCS and whether a history of BC and hormone therapy (e.g., TAM or TOR) can alter their prognosis.

TABLE 1. Characteristics of the patients with UCS in relation to their history of BC and of hormone therapy

	With a History of BC				
Factors	**Hormone Therapy**	**No Hormone Therapy**	**Subtotal**	**Without a History of BC**	**Total**
No. patients	6	4	10	41	51
Age, y	54–80	56–68	54–80	36–79	36–80
Mean, y	68.5	63.3	66.4	60.7	61.8
Median, y	71.5	64.5	67	62	63
≤56	1	1	2	13	15
>56	5	3	8	28	36
Menstrual status					
Premenopausal	0	0	0	8	8
Postmenopausal	6	4	10	33	43
Serum LDH					
Within normal limits	5	2	7	31	38
>Upper normal limits	1	2	3	10	13
Surgical procedures					
TAH + BSO	3	2	5	17	22
RAH or TAH + BSO + PLA	3	2	5	24	29
Sarcomatous component					
Homologous	4	3	7	27	34
Heterologous	2	1	3	14	17
Carcinomatous component					
Endometrioid	6	3	9	28	37
Non-endometrioid	0	1	1	13	14
Residual tumor					
None	6	2	8	34	42
Any	0	2	2	7	9
FIGO stage					
I	4	1	5	14	19
II	1	0	1	6	7
III	1	2	3	17	20
IV	0	1	1	4	5
Classified FIGO stage					
I–IIIa	5	2	7	32	39
IIIb–IV	1	2	3	9	12

TAH, total abdominal hysterectomy; RAH, radical abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; PLA, pelvic lymphadenectomy.

MATERIALS AND METHODS

Patients

Between January 1997 and December 2007, we treated 51 patients with UCS at the National Cancer Center Hospital, Japan. We reviewed the medical and pathological records of these patients. The data on whether the UCS patients had BC and had undergone hormone therapy, such as TAM and TOR, in addition to other possible prognostic factors of UCS were extracted from their records. According to the Japanese ethical guideline for epidemiologic study, this study was approved by the institutional review board of the National Cancer Center.

Our standard surgical treatment for endometrial cancer, including UCS, consists of total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. We performed radical abdominal hysterectomy in patients with apparent cervical involvement or those with a preoperative diagnosis of cervical carcinoma. Patients with biopsy-proven lymph node metastases also underwent para-aortic lymphadenectomy. In patients with no or superficial myometrial invasion on macroscopic examination of the resected uterus, pelvic lymphadenectomy was omitted and only palpation and sampling of swollen nodes were performed. In patients with extrauterine tumor spread, 6 cycles of postoperative chemotherapy were provided. Paclitaxel/carboplatin combination (TC regimen) and cyclophosphamide/doxorubicin/cisplatin combination (CAP regimen) chemotherapies were administered to 10 and 2 patients, respectively. Other treatment regimens of ifosfamide/cisplatin combination or doxorubicin/dacarbazine combination chemotherapy were administered to 1 patient each. All the patients underwent primary surgical treatment, and no neoadjuvant chemotherapy was performed. Before the start of treatment, written informed consent was obtained from all of the patients.

Statistical Analysis

Patient survival was measured from the day of starting treatment, that is, the day of surgery. Survival curves were determined by the Kaplan-Meier product limit method. Factors influencing survival were analyzed using the log-rank test (univariate) and Cox proportional hazards regression analysis (multivariate). A value of $P < 0.05$ was considered to indicate statistical significance. These analyses were performed using SPSS version 11.0 (SPSS Inc., Chicago, IL). On multivariate analyses, stepwise backward screening was performed with an exclusion $P = 0.05$ to identify independent prognostic factors. Contingency table analysis was performed using Fisher exact test or χ^2 test for trends. Differences in age were examined by nonpaired Student t test.

RESULTS

Associations Between UCS and a History of BC and of Hormone Therapy

The characteristics of the 51 patients with UCS were classified according to their histories of BC and hormone therapy and are summarized in Table 1. Ten (19.6%) of the 51 patients had a history of BC, and 6 patients (11.8%) had

TABLE 2. Characteristics of the patients with UCS and with a history of BC

Case	Age, y	FIGO Stage	BC Laterality	BC to UCS, y	Treatment	Residual Tumor	Carcinomatous Component	Sarcomatous Component	Hormone Therapy, y	Outcome
1	59	Ib	Right	13	TAH + BSO + PLA	No	Endometrioid	Homo	TAM (2)	DOD at 5 mo
2	68	IVb	Left	Synchronous	TAH + BSO + OMT	Yes	Serous	Hetero	No	DOD at 3 mo
3	63	Ib	Left, right	20, 5	TAH + BSO + PLA	No	Endometrioid	Homo	No	NED at 62 mo
4	71	Ic	Unknown	26	TAH + BSO	No	Endometrioid	Homo	TAM (5)	NED at 48 mo
5	80	Ic	Right	4	TAH + BSO	No	Endometrioid	Hetero	TAM (4)	DOD at 7 mo
6	66	IIIb	Right, left	30, 7	TAH + BSO	Yes	Endometrioid	Homo	No	DOD at 35 mo
7	54	Ib	Right	5	TAH + BSO + PLA	No	Endometrioid	Homo	TAM (2)	NED at 63 mo
8	56	IIIa	Right	11	TAH + BSO + PLA	No	Endometrioid	Homo	No	NED at 61 mo
9	75	IIIc	Left	8	TAH + BSO + PLB	No	Endometrioid	Hetero	TOR (5)	DOD at 19 mo
10	72	IIa	Right	7	TAH + BSO + PLA	No	Endometrioid	Homo	TOR (5)	DOD at 22 mo

TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; PLA, pelvic lymphadenectomy; PLB, pelvic lymph node biopsy; OMT, omentectomy; Homo, homologous; Hetero, heterologous; DOD, died of disease; NED, no evidence of disease.

a history of hormone therapy. The median follow-up period of the patients, excluding those who died, was 59 months (range, 12–85 months). Although the patients with a history of hormone therapy were slightly older than those without a history of BC, the difference was not statistically significant (mean age, 68.5 vs 60.7, $P = 0.087$, nonpaired Student t test). The patients with a history of hormone therapy seemed to have earlier stage UCS than those without a history of BC, but this difference was not significant ($P = 0.090$, χ^2 test for trends). The differences in the distributions of the other prognostic factors among the groups were also not statistically significant (P values not shown).

Characteristics of the Patients With a History of BC

The detailed characteristics of the 10 patients with a history of BC are shown in Table 2. All of the 10 patients underwent surgery for BC, and 6 patients (60%) received additional hormone therapy (4 patients with TAM and 2 patients with TOR). The durations of TAM treatment ranged from 2 to 5 years and that of TOR was 5 years. The mean intervals between BC and incidence of UCS in patients with and without a history of hormone therapy were 10.5 years (range, 4–26 years) and 15.3 years (range, 0–30 years), respectively. The interval between BC and incidence of UCS in the 2 patients with bilateral BC was calculated from the time of initial BC diagnosis. The difference in the interval between BC and incidence of UCS was not statistically significant ($P = 0.490$, nonpaired Student t test). The mean interval between hormone therapy cessation and incidence of UCS was 6.7 years (range, 0–21 years).

Analysis of Prognostic Factors

We performed both univariate and multivariate analyses to screen for potential prognostic factors of UCS. Table 3 lists the factors analyzed and the results. The prognostic factors found to be significant from the univariate analysis were age greater than 56 years, elevated serum lactate dehydrogenase (LDH) levels, presence of residual tumors, FIGO (International Federation of Gynecology and Obstetrics) stage higher than stage IIIa, and carcinomatous components other than endometrioid adenocarcinoma. Regarding multivariate analysis, all 11 factors were included in the Cox proportional hazards model, and stepwise backward analysis was performed. The results from this analysis revealed 6 independently significant prognostic factors (Table 3). The presence of residual tumors, FIGO stage higher than stage IIIa, and carcinomatous components other than endometrioid adenocarcinoma were again identified as significant prognostic factors. In addition, a history of BC, history of TAM use, and history of TOR use were also identified as independently significant prognostic factors.

Survival of Patients With UCS in Relation to Their History of BC and of Hormone Therapy

Figure 1 shows the survival curves of the patients with UCS. The 51 patients were divided into 3 groups based on their history of BC and of hormone therapy: patients with UCS not related to BC (n = 41), patients with UCS subsequent

TABLE 3. Univariate and multivariate analyses to identify significant prognostic factors for patients with UCS

	Univariate Analysis	Multivariate Analysis		
Factors	***P***	**Risk Ratio**	**95% CI**	***P***
Age (>56 [n = 36] vs ≤56 [n = 15]), y	0.038	—	—	NS
Menstrual status (postmenopause [n = 43] vs premenopause [n = 8])	0.651	—	—	NS
Serum LDH level (>upper normal limit [n = 13] vs within normal limits [n = 38])	<0.001	—	—	NS
Surgical procedures (RAH or TAH + BSO + PLA [n = 29] vs TAH + BSO [n = 22])	0.153	—	—	NS
Residual tumor (any [n = 9] vs none [n = 42])	<0.001	8.942	2.791–28.647	<0.001
FIGO stage (IIIb–IV [n = 12] vs I–IIIa [n = 39])	<0.001	4.116	1.296–13.074	0.016
Sarcomatous component (heterologous [n = 17] vs homologous [n = 34])	0.107	—	—	NS
Carcinomatous component (non-endometrioid [n = 14] vs endometrioid [n = 37])	0.017	2.896	1.088–7.708	0.033
BC (positive [n = 10] vs negative [n = 41])	0.869	0.139	0.022–0.886	0.037
TAM use (positive [n = 4] vs negative [n = 47])	0.932	15.895	1.461–172.913	0.023
TOR (positive [n = 2] vs negative [n = 49])	0.300	16.872	1.676–169.870	0.016

RAH, radical abdominal hysterectomy; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; PLA, pelvic lymphadenectomy; NS, not significant.

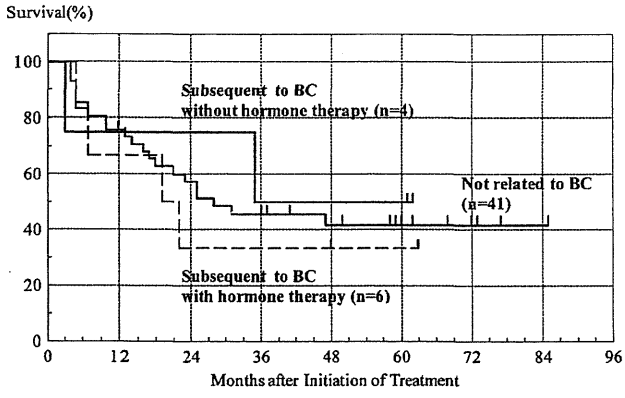

FIGURE 1. Survival curves for patients with UCS with respect to their history of BC and of hormone therapy. The survival rates of patients with UCS unrelated to BC (n = 41), patients with UCS subsequent to BC without hormone therapy (n = 4), and patients with UCS subsequent to BC with hormone therapy (n = 6) are shown in solid black, solid gray, and dotted black lines, respectively.

to BC without hormone therapy (n = 4), and patients with UCS subsequent to BC with hormone therapy (n = 6). Median survival periods and 5-year survival rates of the patients in each of the abovementioned groups were 28 months and 41.8%, 35 months and 50.0%, and 19 months and 33.3%, respectively. The differences in survival rates were not statistically significant on univariate analysis (P = 0.828, log-rank test).

DISCUSSION

In the present study, we investigated the characteristics of patients with UCS and investigated whether a history of BC and/or a history of hormone therapy for BC affected the prognosis of UCS.

We found relatively high incidences of patients with a history of BC (19.6%) and of hormone therapy (11.8%) among those with UCS. A history of pelvic radiation is a well-known risk factor for UCS. Our study population included 2 patients (3.9%) with a history of pelvic radiation (cases 5 and 6; Table 2). Both patients had a history of BC, with one having a history of hormone therapy. Although it is not clear which factors were associated with the development of UCS in these patients, the proportions of patients with histories of BC and hormone therapy were very high. Taking into account the lifetime cumulative incidence of BC that is about 5% in Japanese women,[15] the proportion of surviving female patients with a history of BC and of hormone therapy among the population is probably less than 5%. Thus, our data suggest an etiologic correlation between UCS and hormone therapy consistent with previous reports[3,6,14] and further suggest a similar correlation between UCS and BC itself.

No significant differences in clinical or pathological characteristics were found among UCS patients, without a history of BC, with a history of BC, or with a history of hormone therapy. Kloos et al.[12] suggested that TAM users had more advanced stages of UCS in their series. In contrast, McCluggage et al.[11] and Arenas et al.[13] suggested earlier stages of UCS in their series of TAM users. Our patients with a history of hormone therapy had a relatively early stage of UCS compared with those without BC, although the difference was not statistically significant (P = 0.090, χ^2 test for trends). Meanwhile, the differences in the interval from BC to incidence of UCS (P = 0.490, nonpaired Student t test) and the age of preceding BC (P = 0.353, nonpaired Student t test, data not shown) were not statistically significant between the patients with a history of BC and those with a history of hormone therapy. Taken together, the characteristics of the UCS patients without a history of BC, with a history of BC, and with a history of hormone therapy were not markedly different from each other.

Several prognostic factors of UCS have been reported previously, the most important being the FIGO stage of the tumor.[16,17] The presence of carcinomatous components other than endometrioid adenocarcinoma is also a poor prognostic factor.[18] On the other hand, the prognostic impact of heterologous sarcomatous components is controversial. In the present study, 5 factors were identified as significant prognostic factors using a univariate analysis. Among these, FIGO stage higher than stage IIIa, the presence of residual tumors, and carcinomatous components of non–endometrioid adenocarcinoma remained as independently significant prognostic factors of UCS on a multivariate analysis, whereas age greater than 56 years and elevated serum LDH levels were not independent prognostic factors on the multivariate analysis. We measured serum LDH levels in the routine preoperative systemic evaluations. The serum LDH level is reported to be higher in patients with endometrial cancer compared with healthy controls, but serum LDH level did not correlate with deep myometrial invasion or high histological grade of endometrial cancer.[19] Our data suggest some correlation with prognosis; thus, further assessment of the meaning of elevated serum LDH level is necessary to address its relevance as a predictive measure of UCS. In contrast, the history of TAM or TOR therapy and the history of BC were identified as independently significant prognostic factors on multivariate analysis, but not on univariate analysis. On univariate analysis, even when we analyzed the prognosis by dividing patients into 3 groups, that is, patients without a history of BC (41 patients), with a history of BC (4 patients), and with a history of hormone therapy (6 patients), no significant differences were found (Fig. 1). However, even when we combined the history of TAM or TOR as the history of hormone therapy, the results of multivariate analysis were almost identical. The relative risk of UCS with a history of hormone therapy and the history of BC were 16.410 (95% confidence interval [CI], 2.044–131.746) and 0.138 (95% CI, 0.022–0.867), respectively. As mentioned above, there were no marked differences in the distributions of other characteristics. Thus, the cumulative nonsignificant differences of other prognostic factors, especially FIGO stage higher than stage IIIa, presence of residual tumors, and carcinomatous component of non–endometrioid adenocarcinoma may conceal the significant prognostic impact of the history of BC, TAM, and TOR

on UCS. In previous reports, a case series suggested poor prognosis of patients with a history of TAM,[11–13] and a case-control study of patients with BC suggested poorer prognosis for patients with a history of long-term TAM use among those with endometrial cancer, including UCS.[3] On the other hand, a follow-up study of patients with BC found no prognostic impact of TAM use in patients with UCS subsequent to BC.[5] To our knowledge, there have been no previous studies analyzing the prognostic impact of the history of BC itself and of hormone therapy among patients with UCS, including those patients without preceding BC. We found that the history of BC was a significantly better prognostic factor of UCS, whereas the history of TAM and TOR treatment was a significantly poor prognostic factor of UCS on our multivariate analysis.

Our data suggest that histories of both BC and hormone therapy for BC are important risk factors for UCS, whereas characteristics of the UCS are similar regardless of the presence of these risk factors. Moreover, the history of BC appears to be a good prognostic factor in UCS patients, whereas a history of hormone therapy is a poor prognostic factor. However, because of the rarity of UCS occurrence and UCS related to BC as shown by Lavie et al,[20] our study is based on a small cohort of patients from a single institution. This is a limitation of our study, along with the retrospective nature of our study. Thus, the results from our study need to be validated by future studies to clarify the association between prognosis of UCS and a history of BC and/or of hormone therapy.

REFERENCES

1. van Leeuwen FE, Benraadt J, Coebergh JW, et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet*. 1994;343:448–452.
2. Bernstein L, Deapen D, Cerhan JR, et al. Tamoxifen therapy for breast cancer and endometrial cancer risk. *J Natl Cancer Inst*. 1999;91:1654–1662.
3. Bergman L, Beelen ML, Gallee MP, et al. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of liver and endometrial cancer risk following tamoxifen. *Lancet*. 2000;356:881–887.
4. Harvey HA, Kimura M, Hajba A. Toremifene: an evaluation of its safety profile. *Breast (Edinburgh, Scotland)*. 2006;15:142–157.
5. Slomovitz BM, Sun CC, Ramirez PT, et al. Does tamoxifen use affect prognosis in breast cancer patients who develop endometrial cancer? *Obstet Gynecol*. 2004;104:255–260.
6. Saadat M, Truong PT, Kader HA, et al. Outcomes in patients with primary breast cancer and a subsequent diagnosis of endometrial cancer: comparison of cohorts treated with and without tamoxifen. *Cancer*. 2007;110:31–37.
7. Altaras MM, Aviram R, Cohen I, et al. Role of prolonged stimulation of tamoxifen therapy in the etiology of endometrial sarcomas. *Gynecol Oncol*. 1993;49:255–258.
8. Evans MJ, Langlois NE, Kitchener HC, et al. Is there an association between long-term tamoxifen treatment and the development of carcinosarcoma (malignant mixed Mullerian tumor) of the uterus? *Int J Gynecol Cancer*. 1995;5:310–313.
9. Fotiou S, Hatjieleftheriou G, Kyrousis G, et al. Long-term tamoxifen treatment: a possible aetiological factor in the development of uterine carcinosarcoma: two case-reports and review of the literature. *Anticancer Res*. 2000;20:2015–2020.
10. Deligdisch L, Kalir T, Cohen CJ, et al. Endometrial histopathology in 700 patients treated with tamoxifen for breast cancer. *Gynecol Oncol*. 2000;78:181–186.
11. McCluggage WG, Abdulkader M, Price JH, et al. Uterine carcinosarcomas in patients receiving tamoxifen. A report of 19 cases. *Int J Gynecol Cancer*. 2000;10:280–284.
12. Kloos I, Delaloge S, Pautier P, et al. Tamoxifen-related uterine carcinosarcomas occur under/after prolonged treatment: report of five cases and review of the literature. *Int J Gynecol Cancer*. 2002;12:496–500.
13. Arenas M, Rovirosa A, Hernandez V, et al. Uterine sarcomas in breast cancer patients treated with tamoxifen. *Int J Gynecol Cancer*. 2006;16:861–865.
14. Curtis RE, Freedman DM, Sherman ME, et al. Risk of malignant mixed Mullerian tumors after tamoxifen therapy for breast cancer. *J Natl Cancer Inst*. 2004;96:70–74.
15. National Cancer Center, The Center for Cancer Control and Information Services. Cumulative cancer incidence/mortality risk. Cancer statistics in Japan 2008. Available at: http://www.ganjoho.jp/public/statistics/backnumber/odjrh3000000vdf1-att/fig09.pdf 2008. Accessed January 8, 2009.
16. Sartori E, Bazzurini L, Gadducci A, et al. Carcinosarcoma of the uterus: a clinicopathological multicenter CTF study. *Gynecol Oncol*. 1997;67:70–75.
17. Iwasa Y, Haga H, Konishi I, et al. Prognostic factors in uterine carcinosarcoma: a clinicopathologic study of 25 patients. *Cancer*. 1998;82:512–519.
18. Silverberg SG, Major FJ, Blessing JA, et al. Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus. A Gynecologic Oncology Group pathologic study of 203 cases. *Int J Gynecol Pathol*. 1990;9:1–19.
19. Koukourakis MI, Kontomanolis E, Giatromanolaki A, et al. Serum and tissue LDH levels in patients with breast/gynaecological cancer and benign diseases. *Gynecol Obstet Invest*. 2009;67:162–168.
20. Lavie O, Barnett-Griness O, Narod SA, et al. The risk of developing uterine sarcoma after tamoxifen use. *Int J Gynecol Cancer*. 2008;18:352–356.

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ORIGINAL ARTICLE

Clinical outcome of pelvic exenteration in patients with advanced or recurrent uterine cervical cancer

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Abstract
Background Pelvic exenteration has attained an important role in the treatment of advanced or recurrent cervical cancer for obtaining a complete cure or longer disease-free survival. The purpose of this study was to evaluate patients undergoing pelvic exenteration and to determine the clinical features associated with outcome and survival.
Methods We retrospectively analyzed the records of 12 patients who underwent pelvic exenteration for uterine cervical cancer between July 2002 and August 2011.
Results Two patients had primary stage IVA cervical adenocarcinoma and 10 patients had recurrent cervical cancer. Eight patients underwent anterior pelvic exenteration, 3 patients underwent total pelvic exenteration, and 1 patient underwent posterior pelvic exenteration. With a median duration of follow-up of 22 months (range 3–116 months), 5 patients were alive without recurrence. Of 5 patients with no evidence of disease, 4 were recurrent or residual tumor, all of whom had common factors, such as a tumor size $\leq$30 mm, negative surgical margins, complete resection, and no lymph node involvement. The 5-year overall survival rate for 12 patients was 42.2 %. Ileus was the most common complication (42 %) and post-operative intestinal anastomosis leaks developed in 3 patients, but no ureteral anastomosis leaks occurred.
Conclusions Pelvic exenteration is a feasible surgical procedure in advanced and/or recurrent cervical cancer patients with no associated post-operative mortality, and the only therapeutic option for complete cure or long-term survival; however, post-operative complications frequently occur.

Keywords Pelvic exenteration · Uterine cervical cancer · Positron emission tomography/computed tomography · Urinary diversion · Complications

Introduction

Cervical cancer is the fifth most common cancer among women in Japan; the mortality from cervical cancer in 2010 was 4.1 per 100,000 of the female population [1]. Radiotherapy and surgery are the cornerstones of management for patients with cervical cancer. Indeed, radiotherapy or concurrent chemoradiotherapy (CCRT) is recommended for patients who are at high risk for recurrence following radical hysterectomy or for patients with advanced stage disease [2]. Despite the clinical advantage of CCRT for cervical cancer, recurrence rates are 50–70 % for patients with locally advanced disease (The International Federation of Gynecology and Obstetrics (FIGO) IIB, III, and IVA stage) [3]. Treatment options in patients with locally recurrent cervical cancer are limited. In fact, approximately 25 % of patients with recurrences outside the irradiated field respond to chemotherapy while only 5 % of patients respond to chemotherapy if the tumor recurs within the irradiated field [4].

Pelvic exenteration (PE) was initially introduced as a palliative procedure in the treatment of advanced pelvic cancer [5]. Of note, the operative mortality rate was as high as 23 % [5]. Due to improvements in reconstructive procedures, surgical techniques, patient selection, and

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peri- and post-operative care, the operative mortality rate has decreased dramatically [6, 7]. Currently, PE has attained an important role in the treatment of advanced or recurrent cervical cancer for obtaining a complete cure or longer disease-free survival.

We performed PEs on 16 patients with uterine cervical cancer, uterine sarcoma, or vulvar cancer between July 2002 and August 2011. In the current study, 12 patients with cervical cancer who underwent PE at a single institution in Japan were reviewed. The purpose of this study was to describe the incidence and severity of complications associated with PE, and to define which patients were more likely to benefit from PE.

Materials and methods

We retrospectively studied the medical records of 12 patients who underwent PE for uterine cervical cancer between July 2002 and August 2011 at the Tohoku University Hospital. The medical records were reviewed and information was gathered with respect to age at the time of surgery, the histologic features of the primary cancer, prior treatment(s), FIGO stage, extent of disease, method of urinary and stool diversion, operative time, blood loss, tumor size, tumor residual, tumor margin status, lymph node metastasis, complications, and present disease status. The survival times of patients alive or lost to follow-up were censored in June 2012.

The selection criteria for PE were central recurrence; age (<70 years); no gross pelvic side-wall involvement; no para-aortic lymph node enlargement; no distant metastases; and good performance status. An informed consent, including the rationale for the procedure and a statement that the procedure could be terminated intra-operatively without completing the resection, was obtained in every case. The diagnosis of recurrent tumor was confirmed by pathologic examinations of a biopsy specimen from each patient, but we did not perform surgical explorations, such as open or laparoscopic biopsies.

All surgical procedure was performed by gynecologic oncologists in collaboration with urologists and general surgeons. Total pelvic exenteration (TPE) involves removal of the reproductive tract, bladder, portions of the ureters, and rectosigmoid colon. Anterior pelvic exenteration (APE) is removal of the reproductive tract, bladder, and portions of the ureters, while posterior pelvic exenteration (PPE) is removal of the reproductive tract and rectosigmoid colon. Pelvic lymphadenectomy is performed for primary stage IVA patient who undergo PE. The recurrent patients after CCRT receive selective biopsy for lymph nodes with suspected metastasis. Intra-operative radiation therapy was not administered to any patient.

All statistical analyses were performed with StatFlex 6.0 (Artec, Inc., Osaka, Japan). Survival probabilities were estimated using the Kaplan–Meier method, and statistical significance was determined by the log-rank test.

Results

Patient characteristics and surgical data of the 12 patients are presented in Table 1. The median age at the time of surgery was 46 years (range 34–63 years). Of the 12 patients, 2 had primary cervical adenocarcinoma (stage IVA) and 10 had recurrent cervical cancer (squamous cell carcinoma, $n = 6$; and adenocarcinoma, $n = 4$). All 10 patients with recurrences had received radiotherapy, 6 of whom underwent hysterectomies before PE.

The median tumor size at the time of PE was 32.5 mm (range 15–82 mm). The operative procedures were APE ($n = 8$), TPE ($n = 3$), and PPE ($n = 1$). The median operative time was 491.5 min (range 266–683 min) and the estimated blood loss was 2537.5 g (range 1565–5572 g). Eight of 12 patients had no macroscopic residual tumor after PE, and as a result the surgical margins had no malignant cells microscopically in 8 cases. The resected specimens from nine patients contained lymph nodes. Of the nine patients, three had positive lymph node metastases and the histopathologic diagnoses were adenocarcinomas. The median hospital stay post-PE was 65.5 days (range 16–103 days).

The surgical outcomes and complications are summarized in Table 2. Ileus was the most common complication, occurring in 5 patients (42 %). Post-operative leaks of intestinal anastomoses developed in 3 patients (25 %). Two patients (17 %) required re-laparotomies because of ileus, a wound infection, or peritonitis. In contrast, no post-operative leaks of ureteral anastomoses were documented. There were no peri-operative deaths and no cardiovascular or thromboembolic events. Two patients (17 %) had no major post-operative complications.

The types of urinary reconstructive procedures and leakages are summarized in Table 3. Before performing PE, 10 patients received pelvic radiation therapy. Only one patient (no. 88) did not require urinary diversion because a PPE was performed. The methods of urinary diversion were ileal conduits ($n = 4$); ureterocutaneostomy ($n = 3$); transverse colon conduits ($n = 3$); and sigmoid colon conduit ($n = 1$). Three patients with ureterocutaneostomies did not require intestinal anastomoses. No patients had ureteral anastomosis leakages. Two patients had ileoileal anastomosis leaks in the ileal conduit using the ileum within the radiation field.

With a median duration of follow-up of 22 months (range 3–116 months), 5 patients were alive without

Table 1 Backgrounds and characteristics

Case	Age	Stage	Histology	Status	Prior treatment	Site of recurrence	PET/CT	Tumor size (mm)	Exent type	Operation hours (min)	Blood loss (g)	Tumor residuals	Margin status	Positive lymph nodes	Length of hospital stay after PE (days)	Survival Period after PE (months)	Progression free period after PE (months)	Disease status
1	63	IB2	SCC	Relapse	Surgery, CCRT	Vaginal stump	(−)	50	TPE	677	3205	None	(−)	(−)	90	3	2	DOD
2	41	IIB	SCC	Relapse	CCRT, Chemotherapy	Uterus	(−)	28	APE	395	2650	None	(−)	(−)	84	116	116	NED
3	45	IB2	AC	Relapse	Surgery	Vaginal stump	(−)	35	APE	490	2600	None	(−)	(+)	100	54	44	DOD
4	41	IVA	AC	Primary	None		(−)	82	APE	502	5572	None	(−)	(+)	103	106	106	NED
5	49	IIIA	SCC	Relapse	CCRT	Uterus	(+)	15	APE	425	1910	None	(−)	(−)	47	99	99	NED
6	34	IIB	SCC	Relapse	CCRT, chemotherapy	Uterus,pelvic lymph nodes	(+)	39	APE	266	1565	None	(−)	Not removed	23	7	2	DOD
7	60	IIB	AC	Relapse	Surgery, CCRT	Vaginal stump	(+)	38	APE	470	1700	<1 cm	(+)	(+)	88	21	10	DOD
8	56	IIIB	SCC	Relapse	CCRT, chemotherapy	Uterus	(+)	25	PPE	342	1780	<1 cm	(+)	Not removed	100	18	5	DOD
9	42	IIB	SCC	Relapse	NAC, surgery, RT, chemotherapy	Vaginal stump	(−)	50	TPE	591	2755	>2 cm	(+)	(−)	32	24	24	AWD
10	47	IVA	AC	Primary	Residual tumor after CCRT		(+)	20	APE	493	1330	None	(−)	(−)	16	23	23	NED
11	36	IB2	AC	Relapse	Surgery, RT, chemotherapy	Vaginal stump, bladder	(+)	25	TPE	683	2475	<1 cm	(+)	Not removed	43	12	4	DOD
12	52	IB2	AC	Relapse	Surgery, CCRT, chemotherapy	Vaginal stump	(+)	30	APE	662	4517	None	(−)	(−)	20	14	14	NED

SCC squamous cell carcinoma, *AC* adenocarcinoma, *CCRT* concurrent chemo-radiation therapy, *NAC* neoadjuvant chemotherapy, *RT* radiation therapy, *PET/CT* positron emission tomography/computed tomography, *PE* pelvic exenteration, *TPE* total pelvic exenteration, *APE* anterior pelvic exenteration, *PPE* posterior pelvic exenteration, *DOD* dead of disease, *AWD* alive with disease, *NED* no evidence of disease

recurrences, 1 was alive with disease, and 6 died of disease at the time the study was concluded. We calculated the predictable overall survival (OS) and progression-free survival (PFS) after undergoing PE for the 12 patients. As shown in Fig. 1, the 5-year OS rate for all patients was 42.2 %. We performed univariate analysis on the previously-described patient prognostic factors; however, none of the factors were statistically significant.

Discussion

Pelvic exenteration was initially introduced in 1948 as a palliative procedure for patients with advanced pelvic cancer [5]. With the advent of surgical diversion techniques, advances in post-operative management, thromboprophylaxis, and the use of prophylactic antibiotics, the associated operative mortality has improved. In the most recently published studies, the operative mortality rate has been reduced to 0–2 % [8–10]. Therefore, the exact surgical indications for PE have gradually changed over time, and PE is currently considered a safe and feasible procedure for select patients.

To select the appropriate candidates for PE, pre-operative imaging is the most important diagnostic tool for assessment. Computed tomography (CT) scans and/or magnetic resonance imaging system (MRIs) have not been reported in sufficient numbers as imaging methods before performing PEs to assess efficacy as therapeutic modalities and in the pre-operative evaluation of lesions [11]. In fact, most of the patients in our series had previously undergone pelvic surgery and/or radiation therapy, thus it was difficult to distinguish between post-radiation pelvic fibrosis and recurrent lower genital tract cancers using CT scans and/or MRIs as imaging modalities. We performed positron emission tomography/CT (PET/CT) scans to identify the recurrent tumors in six patients who had surgery after 2004. All of the patients with central disease detected by PET/CT had histopathologic confirmation of the surgical specimens. These six patients underwent CT and/or MRI prior to PET/CT; uterine relapse was not detected in two patients by CT scan and 3 patients by MRI. These results, as well as the results in previous reports [11, 12] indicate that PET/CT is the most useful modality with which to determine eligibility for PE.

Factors such as positive node status, tumor size, side wall fixation, histologic type, and margin status, have been shown to be associated with prognosis in patients with advanced cervical cancer [7, 8, 13–19]. In our series, 5

Table 2 Surgical outcome and complications ($n = 12$)

	Patients
Early and late operative complications	
Ileus	5 (42 %)
Insufficiency of the intestinal anastomosis	3 (25 %)
Re-laparotomy	2 (17 %)
Wound infection	2 (17 %)
No complication	2 (17 %)
Pelvic abscess	1 (8 %)
Infectious lymphocele	1 (8 %)
Infection of urinary tract	1 (8 %)
Severe appetite loss	1 (8 %)
Cardiovascular and/or thromboembolic events	0 (0 %)
Insufficiency of the ureteral anastomosis	0 (0 %)
Secondary bleeding	0 (0 %)
Operative mortality	0 (0 %)

Table 3 Types of urinary reconstructive procedures and leak

Case	Exent type	Method of urinary diversion	RT before PE	Leak of intestinal anastomosis	Leak of ureteral anastomosis
1	TPE	Sigmoid colon conduit	+	−	−
2	APE	Ileal conduit	+	+	−
3	APE	Ileal conduit	−	−	−
4	APE	Ileal conduit	−	−	−
5	APE	Ureterocutaneostomy	+	−[a]	−[b]
6	APE	Ureterocutaneostomy	+	−[a]	−[b]
7	APE	Ileal conduit	+	+	−
8	PPE	No urinary diversion	+	−[a]	−[b]
9	TPE	Ureterocutaneostomy	+	−[a]	−[b]
10	APE	Transverse colon conduit	+	−	−
11	TPE	Transverse colon conduit	+	−	−
12	APE	Transverse colon conduit	+	−	−

RT radiation therapy, *PE* pelvic exenteration, *TPE* total pelvic exenteration, *APE* anterior pelvic exenteration, *PPE* posterior pelvic exenteration

[a] No intestinal anastomosis

[b] No ureteral anastomosis

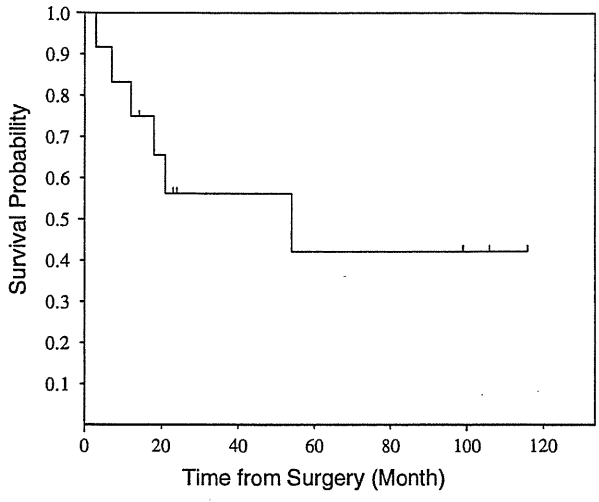

Fig. 1 Overall survival for the entire patients

patients (41.7 %) had no evidence of disease after PE (nos. 2, 4, 5, 10, and 12). Moreover, 2 patients (nos. 2 and 5) had long-term survival >8 years in spite of recurrence. Of the 5 patients with no evidence of disease, 4 (nos. 2, 5, 10, and 12) were treated for recurrences or residual tumor. All 4 patients had common factors: tumor size ≤30 mm, negative surgical margins, complete resection, and no lymph node involvement. Although the number of patients was too small to demonstrate a statistical difference, these factors are thought to be important in selecting candidates for PE. In contrast, patient no. 4 had long-term survival, despite a bulky tumor (>80 mm), positive lymph nodes, and cervical adenocarcinoma. Patient no. 4 was diagnosed with FIGO stage IVA cervical adenocarcinoma and underwent PE primarily. The therapeutic strategy for stage IVA cervical cancer remains controversial. Surgical resection for patients with stage IVA cervical cancer is not recommended in the United States and Japan [2, 20]. In contrast, half of the patients with stage IVA undergo PE primarily in Germany [17]. Marnitz et al. [17] reported that the overall cumulative survival after PE was 52.5 % in the primary treatment group and tumor-free resection margin was significantly correlated with a good prognosis. Our cases also achieved tumor-free surgical margins; therefore, PE may be an alternative to primary chemoradiation if the tumor is considered to be completely resectable.

PE, in some situations, is associated with severe complications. Intestinal anastomosis leaks cause peritonitis and inevitably lead to re-laparotomies, resulting in lengthy hospital stays. In our series, insufficiency of the intestinal anastomosis occurred in 3 of 8 cases (37.5 %), which is higher than previous reports (19.1–29.8 %) [21, 22]. All three patients with intestinal leakages had irradiated small intestines with normal appearances. On the basis of these results, we used a transverse colonic conduit for urinary diversion in the current three patients, and had no post-operative intestinal leakages at the time the study was concluded. We deem transverse colonic conduits to be suitable in patients with previous radiation therapy.

In conclusion, PE is a feasible surgical procedure, especially in select patients with recurrent tumors ≤30 mm in size, negative surgical margins, and no lymph node involvement, and is a valuable option for cure or long-term survival, although post-operative complications remain high. Intra-operative procedures, such as urinary diversion, affect complications during the early post-operative period and will continue to be revised to further reduce the complication rate. Cooperation with general surgeons and/or urologists, intensive post-operative management, and patient selection are the cornerstones to improve survival and quality of life in patients with advanced and/or recurrent cervical cancer.

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

References

1. Center for Cancer Control and Information Services (2011) Vital Statistics Japan edited by Ministry of Health, Labour and Welfare. National Cancer Center. Available via DIALOG. http://ganjoho.jp/professional/statistics/statistics (page 17)
2. Nagase S, Inoue Y, Umesaki N et al (2010) Evidence-based guidelines for treatment of cervical cancer in Japan. Japan Society of Gynecologic Oncology (JSGO) 2007 edition. Int J Clin Oncol 15(2):117–124
3. Rose PG, Bundy BN, Watkins EB et al (1999) Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 15;340(15):1144–1153 (Erratum in: N Engl J Med 1999 26;341(9):708)
4. Brader KR, Morris M, Levenback C et al (1998) Chemotherapy for cervical carcinoma: factors determining response and implications for clinical trial design. J Clin Oncol 16(5):1879–1884
5. Brunschwig A (1948) Complete excision of the pelvic viscera for advanced carcinoma. Cancer 1:177–183
6. Berek JS, Howe C, Lagasse LD et al (2005) Pelvic exenteration for recurrent gynecologic malignancy: survival and morbidity analysis of the 45-year experience at UCLA. Gynecol Oncol 99:153–159
7. Maggioni A, Roviglione G, Landoni F et al (2009) Pelvic exenteration: ten-year experience at the European Institute of Oncology in Milan. Gynecol Oncol 114:64–68
8. Jurado M, Alcazar JL, Martinez-Monge R et al (2010) Resectability rates of previously irradiated recurrent cervical cancer (PIRCC) treated with pelvic exenteration: is still the clinical involvement of the pelvis wall a real contraindication? A twenty-year experience. Gynecol Oncol 116:38–43
9. McLean KA, Zhang W, Dunsmoor-Su RF et al (2011) Pelvic exenteration in the age of modern chemoradiation. Gynecol Oncol 121(1):131–134
10. Khoury-Collado F, Einstein MH, Bochner BH et al (2012) Pelvic exenteration with curative intent for recurrent uterine malignancies. Gynecol Oncol 124(1):42–47
11. Husain A, Akhurst T, Larson S et al (2007) A prospective study of the accuracy of ^{18}Fluorodeoxyglucose positron emission

tomography (^{18}FDG PET) in identifying sites of metastasis prior to pelvic exenteration. Gynecol Oncol 106:177–180
12. Havrilesky LJ, Wong TZ, Secord AA et al (2003) The role of PET scanning in the detection of recurrent cervical cancer. Gynecol Oncol 90(1):186–190
13. Rutledge FN, McGuffee VB (1987) Pelvic exenteration: prognostic significance of regional lymph node metastasis. Gynecol Oncol 26:347–380
14. Morely GW, Hopkins MP, Lindennaur SM et al (1989) Pelvic exenteration, University of Michigan: 100 patients at 5 years. Obstet Gynecol 74:934–942
15. Saunders N (1995) Pelvic exenteration: by whom and for whom? Lancet 345:5–6
16. Numa F, Ogata H, Suminami Y et al (1997) Pelvic exenteration for the treatment of gynecological malignancies. Arch Gynecol Obstet 259:133–138
17. Marnitz S, Dowdy S, Lanowska M et al (2009) Exenterations 60 years after first description: results of a survey among US and German Gynecologic Oncology Centers. Int J Gynecol Cancer 19(5):974–977
18. Forner DM, Lampe B (2011) Exenteration as a primary treatment for locally advanced cervical cancer: long-term results and prognostic factors. Am J Obstet Gynecol 205:148.e1–6
19. Benn T, Brooks RA, Zhang Q et al (2011) Pelvic exenteration in gynecologic oncology: a single institution study over 20 years. Gynecol Oncol 122:14–18
20. National Comprehensive Cancer Network (2006) NCCN clinical practice guidelines in oncology cervical cancer V2.2006. http://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf
21. Marnitz S, Kohler C, Muller M et al (2006) Indication for primary and secondary exenterations in patients with cervical cancer. Gynecol Oncol 103:1023–1030
22. Fotopoulou C, Neumann U, Kraetschell R et al (2010) Long-term clinical outcome of pelvic exenteration in patients with advanced gynecological malignancies. J Surg Oncol 101:507–512

Original Articles

Efficacy of neoadjuvant chemotherapy followed by radical hysterectomy in locally advanced non-squamous carcinoma of the uterine cervix: a retrospective multicenter study of Tohoku Gynecologic Cancer Unit

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Summary

Objective: Radical hysterectomy (RH) is a standard treatment for locally advanced non-squamous cell carcinoma (N-SCC) of the uterine cervix, but there have been no reports on whether neoadjuvant chemotherapy (NAC) followed by radical hysterectomy could improve the outcome of patients with this disease. *Materials and Methods:* This multicenter retrospective study enrolled 77 patients with Stage IB2 to IIB N-SCC of the uterine cervix. Of these, 27 patients were treated with NAC prior to radical hysterectomy (NAC group) and 50 with RH alone (RH group). The two-year recurrence-free survival (RFS) rate, progression-free survival (PFS), and overall survival (OS) were compared between the two groups. Clinical parameters such as clinical stage, histological type, and post-operative treatment were also examined between the groups. *Results:* While the two-year RFS rates were 81.5% and 70.0% in NAC and RH groups, respectively ($p = 0.27$) and the median PFS was 51 months and 35 months in NAC and RH groups, respectively ($p = 0.35$), the median OS was 58 months and 48 months in NAC and RH groups, respectively, which was significant ($p = 0.0014$). The median OS of patients with mucinous adenocarcinoma in NAC group was significantly higher than that in RH group: 58 months versus 37 months ($p = 0.03$). *Conclusion:* NAC prior to RH may offer the prognostic advantage of patients with locally advanced N-SCC of the uterine cervix, especially mucinous adenocarcinoma.

Key words: Uterine cervical carcinoma; Non-squamous cell carcinoma; Neoadjuvant chemotherapy; Radical hysterectomy; Outcome.

Introduction

Radical hysterectomy and radiotherapy are a traditional therapeutic modality for invasive carcinoma of the uterine cervix in Japan. Since some observations showed that chemo-radiotherapy with cisplatin offered the advantage of clinical outcome in locally advanced carcinoma of the uterine cervix, chemotherapy has become the treatment of preference of uterine cervical carcinoma [1-7]. The Italian multicenter randomized study, which enrolled patients with locally advanced Stage IB2 to IIB squamous cell carcinoma of the uterine cervix, showed that NAC prior to RH improved the patient outcome as compared to conventional radiation therapy alone [8]. Combination of docetaxel and carboplatin in the neoadjuvant setting for patients with advanced or recurrent uterine cervical malignancy showed complete or partial response in all of patients with uterine cervical adenocarcinoma, suggesting that the combination may be quite promising for treatment of uterine cervical adenocarcinoma [9]. However, there is no evidence that NAC improves the outcome of patients with uterine cervical adenocarcinoma. The aim of this multicenter study was to retrospectively evaluate whether NAC can improve the outcome of patients with locally advanced N-SCC of the uterine cervix.

Materials and Methods

This study enrolled 77 patients with Stage IB2 to IIB N-SCC of the uterine cervix who underwent RH at the institutions belonging to the Tohoku Gynecologic Cancer Unit (TGCU) between January 1996 and December 2008. Of these, 27 patients were treated with NAC prior to RH (NAC group), and 50 patients were treated with RH alone (RH group). The two-year recurrence-free survival (RFS) rate, progression-free survival (PFS), and overall survival (OS) were compared between the two groups. Clinical parameters, such as: clinical stage, histological type, and postoperative treatment were also examined between the groups.

The PFS and OS in the two groups were calculated by the Kaplan-Meier method, and the statistical significance of differences in the cumulative curves between the two groups was evaluated by log-rank test. Categorical variables comparisons were conduced by two-tailed Chi square or Mann-Whitney U test where appropriate. A result was deemed significant at $p < 0.05$.

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Results

Patient characteristics

The median age was 49 and 45 years in NAC and RH groups, respectively. Eleven (40.7%) and 29 (58.0%) patients had Stage IB2 disease in NAC and RH groups, respectively, and 16 (59.3%) and 21 (42.0%) patients had Stage II disease NAC and RH groups, respectively. In regard to the histological type, 13 patients had mucinous adenocarcinoma, four had endometrioid adenocarcinoma, three had clear cell carcinoma, and seven had adenosquamous carcinoma in the NAC group, while 27 patients had mucinous adenocarcinoma, nine had endometrioid adenocarcinoma, two had clear cell carcinoma, nine had adenosquamous carcinoma, and three had other types in RH group. Of the 27 patients in NAC group and 50 in RH group, 19 (70.4%) and 40 (80.0%) underwent any postoperative treatments, respectively (Table 1).

Table 1. — *Patient characteristics.*

Variable	NAC (n = 27)	RH (n = 50)	p value
Median age in years [range]	49 [30-63]	45 [25-76]	$p = 0.85$*
Stage			
IB2	11 (40.7)	29 (58.0)	$p = 0.15$**
II			
IIA	0	6 (12.0)	
IIB	16 (59.3)	15 (30.0)	
Histological type			
Adenocarcinoma			
mucinous	13 (48.1)	27 (54.0)	$p = 0.98$**
endometrioid	4 (14.9)	9 (18.0)	
clear cell	3 (11.1)	2 (4.0)	
Adenosquamous carcinoma	7 (25.9)	9 (18.0)	
Others	0	3 (6.0)	
Adjuvant therapy			
administered	8 (29.7)	10 (20.0)	$p = 0.34$**
not administered			
Chemotherapy	9 (33.3)	16 (32.0)	
Chemoradiation therapy	5 (18.5)	14 (28.0)	
Radiotherapy	5 (18.5)	10 (20.0)	

*Mann-Whitney U test, **Chi-square test, numbers of parenthesis represent %.

NAC regimens and number of cycles

Because this was a retrospective and multicenter study, the combination of anti-cancer agents utilized was heterogeneous as shown in Table 2. Of the 27 patients in NAC group, eight received DC: seven patients received two cycles and one patient received three cycles. Five patients received cisplatin alone. Four patients received MEP: one patient received one cycle, two patients received two cycles, and one patient received three cycles. Three patients received TC of two cycles. Three patients received FCAP: one patient received one cycle and two patients received three cycles. Other four patients received cisplatin/CPT-11 of two cycles, cisplatin/Adriamycin of two cycles, cisplatin/mitomycin C of three cycles, and carboplatin/actinomycin D of three cycles, respectively.

Table 2. — *List of NAC regimens.*

Regimen	No. of patients
DC (Docetaxel 70 mg/m², carboplatin AUC6 day 1 q21 days)	8
Cisplatin alone (total 200 mg/body for 3 days)	5
MEP (MMC 10 mg/m² day 1, etoposide100 mg/m² days 1,3,5, cisplatin 50 mg/m² day 1, q28 days)	4
TC (Paclitacel 175 mg/m², carboplatin AUC6 day 1 q21 days)	3
FCAP (5-FU 200 mg/body, CPM100 mg/body, cisplatin 20 mg/m² days 1-7, ADM 35 mg/m² day 7)	3
Cisplatin/CPT-11 (cisplatin 70 mg/m² day 1, CPT-11 70 mg/m² days 1,8 q21 days)	1
Cisplatin/ADM (cisplatin 100 mg/body, ADR 40 mg/body days 1,2 q21 days)	1
Cisplatin/MMC (cisplatin 50 mg/body, MMC 4 mg/body day 1 q21 days)	1
Carboplatin/Actinomycin D (Carboplatin 300 mg/body, Actinomycin D 1.5 mg/body day 1 q21 days)	1

MMC: mitomycin C; CPM: cyclophosphamide; ADM: adriamycin.

Comparison of clinical outcome between NAC and RH groups

The two-year RFS rate was 81.5% in NAC group and 70.0% in RH group ($p = 0.27$, Table 3). The median PFS was 51 months (range, 14-157 months) in NAC group and 35 months (range, 4-157 months) in RH group ($p = 0.35$, Table 3). On the other hand, the median OS was 58 months (range, 15-157 months) in NAC group and 48 months (range, 9-157 months) in RH group, which was significant ($p = 0.0014$, Table 3 and Figure 1A).

Table 3. — *Comparison of the clinical outcome between the two groups.*

	NAC (n = 27)	RH (n = 50)	p value
Two-year RFS rate	81.5% (22/27)	70.0% (35/50)	$p = 0.27$
Median PFS (range)	51 months (14-157)	35 months (4-157)	$p = 0.35$
Median OS (range)	58 months (15-157)	48 months (9-157)	$p = 0.0014$

RFS: recurrence free survival; PFS: progression-free survival; OS: overall survival.

Comparison of clinical outcome according to clinical parameters

There were no significant differences in the median PFS and OS between NAC and RH groups according to stage, histological type and adjuvant therapy, except mucinous adenocarcinoma (Table 4). While the median PFS of patients with mucinous adenocarcinoma was 58 months (range, 8-124 months) in NAC group and 33 months (range, 4-125 months) in RH group ($p = 0.34$), the median OS of those with mucinous adenocarcinoma was 58 months (range, 24-124 months) in NAC group and 37 months (range, 9-125 months) in RH group, which was significant ($p = 0.03$) (Table 4 and Figure 1B).

Clinical outcome according to therapeutic modality after NAC and radical surgery

The outcome of patients who underwent chemotherapy or chemoradiotherapy or radiotherapy after NAC and RH were compared. As shown in Table 5, chemotherapy after NAC and surgery prolonged PFS and OS, and increased

Table 4. — *Comparison of the clinical outcome according to clinical parameters.*

Clinical parameters	Median PFS			Median OS		
	NAC	RH	*p* value	NAC	RH	*p* value
Stage						
IB2	64 (11-157)	37 (9-157)	0.26	64 (15-157)	54 (12-157)	0.26
II	33 (4-124)	45 (4-92)	0.45	39 (16-124)	45 (9-92)	0.40
Histological type						
Adenocarcinoma						
mucinous	58 (8-124)	33 (4-125)	0.34	58 (24-124)	37 (9-125)	0.03
endometrioid	31 (10-97)	70 (14-97)	0.29	31 (10-97)	70 (20-97)	0.49
clear cell	22 (4-108)	64 (12-106)	0.89	22 (16-108)	83 (60-106)	0.41
Adenosquamous	36 (12-157)	45 (12-157)	0.11	43 (21-157)	46 (12-157)	0.31
Adjuvant therapy						
administered	77 (25-157)	31 (5-157)	0.18	77 (35-157)	32 (12-157)	0.24
not administered	33 (4-124)	47 (4-106)	0.66	39 (16-124)	51 (9-106)	0.61

Numbers show months: Parenthesis means range. PFS: progression-free survival; OS: overall survival.

Table 5. — *Clinical outcome according to therapeutic modality after NAC and radical surgery.*

	Chemotherapy (n = 9)	Chemoradiotherapy (n = 5)	Radiotherapy (n = 5)
PFS (months)	42 (10-108)	30 (4-76)	22 (8-97)
OS (months)	42 (19-108)	30 (16-76)	31 (22-97)
Two-year RFS rate	88.9%	60.0%	60.0%

PFS: progression-free survival; OS: overall survival; RFS: recurrence free survival.

the two-year RFS rate compared to chemoradiotherapy or radiotherapy after NAC and surgery, although they did not reach significance.

Discussion

Numerous phase II studies have reported the favorable effects of NAC in the treatment of locally advanced carcinoma of the uterine cervix. The authors have previously reported the efficacy and safety of NAC with cisplatin plus irinotecan in this disease [10]. However, few randomized clinical trials (RCT) have evaluated the effect of NAC in the clinical outcome of patients with this disease. Sardi *et al.* reported a significant improvement of the seven-year survival rate in patients treated by NAC and radical surgery and radiotherapy (65%), as compared with that in those treated by radical surgery and radiotherapy (41%) in a four-arm randomized controlled trial (RCT) (NAC and radical surgery and radiotherapy, radical surgery and radiotherapy, radiotherapy alone, and NAC and radiotherapy) [11]. However, the retrospective study did not show obvious improvement of the five-year survival rate in patients with Stage IB2 carcinoma of the uterine cervix treated by NAC prior to surgery, as compared with that in those treated by surgery alone (80% versus 69%) [12]. These two reports were conducted in patients with SCC of the uterine cervix. Since N-SCC of the uterine cervix has recently increased in Japan, it is an important issue to evaluate the effectiveness of NAC in the outcome of patients with N-SCC of the uterine cervix. Some evidence showed that the outcome of patients with N-SCC of the uterine cervix was poorer than that of patients with SCC of the uterine cervix [13, 14], because of the higher incidence of lymph node metastases at a relatively early stage of the disease, and a lower sensitivity to radiotherapy in N-SCC of the uterine cervix [15, 16]. Chemotherapy is therefore expected to have a greater beneficial effect on the outcome of patients with N-SCC than radiotherapy or chemoradiation therapy. Because the present study was conducted retrospectively in multicenters, the combination of anti-cancer agents used was heterogeneous. The NAC regimens used in this study invariably included one of platimun derivatives, such as cisplatin and carboplatin, so platimun agents seem favorable for chemotherapy prior to surgery in N-SCC of the uterine cervix.

The two-year RFS rate and the median PFS were better in NAC group than in RH group, which were not significant, whereas the median OS in NAC group was significantly longer than in RH group ($p = 0.0014$). Furthermore, prognostic analysis in clinical parameters showed that the median OS of patients with mucinous adenocarcinoma in NAC group was significantly longer than in RH group ($p = 0.03$), although other histological types and postoperative treatment did not significantly affect the prognosis of patients between NAC and RH groups. These results suggest that NAC may offer the prognostic advantage of patients with locally advanced N-SCC of the uterine cervix, especially mucinous adenocarcinoma. Because mucinous adenocarcinoma accounts for approximately 70% out of adenocarcinomas of the uterine cervix, NAC may improve prognosis of patients with N-SCC of the uterine cervix, although NAC should be used individually at the present time.

The present study showed that chemotherapy after NAC and surgery prolonged PFS and OS, compared to chemoradiotherapy or radiotherapy after NAC and surgery, which did not reach significance. Tattersall *et al.* reported that primary chemotherapy followed by radiotherapy significantly decreased the survival rate of patients with uterine cervical carcinoma compared to those who were treated by radiotherapy alone [17]; furthermore, meta-analysis showed that chemotherapy followed by radiotherapy did not improve the survival time