cancer patients treated with radical hysterectomy plus postoperative CCRT seems yet conclusive.

The purpose of the current study is to examine the significance of adenocarcinoma of the cervix compared with squamous cell carcinoma in early stage cervical cancer treated with radical hysterectomy.

Material and methods

Patients

Permission to proceed with the data acquisition and analysis was obtained from the Institutional Review Board (IRB) of Osaka University Hospital and Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan. Informed consent was obtained from all patients. A list of patients who had undergone radical hysterectomy and pelvic lymphadenectomy for FIGO stage IA2–IIB cervical cancer from January 1998 to December 2008 was generated from our institutional tumor registries. Then, through a chart review, patients with AC or SCC histology were identified. Twenty patients with adenosquamous carcinoma, 5 small cell carcinoma, 3 glassy cell carcinoma, 1 undifferentiated carcinoma, 1 large cell neuroendocrine carcinoma, 1 mesonephric adenocarcinoma, and 1 adenoid basal carcinoma were not included in the study. Finally, a total of 520 patients (377 SCC and 143 AC) were selected for the statistical analysis. In our institutions, the histological classification of cancers was performed by two independent gynecologic pathologists based on the World Health Organization (WHO) staging system for tumors of the uterine cervix [19]. The patients were clinically staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging criteria.

Of a total of 520 patients, 295 were treated within the context of previous clinical studies [20–23].

Treatments

Surgery

All the patients were treated with type III radical hysterectomy and pelvic lymphadenectomy, as reported previously [22]. The lymphadenectomy procedure included complete bilateral pelvic lymphadenectomy with the aim of removing all of the external iliac, internal iliac, common iliac, obturator, suprainguinal, and presacral lymph nodes. When PALN metastasis was suspected on the preoperative CT scan or by intraoperative palpation, a nodal resection was performed for histological confirmation. Patients who had histologically-confirmed PALN metastasis were excluded from the study.

Postoperative radiotherapy

Postoperative radiotherapy is indicated when a patient's pathological report displays any of the following prognostic factors (high-risk group): parametrial invasion, pelvic lymph node metastasis, or a positive surgical margin, or one of the following prognostic factors (intermediate-risk group): deep stromal invasion, lymphovascular space invasion, or a large tumor (over 4 cm in diameter). A group of patients without any of the aforementioned risk factors and who therefore did not receive postoperative adjuvant therapy was classified as low-risk group.

Standard adjuvant treatment after radical hysterectomy in our institution comprises external beam pelvic radiotherapy plus concurrent chemotherapy (CCRT), as reported previously [20–22,24]. Patients who declined concurrent chemotherapy or who suffered from cervical cancer before April 1999 were treated with pelvic radiotherapy alone.

Twenty-six (5.0%) patients whose pathological reports revealed multiple pelvic node metastases were treated with extended field radiotherapy (EFRT) without concurrent chemotherapy, as reported previously [21].

Follow-up

The patients were followed-up regularly by both gynecological oncologists and radiation oncologists, as reported previously [25,26]. The median follow-up duration was 61 months (range: 6–164 months) in the SCC group and 62 months (range: 11–183 months) in the AC group.

Statistical analysis

The differences between the two groups with respect to categorical variables such as clinical stage, histology, parametrial involvement, deep stromal invasion, surgical margin status, and the recurrence rate were assessed with Fisher's exact test, and odds ratios and 95% confidence intervals (95%CI) were determined. Continuous variables such as age, maximum tumor diameter, and the pretreatment hemoglobin level were analyzed with the Student's *t* test or Mann Whitney *U* test as appropriate. Survival curves were constructed using the Kaplan–Meier method, and the significance of survival differences was determined with the Log-rank test. The Cox proportional hazards regression test with stepwise variable election (conditional backward method) was performed to assess the ability of the prognostic factors to predict survival outcomes (expressed as the hazard ratio and 95%CI). All statistical analyses were two-tailed, and p-values of less than 0.05 were considered statistically significant. The MedCalc (MedCalc Software, Mariakerke, Belgium) or Statistical Package for Social Scientists software (SPSS, version 12.0, IL) was used for all analyses.

Results

Survival outcomes according to the pathological risk factors

Five hundred and twenty patients were included in this retrospective study. Three hundred and seventy-seven patients (72.5%) had SCC, and 143 (27.5%) had AC. Of these, the low-, intermediate-, and high-risk groups contained 225 (43.3%), 123 (23.7%), and 172 (33.1%) patients, respectively. The characteristics of the patients in the SCC group were similar to those in the AC group (Table 1). All of the patients in the intermediate- and high-risk groups received adjuvant radiotherapy after radical hysterectomy. None of the patients in the low-risk group received adjuvant therapy.

In the low-risk group, recurrence was observed in 5 (3.4%) patients in the SCC group and 5 (6.3%) patients in the AC group ($P=0.33$). The estimated 5-year disease-specific survival (DSS) rates in the SCC group and AC group were 99.1% and 95.9%, respectively ($P=0.10$); i.e., there was no difference in survival between the AC and SCC groups (Table 1, Fig. 1A).

In the intermediate-risk group, recurrence was observed in 11 (11.6%) patients in the SCC group and 8 (28.6%) patients in the AC group. The estimated 5-year DSS rates in the SCC group and AC group were 89.4% and 80.6%, respectively. When the two groups were compared, the patients with AC displayed a significantly higher recurrence rate (odds ratio 3.06, 95%CI 1.09–8.58, $P=0.039$) and poorer DSS (hazard ratio: 2.86, 95%CI: 1.06–7.69, $P=0.03$) than the patients with SCC (Table 1, Fig. 1B).

In the high-risk group, recurrence was seen in 40 (29.4%) patients in the SCC group and 23 (63.9%) patients in the AC group. The estimated 5-year DSS rates in the SCC group and AC group were 80.4% and 49.5%, respectively. When the two groups were compared, the patients with AC histology displayed a significantly higher recurrence rate (odds ratio: 4.25, 95%CI: 1.96–9.20, $P<0.001$) and poorer DSS (hazard ratio: 2.88, 95%CI: 1.59–5.21, $P<0.001$) than the patients with SCC histology (Table 1, Fig. 1C).

Survival outcomes according to the mode of adjuvant radiotherapy

By combining the patients in the intermediate- and high-risk groups, we next investigated the survival difference between AC and SCC

Table 1
Patient characteristics and treatment outcomes according to the pathological risk factors.

		Low-risk group (n=225)					Intermediate-risk group (n=123)					High-risk group (n=172)				
		SCC	(%)	AC	(%)	P-value	SCC	(%)	AC	(%)	P-value	SCC	(%)	AC	(%)	P-value
Patient characteristics																
Number of patients		146		79			95		28			136		36		
Age	Median	43		45		P=0.21	50		50		P=0.62	52		54		P=0.59
	Range	24–72		29–75			26–69		28–70			27–71		19–84		
FIGO stage	IA	33	22.6	2	2.5	P<0.001	0	0.0	0	0.0	P=0.27	0	0.0	0	0.0	P=0.09
	IB1	101	69.2	76	96.2		54	56.8	18	64.3		46	33.8	5	13.9	
	IB2	3	2.0	1	1.3		15	15.8	7	25.0		13	9.6	5	13.9	
	IIA	9	6.2	0	0.0		24	25.3	3	10.7		19	14.0	8	22.2	
	IIB	0	0.0	0	0.0		2	2.1	0	0.0		58	42.6	18	50.0	
Pelvic nodal metastasis	Negative	146	100.0	79	100.0	P=1.0	95	100.0	28	100.0	P=1.0	32	23.5	12	33.3	P=0.28
	Positive	0	0.0	0	0.0		0	0.0	0	0.0		104	76.5	24	66.7	
Parametrial invasion	Negative	146	100.0	79	100.0	P=1.0	95	100.0	28	100.0	P=1.0	57	41.9	15	41.7	P=1.0
	Positive	0	0.0	0	0.0		0	0.0	0	0.0		79	58.1	21	58.3	
Margin status	Negative	146	100.0	79	100.0	P=1.0	95	100.0	28	100.0	P=1.0	122	89.7	32	88.9	P=1.0
	Positive	0	0.0	0	0.0		0	0.0	0	0.0		14	10.3	4	11.1	
Stromal invasion	Less than half	146	100.0	79	100.0	P=1.0	16	16.8	6	21.4	P=0.58	14	10.3	5	13.9	P=0.55
	More than half	0	0.0	0	0.0		79	83.2	22	78.6		122	89.7	31	86.1	
LVSI	Negative	114	78.1	66	83.5	P=0.38	23	24.2	8	28.6	P=0.63	6	4.4	2	5.6	P=0.67
	Positive	32	21.9	13	16.5		72	75.8	20	71.4		130	95.6	34	94.4	
Maximal tumor diameter [a]	Median (mm)	10		20		P=0.001	30		25		P=0.26	40		38		P=0.81
Ovarian preservation	Yes	69	47.3	8	10.1	P<0.001	20	21.1	0	0	P=0.007	5	3.7	1	2.8	P=1.0
	No	77	52.7	71	89.9		75	78.9	28	100		131	96.3	35	97.2	
Postoperative treatment	None	146	100.0	79	100.0	P=1.0	0	0.0	0	0.0	P=0.37	0	0.0	0	0.0	P=0.093
	RT	0	0.0	0	0.0		33	34.7	7	25.0		54	39.7	20	55.6	
	CCRT	0	0.0	0	0.0		62	65.3	21	75.0		82	60.3	16	44.4	
Treatment outcomes																
5-year survival	DSS (%)	99.1		95.9		P=0.10	89.4		80.6		P=0.03	80.4		49.5		P<0.001
	PFS (%)	96.5		93.5		P=0.32	87.9		68.8		P=0.034	70.5		36.3		P<0.001
Patients with recurrences	Number (%)	5	3.4	5	6.3	P=0.33	11	11.6	8	28.6	P=0.039	40	29.4	23	63.9	P<0.001

SCC, squamous cell carcinoma; AC, adenocarcinoma; LVSI, lymphovascular space involvement; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; DSS, disease specific survival; PFS, progression free survival.
[a] The maximal tumor diameter was measured three-dimensionally based on T2-weighted images.

according to the type of adjuvant radiotherapy employed after radical hysterectomy. As shown in Table 2, among a total of 295 patients who displayed intermediate- or high-risk prognostic factors, 114 (38.6%) received postoperative radiotherapy alone and 181 (61.4%) received postoperative concurrent chemoradiotherapy. In the RT group, 87 (76.3%) patients demonstrated SCC histology and 27 (23.7%) displayed AC histology. There were no significant differences in patient characteristics except for pelvic nodal status (Table 2). When DSS was compared according to histological subtype, the patients with AC had significantly poorer DSS than those with SCC in both the RT group (P=0.003, Fig. 1D) and CCRT group (P=0.017, Fig. 1E).

To further investigate the prognostic significance of AC histology, we conducted multivariate analyses using the patients in the intermediate- and high-risk groups. As shown in Table 3, multivariate analysis identified three independent prognostic factors for predicting decreased DSS in patients who had received postoperative radiotherapy alone: pelvic nodal metastasis (P=0.029), large tumor (P=0.043), and AC histology (P=0.002). Similarly, in patients who received postoperative CCRT, positive pelvic node (P<0.001) and AC histology (P<0.001) were identified as independent predictors of decreased DSS.

To elucidate which AC patients are at high risk of displaying resistance to the current standard treatment (radical hysterectomy followed by adjuvant CCRT), we conducted a multivariate analysis involving the patients who received postoperative CCRT. As shown in Table 4, pelvic nodal metastasis remained as the only independent predictor of decreased DSS. When DSS was compared according to pelvic nodal status, the AC patients with pelvic nodal metastasis showed significantly poorer DSS than those without pelvic node metastasis (hazard ratio: 12.9, 95%CI: 3.20–52.0, P<0.001, Fig. 2A). Similarly, in SCC patients treated with postoperative CCRT, pelvic nodal metastasis was significantly associated with poorer DSS than the pelvic node-negative patients (hazard ratio: 3.51, 95%CI: 1.10–11.2, P=0.024, Fig. 2B). However, magnitude of the impact of pelvic nodal metastasis was larger in AC histology than SCC histology (hazard ratio: 12.9 versus 3.51, Table 4).

Pattern of recurrence

In the SCC group, 18 (4.8%) patients developed pelvic recurrence, 26 (6.9%) developed distant recurrence, and 12 (3.2%) developed both pelvic and distant recurrences. In the AC group, 14 (9.8%) patients developed pelvic recurrence, 18 (12.6%) developed distant recurrence, and 4 (2.8%) developed both pelvic and distant recurrences. None of the patients with ovarian preservation developed ovarian recurrence across the two groups (SCC and AC groups, n=94 and 9, respectively). When the two groups were compared, the pattern of recurrence did not differ significantly between the two treatment groups (P=0.43). However, a distinctive pattern of recurrence was observed in the AC group: Seven out of 36 recurrences (19.4%) involved peritoneal dissemination in the AC group while no peritoneal dissemination was observed in the SCC group (P<0.001).

Discussion

On the basis of the results from recent prospective randomized clinical trial (GOG109 and SWOG87-97) investigating the role of postoperative CCRT in early stage cervical cancer patients with high-risk prognostic factors, concurrent chemotherapy combined with pelvic radiotherapy has become the standard adjuvant treatment for cervical cancer, regardless of the histological subtype [27]. In a separate subanalysis of their study, patients with AC and adenosquamous carcinoma had poorer prognosis than SCC when the patient was treated with radiotherapy alone [27]. However, no such survival difference was seen among the patients who received CCRT. As only 50 patients (30 in the CCRT group and 20 in the RT group) were included in their

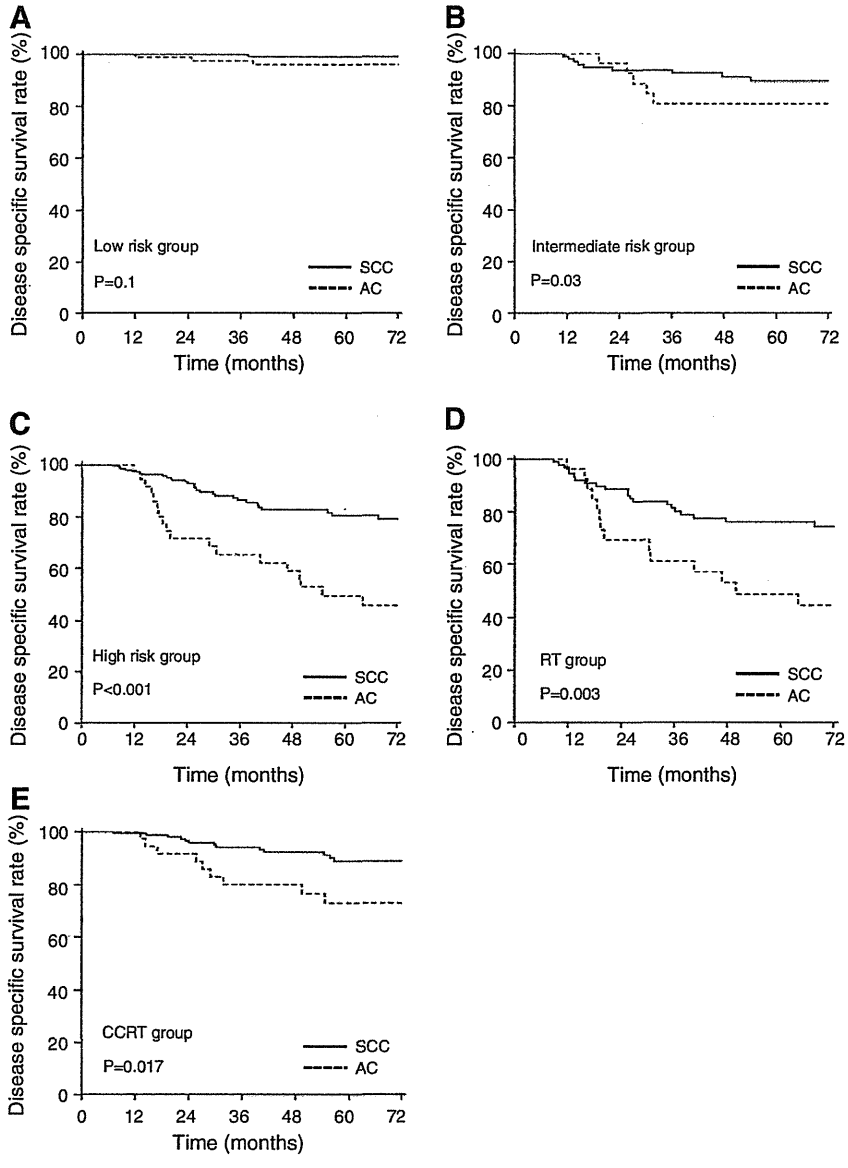

Fig. 1. Survival significance of adenocarcinoma of the cervix. A) Low-risk group. The disease-specific survival (DSS) rate in the SCC group was equivalent to that in the AC group (Log-rank, p = 0.10). B) Intermediate-risk group. The DSS rate was significantly lower in the AC group than in the SCC group (Log-rank, p = 0.03). C) High-risk group. The DSS rate was significantly lower in the AC group than in the SCC group (Log-rank, p < 0.001). D) RT group. The DSS rate was significantly lower in the AC group than in the SCC group (Log-rank, p = 0.003). E) CCRT group. The DSS rate was significantly lower in the AC group than in the SCC group (Log-rank, p = 0.017).

study and some of them had adenosquamous carcinoma, it remains uncertain whether the effects of adding concurrent chemotherapy to pelvic radiotherapy cancel out the adverse prognostic impact of AC histology in patients with early stage cervical cancer [27].

In the current study, as shown in Fig. 1 and Table 3, although the AC patients displayed a poorer prognosis than the SCC patients in the intermediate- and high-risk groups, no significant survival difference was detected in the low-risk group. Importantly, the patients with AC displayed decreased survival compared with the patients with SCC in both the RT and CCRT groups. Our findings are opposite to those from previous report demonstrating that the addition of concurrent chemotherapy to pelvic radiotherapy abolished the adverse prognostic impact of AC histology [27]. Thus, the prognostic significance of AC histology in patients treated with radical surgery plus adjuvant CCRT merits further investigation.

The prognostic factors in early stage AC patients who were primarily treated with radical surgery have been reported to include positive pelvic nodes, parametrial invasion, a positive surgical margin, a large tumor, lymphovascular space involvement, deep stromal invasion, and clinical stage [5,11,12,18,28]. Among these variables, clinical stage and nodal status appear to be particularly important prognostic factors for survival in AC patients. In previous reports, the survival difference between AC and SCC was minimal in clinical stage I disease, but marked in stage II disease [11,12,28]. Furthermore, although the survival difference between AC and SCC was minimal in node-negative patients, AC was associated with significantly reduced survival in node-positive patients [5,12,18,28].

Our multivariate analysis demonstrated that pelvic node metastasis is an independent prognostic factor for survival in the AC patients treated with postoperative CCRT (Table 4). Therefore, to improve the prognosis of such patients, novel treatment strategies for pelvic node-positive AC patients need to be investigated. One strategy that might improve patient outcomes is the use of additional consolidation chemotherapy after postoperative CCRT to treat patients with nodal-

Table 2
Patient characteristics according to the mode of adjuvant radiotherapy.

		RT-group (n=114)					CCRT-group (n=181)				
		SCC	(%)	AC	(%)	P-value	SCC	(%)	AC	(%)	P-value
Patient characteristics											
Number of patients		87		27			144		37		
Age	Median	51		49		P=0.41	52		52		P=0.36
	Range	28–68		19–84			26–71		31–70		
FIGO stage	IA	0	0	0	0	P=0.52	0	0	0	0	P=0.20
	IB1	27	31.0	6	22.2		73	50.7	17	45.9	
	IB2	11	12.6	5	18.5		17	11.8	7	18.9	
	IIA	20	23.0	9	33.3		23	16.0	2	5.4	
	IIB	29	33.3	7	25.9		31	21.5	11	29.7	
Pelvic nodal metastasis	Negative	42	48.3	10	37.0	P=0.38	85	59.0	30	81.1	P=0.013
	Positive	45	51.7	17	63.0		59	41.0	7	18.9	
Parametrial invasion	Negative	56	64.4	20	74.1	P=0.48	96	66.7	23	62.2	P=0.70
	Positive	31	35.6	7	25.9		48	33.3	14	37.8	
Margin status	Negative	78	89.7	25	92.6	P=1.0	139	96.5	35	94.6	P=0.63
	Positive	9	10.3	2	7.4		5	3.5	2	5.4	
Stromal invasion	Less than half	13	14.9	7	25.9	P=0.25	17	11.8	4	10.8	P=1.0
	More than half	74	85.1	20	74.1		127	88.2	33	89.2	
LVSI	Negative	12	13.8	3	11.1	P=1.0	17	11.8	7	18.9	P=0.28
	Positive	75	86.2	24	88.9		127	88.2	30	81.1	
Maximal tumor diameter [a]	Median (mm)	40		40		P=0.75	33		30		P=0.36
Ovarian preservation	Yes	4	4.6	1	3.7	P=1.0	19	13.2	0	0	P=0.015
	No	83	95.4	26	96.3		125	86.8	37	100	
Pretreatment hemoglobin [b]	Mean (g/dL)	11.6		11.6		P=0.98	12.1		12.0		P=0.64

SCC, squamous cell carcinoma; AC, adenocarcinoma; LVSI, lymphovascular space involvement; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; DSS, disease specific survival; PFS, progression free survival.
[a] The maximal tumor diameter was measured three-dimensionally based on T2-weighted images.
[b] Hemoglobin level just before the start of radiotherapy.

positive AC. The Gynecologic Oncology Group (GOG) is currently conducting a phase III clinical trial (GOG0724) comparing postoperative cisplatin-based CCRT with or without consolidation chemotherapy using carboplatin and paclitaxel [29]. In the current study, among 37 patients with AC histology who were treated with postoperative CCRT, 8 (21.6%) developed recurrence at distant anatomical sites. Thus, with the aim of controlling distant metastasis and prolonging survival, the clinical benefit of adding consolidation chemotherapy to postoperative CCRT needs to be evaluated in future clinical trials.

As shown in Table 1, the estimated 5-year DSS rate of 49.5% among the high risk group in AC patients was lower than the results reported in the literature (Table 1). Therefore, it is of great interest to address the issue that surgical approach is more effective than definitive radiotherapy in the high risk group patients. We have recently reported

Table 3
Multivariate analysis for disease specific survival.

Covariate		RT-group (n=114)					CCRT-group (n=181)				
		No.	Univariate analysis		Stepwise multivariate analysis[a]		No.	Univariate analysis		Stepwise multivariate analysis[a]	
			HR (95%CI)	P-value	HR (95%CI)	P-value		HR (95%CI)	P-value	HR (95%CI)	P-value
Age	≤50	55	0.95 (0.51–1.79)	P=0.88			85	1.65 (0.70–3.90)	P=0.25		
	>50	59					96				
FIGO stage	≤IB1	33	2.57 (1.077–6.14)	P=0.027			90	1.79 (0.76–4.22)	P=0.18		
	≥IB2	81					91				
Histology	SCC	87	2.59 (1.37–4.92)	P=0.0025	2.80 (1.46–5.36)	P=0.002	144	2.68 (1.16–6.18)	P=0.017	5.46 (2.20–13.5)	P<0.001
	AC	27					37				
Pelvic nodal metastasis	Negative	49	2.25 (1.15–4.41)	P=0.016	2.12 (1.08–4.18)	P=0.029	115	4.14 (1.70–10.1)	p<0.001	7.02 (2.69–18.3)	P<0.001
	Positive	65					66				
Parametrial invasion	Negative	76	1.16 (0.59–2.25)	P=0.67			119	2.02 (0.89–4.58)	P=0.086		
	Positive	38					62				
Margin status	Negative	103	1.73 (0.73–4.14)	P=0.21			174	2.81 (0.66–12.0)	P=0.15		
	Positive	11					7				
Deep stromal invasion	Negative	20	1.07 (0.47–2.42)	P=0.88			21	0.98 (0.29–3.31)	P=0.98		
	Positive	94					160				
LVSI	Negative	15	2.19 (0.67–7.14)	P=0.18			24	24.8 (0.12–5298)	P=0.067		
	Positive	99					157				
Maximum tumor diameter[b]	≤40 mm	19	01.79 (0.95–3.38)	p=0.067	1.94 (1.02–3.70)	P=0.043	68	0.73 (0.29–1.84)	P=0.50		
	>40 mm	95					113				
Pretreatment hemoglobin[c]	<11 g/dL	38	1.62 (0.80–3.26)	p=0.18			25	0.87 (0.30–2.57)	P=0.80		
	≥11 g/dL	76					156	1.65 (0.70–3.90)			

HR, hazard ratio; 95%CI, 95% confidence interval; SCC, squamous cell carcinoma; AC, adenocarcinoma; LVSI, Lymphovascular space involvement.
[a] Conditional backward method was used for stepwise multivariate analysis and only statistically significant variables are shown in the table.
[b] The maximal tumor diameter was measured three-dimensionally based on T2-weighted images.
[c] Hemoglobin level just before the start of radiotherapy.

Table 4
Multivariate analysis for disease specific survival (AC or SCC patients treated with CCRT).

Covariate		Adenocarcinoma/CCRT-group (n=37)					Squamous cell carcinoma/CCRT-group (n=144)				
		No.	Univariate analysis		Stepwise multivariate analysis[a]		No.	Univariate analysis		Stepwise multivariate analysis[a]	
			HR (95%CI)	P-value	HR (95%CI)	P-value		HR (95%CI)	P-value	HR (95%CI)	P-value
Age	≤50	17	1.57 (0.39–6.30)	P=0.52			68	1.59 (0.53–4.76)	P=0.40		
	>50	20					76				
FIGO stage	≤IB1	17	2.18 (0.54–8.72)	P=0.26			73	1.61 (0.54–4.83)	P=0.39		
	≥IB2	20					71				
Pelvic nodal metastasis	Negative	30	12.9 (3.20–52.0)	P<0.001	12.9 (3.20–52.0)	P<0.001	85	3.51 (1.10–11.2)	P=0.024	3.51 (1.10–11.2)	P=0.024
	Positive	7					59				
Parametrial invasion	Negative	23	2.26 (0.61–8.42)	P=0.21			96	1.85 (0.65–5.28)	P=0.24		
	Positive	14					48				
Margin status	Negative	35	3.21 (0.40–25.8)	P=0.25			139	2.30 (0.30–17.6)	P=0.41		
	Positive	2					5				
Deep stromal invasion	Negative	4	0.49 (0.10–2.36)	P=0.36			17	2.03 (0.27–15.5)	P=0.49		
	Positive	33					127				
LVSI	Negative	7	27.9 (0.21–37,134)	P=0.15			17	24.1 (0.01–40,584)	P=0.19		
	Positive	30					127				
Maximum tumor diameter[b]	≤40 mm	11	0.31 (0.01–20.0)	P=0.084			57	1.45 (0.50–4.17)	P=0.49		
	>40 mm	26					87				
Pretreatment hemoglobin[c]	<11 g/dL	9	0.60 (0.15–2.41)	P=0.47			16	2.21 (0.29–17.1)	P=0.44		
	≥11 g/dL	28					128				

HR, hazard ratio; 95%CI, 95% confidence interval; SCC, squamous cell carcinoma; AC, adenocarcinoma; LVSI, Lymphovascular space involvement.
[a] Conditional backward method was used for stepwise multivariate analysis and only statistically significant variables are shown in the table.
[b] The maximal tumor diameter was measured three-dimensionally based on T2-weighted images.
[c] Hemoglobin level just before the start of radiotherapy.

a study that the definitive radiotherapy is associated with comparable survival outcomes with less treatment-related toxicities when compared to radical hysterectomy followed by postoperative radiotherapy in patients with FIGO stage IIB cervical cancer [22]. However, the effectiveness of radical surgery compared to definitive radiotherapy in FIGO stage IA2–IIA patients remains undetermined, and thus needs to be investigated in the future studies.

The following limitations of our study need to be addressed. The adjuvant radiotherapy has not been standardized in the current study: nedaplatin instead of cisplatin has been employed as a radiosensitizer in our institutions, and adjuvant EFRT without concurrent chemotherapy has been employed instead of pelvic CCRT in 20 patients with multiple pelvic node metastases. Moreover, due to its retrospective nature, potential confounding biases might have been missed in the analysis, such as the selection bias introduced by the physicians when determining and allocating the treatment modality. These factors can only be eliminated in a prospective randomized controlled study.

In conclusion, we showed that the histological subtype of early stage cervical cancer impacts on survival outcome, and patients with adenocarcinoma were associated with poorer prognosis than squamous cell carcinoma in intermediate- and high-risk pathological factors, regardless of the type of postoperative radiotherapy after radical hysterectomy. Novel treatment strategies that are specifically tailored to early stage cervical adenocarcinoma are needed.

Conflict of interest statement
The authors declare that they have no conflicts of interest.

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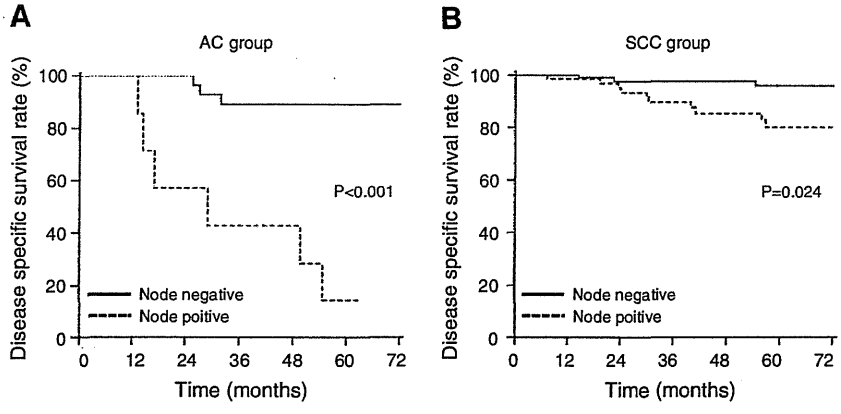

Fig. 2. Risk factors modulating the response to therapy in adenocarcinoma of the cervix. A) DSS in AC patients treated with radical surgery plus adjuvant CCRT based on pelvic nodal status. The node-negative AC patients displayed significantly longer DSS than the node-positive patients (Log-rank, p<0.001). B) DSS in SCC patients treated with adjuvant CCRT based on pelvic nodal status. The node-negative SCC patients displayed significantly longer DSS than the node-positive patients (Log-rank, p=0.024).

References

[1] Wang SS, Sherman ME, Hildesheim A, Lacey Jr JV, Devesa S. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976–2000. Cancer 2004;100:1035–44.
[2] Kjörstad KE. Adenocarcinoma of the uterine cervix. Gynecol Oncol 1977;5:219–23.
[3] National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Cervical Cancer—v.1. www.nccn.org/professionals/physician_gls/f_guidelines.asp 2006.
[4] Katanyoo K, Sanguanrungsirikul S, Manusirivithaya S. Comparison of treatment outcomes between squamous cell carcinoma and adenocarcinoma in locally advanced cervical cancer. Gynecol Oncol 2012;125:292–6.
[5] Nakanishi T, Ishikawa H, Suzuki Y, Inoue T, Nakamura S, Kuzuya K. A comparison of prognoses of pathologic stage Ib adenocarcinoma and squamous cell carcinoma of the uterine cervix. Gynecol Oncol 2000;79:289–93.
[6] Lee YY, Choi CH, Kim TJ, et al. A comparison of pure adenocarcinoma and squamous cell carcinoma of the cervix after radical hysterectomy in stage IB–IIA. Gynecol Oncol 2011;120:439–43.
[7] Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH. Outcomes after radical hysterectomy in patients with early-stage adenocarcinoma of uterine cervix. Br J Cancer 2010;102:1692–8.
[8] Hopkins MP, Morley GW. A comparison of adenocarcinoma and squamous cell carcinoma of the cervix. Obstet Gynecol 1991;77:912–7.
[9] Berek JS, Hacker NF, Fu YS, Sokale JR, Leuchter RC, Lagasse LD. Adenocarcinoma of the uterine cervix: histologic variables associated with lymph node metastasis and survival. Obstet Gynecol 1985;65:46–52.
[10] Kleine W, Rau K, Schwoeorer D, Pfleiderer A. Prognosis of the adenocarcinoma of the cervix uteri: a comparative study. Gynecol Oncol 1989;35:145–9.
[11] Chen RJ, Lin YH, Chen CA, Huang SC, Chow SN, Hsieh CY. Influence of histologic type and age on survival rates for invasive cervical carcinoma in Taiwan. Gynecol Oncol 1999;73:184–90.
[12] Irie T, Kigawa J, Minagawa Y, et al. Prognosis and clinicopathological characteristics of Ib–IIb adenocarcinoma of the uterine cervix in patients who have had radical hysterectomy. Eur J Surg Oncol 2000;26:464–7.
[13] Look KY, Brunetto VL, Clarke-Pearson DL, et al. An analysis of cell type in patients with surgically staged stage IB carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 1996;63:304–11.
[14] Ayhan A, Al RA, Baykal C, Demirtas E, Yüce K, Ayhan A. A comparison of prognoses of FIGO stage IB adenocarcinoma and squamous cell carcinoma. Int J Gynecol Cancer 2004;14:279–85.
[15] Grisaru D, Covens A, Chapman B, et al. Does histology influence prognosis in patients with early-stage cervical carcinoma? Cancer Dec 15 2001;92:2999–3004.
[16] Kasamatsu T, Onda T, Sawada M, et al. Radical hysterectomy for FIGO stage I–IIB adenocarcinoma of the uterine cervix. Br J Cancer 2009;100:1400–5.
[17] Lee KB, Lee JM, Park CY, Lee KB, Cho HY, Ha SY. What is the difference between squamous cell carcinoma and adenocarcinoma of the cervix? A matched case–control study. Int J Gynecol Cancer 2006;16:1569–73.
[18] Shingleton HM, Bell MC, Fremgen A, et al. Is there really a difference in survival of women with squamous cell carcinoma, adenocarcinoma, and adenosquamous cell carcinoma of the cervix? Cancer 1995;76:1948–55.
[19] WHO. In: Tavassoli FA, Stratton MR, editors. WHO classification of tumours: pathology and genetics of tumours of the breast and female genital organs. Chapter 5: Tumours of the Uterine CervixLyon: IARC Press; 2002. p. 259–89.
[20] Mabuchi S, Morishige K, Isohashi F, et al. Postoperative concurrent nedaplatin-based chemoradiotherapy improves survival in early-stage cervical cancer patients with adverse risk factors. Gynecol Oncol 2009;115:482–7.
[21] Mabuchi S, Okazawa M, Isohashi F, et al. Postoperative whole pelvic radiotherapy plus concurrent chemotherapy versus extended-field irradiation for early-stage cervical cancer patients with multiple pelvic lymph node metastases. Gynecol Oncol 2011;120:94–100.
[22] Mabuchi S, Okazawa M, Isohashi F, et al. Radical hysterectomy with adjuvant radiotherapy versus definitive radiotherapy alone for FIGO stage IIB cervical cancer. Gynecol Oncol 2011;123:241–7.
[23] Okazawa M, Mabuchi S, Isohashi F, et al. The prognostic significance of multiple pelvic node metastases in cervical cancer patients treated with radical hysterectomy plus adjuvant chemoradiotherapy. Int J Gynecol Cancer 2012;22:490–7.
[24] Mabuchi S, Kimura T. Nedaplatin: a radiosensitizing agent for patients with cervical cancer. Chemother Res Pract 2011;2011:963159.
[25] Mabuchi S, Isohashi F, Yoshioka Y, et al. Prognostic factors for survival in patients with recurrent cervical cancer previously treated with radiotherapy. Int J Gynecol Cancer 2010;20:834–40.
[26] Mabuchi S, Isohashi F, Maruoka S, et al. Post-treatment follow-up procedures in cervical cancer patients previously treated with radiotherapy. Arch Gynecol Obstet 2012;286:179–85.
[27] Peters III WA, Liu PY, Barrett II RJ, Stock RJ, Monk BJ, Berek JS, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18:1606–13.
[28] Kodama J, Seki N, Masahiro S, et al. Prognostic factors in stage IB–IIB cervical adenocarcinoma patients treated with radical hysterectomy and pelvic lymphadenectomy. J Surg Oncol 2010;101:413–7.
[29] Kitchener HC, Hoskins W, Small Jr W, Thomas GM, Trimble EL. The development of priority cervical cancer trials: a Gynecologic Cancer InterGroup report. Int J Gynecol Cancer 2010;20:1092–100.

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Dose-Volume Histogram Predictors of Chronic Gastrointestinal Complications After Radical Hysterectomy and Postoperative Concurrent Nedaplatin-Based Chemoradiation Therapy for Early-Stage Cervical Cancer

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Summary

In this study, dose-volume histogram parameters of the small bowel loops were predictive for the development of chronic gastrointestinal (GI) complications after postoperative concurrent nedaplatin-based chemoradiation therapy for early-stage cervical cancer. Multivariate analysis indicated that V40 (volume receiving more than 40 Gy) of the small bowel loops and smoking were independent predictors of GI complications.

Purpose: The purpose of this study was to evaluate dose-volume histogram (DVH) predictors for the development of chronic gastrointestinal (GI) complications in cervical cancer patients who underwent radical hysterectomy and postoperative concurrent nedaplatin-based chemoradiation therapy.

Methods and Materials: This study analyzed 97 patients who underwent postoperative concurrent chemoradiation therapy. The organs at risk that were contoured were the small bowel loops, large bowel loop, and peritoneal cavity. DVH parameters subjected to analysis included the volumes of these organs receiving more than 15, 30, 40, and 45 Gy (V15-V45) and their mean dose. Associations between DVH parameters or clinical factors and the incidence of grade 2 or higher chronic GI complications were evaluated.

Results: Of the clinical factors, smoking and low body mass index (BMI) (<22) were significantly associated with grade 2 or higher chronic GI complications. Also, patients with chronic GI complications had significantly greater V15-V45 volumes and higher mean dose of the small bowel loops compared with those without GI complications. In contrast, no parameters for the large bowel loop or peritoneal cavity were significantly associated with GI complications. Results of the receiver operating characteristics (ROC) curve analysis led to the conclusion that V15-V45 of the small bowel loops has high accuracy for prediction of GI complications. Among these parameters, V40 gave the highest area under the ROC curve. Finally, multivariate analysis was performed with V40 of the small bowel loops and 2 other clinical parameters that were judged to be potential risk factors for chronic GI complications: BMI and smoking. Of these 3 parameters, V40 of the small bowel loops and smoking emerged as independent predictors of chronic GI complications.

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Conclusions: DVH parameters of the small bowel loops may serve as predictors of grade 2 or higher chronic GI complications after postoperative concurrent nedaplatin-based chemoradiation therapy for early-stage cervical cancer. © 2013 Elsevier Inc.

Introduction

Adjuvant whole-pelvic radiation therapy (RT) after radical hysterectomy reduces locoregional recurrence in cervical cancer patients after surgery with adverse risk factors (1, 2). However, patients undergoing whole-pelvic RT after radical hysterectomy may suffer severe gastrointestinal (GI) complications with an incidence varying from 3%-13% for patients treated with pelvic RT alone (1-3). Moreover, while adjuvant concurrent chemoradiation therapy has been shown in several studies to improve survival rates for high-risk cervical cancer patients compared with adjuvant RT alone, GI complications were observed more frequently in conjunction with concurrent chemoradiation therapy than with RT alone (4). Therefore it is important to improve the feasibility of adjuvant concurrent chemoradiation therapy by reducing GI complications.

Because the small bowel is one of the critical organs involved in GI complications, a predictive model of acute GI complications of the small bowel has been established with the aid of Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) (5). However, the correlation between dose-volume effect and chronic GI complications of the small bowel has not been extensively investigated.

Since 2000, we have been using postoperative concurrent nedaplatin-based chemoradiation therapy for early-stage cervical cancer patients with adverse risk factors (6). The purpose of the study reported here was to evaluate dose-volume histogram (DVH) predictors for the development of chronic GI complications in cervical cancer patients who underwent radical hysterectomy and postoperative concurrent nedaplatin-based chemoradiation therapy.

Methods and Materials

Patients

A total of 131 patients with cervical cancer received radical hysterectomy and postoperative RT at our institute between April 2000, when we started to use postoperative concurrent nedaplatin-based chemoradiation therapy, and September 2010. Treatment criteria for postoperative RT were previously described (6, 7). Thirty-four of these patients were excluded from the study: 18 who received extended-field radiation therapy alone because of multiple lymph node metastases (7), 9 who refused concurrent chemotherapy, 3 who received intracavitary brachytherapy with whole-pelvic RT because of a close surgical margin, and 4 early patients who did not undergo radiation treatment planning computed tomography (CT) with a 2-dimensional (2D) era. The remaining 97 patients treated with concurrent chemoradiation therapy were analyzed for this study with a minimum follow-up period of 3 months. This study was approved by our institutional review board.

Radiation therapy and chemotherapy

Whole-pelvic RT was delivered with 2D planning in 65 patients between April 2000 and March 2008 and with 3-dimensional (3D) conformal treatment planning in 32 patients starting April 2008. During the 2D era, RT was delivered using 10-megavolt X rays from a linear accelerator with the anteroposterior parallel opposing technique. The superior margin of the whole-pelvic RT was at the upper edge of the fifth lumbar vertebra and the inferior margin was the inferior edge of the obturator foramen. Laterally, the field extended 2 cm beyond the lateral margins of the bony pelvic wall. After we defined an isocenter or field-shape in the X-ray simulator, CT with the isocenter position marked was performed with 5.0-mm slices without filling the bladder to calculate the monitor unit and check the dose distribution. The CT scan range was from the upper edge of L3 to at least 7 cm below the bottom of the obturator foramen. The dose distribution was calculated using a commercial treatment planning system (FOCUS; Elekta, Stockholm Sweden). The prescribed RT doses were 50 Gy administered in 25 fractions over 5 weeks at the center of the body. Multileaf collimators were used to block the upper and lower corners of the radiation field. No target volume or organ at risk was delineated before treatment. Since April 2008, all patients have been treated with 3D conformal treatment planning. RT planning CT was performed with 2.5-mm slices with normal quiet breathing and a full-bladder scan. The CT scan range was the same as that used in 2D planning. A commercial treatment planning system (XiO TPS; Elekta) was used to design the radiation fields. The clinical target volume (CTV) comprised a central vaginal CTV and a regional nodal CTV. The former included the proximal vagina and paravaginal tissues and the latter consisted of the common iliac, external and internal iliac, and presacral lymph nodes. CTVs were contoured according to the consensus guidelines of the Radiation Therapy Oncology Group (RTOG) 0418 (8) and its atlas on the RTOG website. The planning target volume (PTV) was generated by using 1.0-cm uniform expansion of the CTV. The prescribed RT doses were 50 Gy at the center of the PTV, administered in 25 fractions over 5 weeks by means of the 3D 4-field box technique. Multileaf collimators were used to cover the PTV with a margin of approximately 5 mm. No organ at risk was delineated before treatment. Nedaplatin (40 mg/m^2) was given intravenously on a weekly basis during the course of whole-pelvic RT for 5 weeks as previously described (6).

Contouring and evaluation of normal structures

The organs at risk that were contoured comprised the small bowel loops, large bowel loop, and peritoneal cavity. All contouring was done retrospectively. The superior and inferior extents of critical organs were outlined on all CT slices containing portions of the PTV (3D) or field margins (2D), including an additional area 2-cm superior and inferior to the limit of the PTV or field margins. Therefore, the organs at risk, including the large bowel loop, small bowel loops, and peritoneal cavity, could not be contoured in full volume. The large bowel loop was contoured first as a single loop continuing from the end of the sigmoid colon to the ascending colon, and the remaining bowel loops were classified as the small bowel loops. A preoperative diagnostic CT scan using oral and intravenous contrast media was performed in 92/97 patients (95%). This preoperative CT scan

was displayed when the organs at risk were contoured using postoperative radiation treatment planning CT. Diagnostic CT images were not fused to the planning scans. In the remaining 5 patients, postoperative radiation treatment planning CT only was used for contouring of the organs at risk. The peritoneal cavity was defined as including the volume surrounding the small bowel loops out to the edge of the peritoneum. The boundaries included the abdominal wall anteriorly and anterolaterally, the retroperitoneal and deep pelvic muscles posterolaterally, and the great vessels, vertebral bodies, and sacrum posteriorly. The rectum and bladder were excluded from the peritoneal cavity volume. DVH parameters subjected to analysis included the mean doses to the small bowel loops, large bowel loop, and peritoneal cavity, and the volumes of these organs receiving more than 15, 30, 40, and 45 Gy (V15-V45).

Follow-up and evaluation of chronic GI complications

The patients were followed up by gynecologic and radiation oncologists on an outpatient basis every month in the first year, every 2 months in the second year, every 3 months in the third year, every 4 months in the fourth year, every 6 months in the fifth year, and annually thereafter until 10 years after treatment. We defined a chronic complication as a GI event that occurred more than 3 months after radiation therapy was started. The severity of the GI complication was classified according to the RTOG/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Score. Toxicity data including the grade of GI complications were collected retrospectively through hospitalization and follow-up records.

Statistical analysis

Associations between selected DVH parameters (V15, V30, V40, V45, and mean dose) and the incidence of grade 2 or higher chronic GI complications were evaluated. The relationships between clinical or DVH parameters and the incidence of chronic GI complications were analyzed with the Mann-Whitney *U* test for quantitative variables and the Fisher exact test for categorical variables. The mean DVH parameters for the small bowel loops, large bowel loop, and peritoneal cavity of patients with and without GI complications were compared by Mann-Whitney *U* test. Receiver operating characteristics (ROC) curve analysis of each of the DVH parameters was performed to select the most relevant threshold for prediction of a grade 2 or higher chronic GI complication. The predictive value of a parameter was evaluated based on the area under the ROC curve (AUC). The AUC reflects the ability of the test to distinguish between patients with and without disease. The optimal threshold for each DVH parameter was defined as the point yielding the minimal value for $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$, which is the point on the ROC curve closest to the upper left-hand corner (9). Multivariate analysis using Cox regression models was performed to identify risk factors associated with grade 2 or higher chronic GI complications. The actuarial incidence of GI complications was calculated with the Kaplan-Meier method and differences between groups were compared by log-rank test. A P value of $<.05$ or a 95% confidence interval not encompassing 1 was considered to be statistically significant. All statistical tests were 2-sided.

Results

The characteristics of the 97 patients are shown in Table 1. The median follow-up period from the start of radiation therapy was 43 months (range 4-111 months). None of the patients experienced a local or distant recurrence within 3 months. The Eastern Cooperative Oncology Group performance status was 0-1 for all patients. The median age of the patients was 51 years old (range 28-70 years old). Twenty-three patients (24%) had a history of smoking, with a median Brinkman index (number of cigarettes per day × smoking years) of 400 (range 100-1200). The median total dose of nedaplatin was 285 mg (range 30-375 mg). Ninety-two patients (95%) received the whole RT dose as planned (50 Gy), but 3 patients (3%) received only 46 Gy and 2 (2%) received 44 Gy because of neutropenia (4 patients) or patient refusal (1 patient). Eighty-one patients (84%) had grade 0-1, 6 (6%) had grade 2, and 10 (10%) had grade 3 chronic GI

Table 1 Patient and treatment characteristics

	No. (%)
Age (y)	
Mean	51
SD	±10
T-stage	
T1	53 (55)
T2	44 (45)
N-stage	
N0	64 (66)
N1	33 (34)
Histology	
SCC	71 (73)
Ad	24 (25)
Others	2 (2)
Smoking	
None	74 (76)
Yes	23 (24)
Diabetes	
None	94 (97)
Yes	3 (3)
Abdominopelvic surgery	
None	94 (97)
Yes	3 (3)
BMI (kg/m^2)	
Mean	21.6
SD	±3.8
RT total dose (Gy)	
50	92 (95)
46	3 (3)
44	2 (2)
RT technique	
2D	65 (67)
3D	32 (33)
Total nedaplatin (mg)	
Mean	274
SD	±52

Abbreviations: 2D = 2-dimensional; 3D = 3-dimensional; Ad = adenocarcinoma; BMI = body mass index; RT = radiation therapy; SCC = squamous cell carcinoma; SD = standard deviation.

Table 2 Univariate analysis (Mann-Whitney *U* test and Fisher exact test) for the development of grade 2 or higher chronic GI complications

Variable	Grade 0-1 No.	Grade 2-3 No.	*P* value
Age (y)			
<52	39	10	.294
≥52	42	6	
Total nedaplatin (mg)			
<285	39	8	.892
≥285	42	8	
T-stage			
T1	46	7	.338
T2	35	9	
N-stage			
N0	53	11	.798
N1	28	5	
Histology			
SCC	60	11	.660
Non-SCC	21	5	
RT total dose			
50 Gy	76	16	.308
<50 Gy	5	0	
RT technique			
2D	57	8	.133
3D	24	8	
Smoking			
None	66	8	.005
Yes	15	8	
BMI (kg/m^2)			
<22	43	14	.011
≥22	38	2	

Abbreviations: 2D = 2-dimensional; 3D = 3-dimensional; BMI = body mass index; GI = gastrointestinal; RT = radiation therapy; SCC = squamous cell carcinoma.

Table 3 Comparison of mean DVH parameters of the small bowel loops, large bowel loop, and peritoneal cavity in patients with and without chronic GI complications (Mann-Whitney *U* test)

	Overall	Grade 0-1	Grade 2-3	*P* value
		Small bowel loops		
		Mean volume ± SE (mL)		
V15	337 ± 15	299 ± 13	527 ± 37	<.001
V30	308 ± 13	273 ± 11	485 ± 29	<.001
V40	289 ± 13	255 ± 11	458 ± 27	<.001
V45	280 ± 12	247 ± 11	444 ± 26	<.001
		Mean dose (cGy ± SE)		
	3,523 ± 80	3,429 ± 86	3,994 ± 160	<.001
		Large bowel loop		
		Mean volume ± SE (mL)		
V15	241 ± 12	241 ± 12	239 ± 34	.730
V30	207 ± 10	210 ± 11	192 ± 23	.550
V40	183 ± 10	189 ± 11	156 ± 17	.331
V45	176 ± 9	182 ± 10	149 ± 16	.321
		Mean dose (cGy ± SE)		
	2,747 ± 62	2,768 ± 66	2,639 ± 174	.487
		Peritoneal cavity		
		Mean volume ± SE (mL)		
V15	1,151 ± 29	1,129 ± 32	1,262 ± 70	.111
V30	1,045 ± 25	1,027 ± 27	1,138 ± 64	.174
V40	974 ± 25	960 ± 27	1,049 ± 65	.336
V45	941 ± 24	927 ± 26	1,013 ± 65	.343
		Mean dose (cGy ± SE)		
	3,421 ± 47	3,387 ± 50	3,596 ± 122	.169

Abbreviations: DVH = dose-volume histogram; GI = gastrointestinal; SE = standard error; V15-45 = volume receiving more than respective dose.

complications. Of the 10 patients with grade 3 GI complications, 5 (5% of all patients) had small bowel obstruction requiring surgery.

The incidence of chronic GI complications was analyzed as a function of clinical factors. Because there were few patients with diabetes or a history of abdominopelvic surgery among the study population, we did not analyze these factors. The results of univariate analyses are shown in Table 2. Smoking habit and low body mass index (BMI; <22) were significantly associated with grade 2 or higher GI complications. The mean DVH parameters of the small bowel loops, large bowel loop, and peritoneal cavity of patients with and without GI complications are shown in Table 3. Patients with grade 2 or higher GI complications had significantly greater V15-V45 volumes in the small bowel loops than did those without GI complications ($P<.001$). The mean dose to the small bowel loops differed significantly for patients with and without GI complications (39.94 vs 34.29 Gy, $P<.001$). In contrast, none of the parameters for the large bowel loop or peritoneal cavity were significantly associated with GI complications.

ROC curve analysis was performed to select the most relevant parameter to identify predictors of grade 2 or higher chronic GI complications among DVH parameters for the small bowel loops. The results are shown in Table 4. Because AUCs for mean dose, V15, V30, V40, and V45 were 0.693, 0.909, 0.912, 0.921, and 0.890, respectively, indicating that V15-V45 have good accuracy for prediction of GI complications. Strong collinearity among V15-V45 was expected in multivariate

Table 4 ROC curve analysis for DVH parameters of small bowel loops in relation to grade 2 or higher chronic GI complications

	AUC	95% CI	Optimal threshold: Value	Optimal threshold: Sensitivity/specificity (%)
Mean dose	0.693	0.580-0.806	3600 cGy	62.5/62.5
V15	0.909	0.855-0.963	380 mL	93.8/82.1
V30	0.912	0.857-0.967	360 mL	93.8/82.1
V40	0.921	0.869-0.972	340 mL	87.5/87.2
V45	0.890	0.819-0.962	340 mL	87.5/85.1

Abbreviations: AUC = area under the ROC curve; CI = confidence interval; DVH = dose-volume histogram; GI = gastrointestinal; ROC = receiver operating characteristics; V15-45 = volume receiving more than respective dose.

Table 5 Multivariate analysis for the development of grade 2 or higher chronic GI complications

Variable	HR (95% CI)	*P* value
V40 of small bowel loops (mL)	1.012 (1.007-1.018)	<.001
BMI (<22 vs ≥22)	3.024 (0.585-15.622)	.187
Smoking (yes vs no)	3.103 (1.023-9.415)	.046

Abbreviations: BMI = body mass index; CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; V40 = volume receiving more than 40 Gy.

analysis. Therefore, we used V40 of the small bowel loops in multivariate analysis because this parameter had the highest AUC value. The optimal threshold for V40 was 340 mL. Thus, multivariate analysis was performed with V40 of the small bowel loops and 2 other clinical parameters that were judged to be potential risk factors for chronic GI complications: BMI and smoking habit. Of these 3 parameters, V40 of the small bowel loops and smoking emerged as independent predictors of GI complications (Table 5).

The overall incidences of grade 2 or higher GI complications were 0% (0/39), 7% (2/29), and 48% (14/29) for patients with V40 values of <250 mL, 250-340 mL, and >340 mL, respectively. Thus, the overall incidence of grade 2 or higher GI complications increased in a volume-dependent manner. Therefore, we performed Kaplan-Meier estimates of the cumulative incidence curves for grade 2 or higher chronic GI complications stratified by V40 of the small bowel loops using the above intervals. The cumulative incidence curves for grade 2 or higher chronic GI complications stratified by V40 of the small bowel loops are shown in Fig. The 3-year cumulative incidences of grade 2 or higher GI complications were 0%, 8.4%, and 46.2% for patients with V40 values of <250 mL, 250-340 mL, and >340 mL, respectively, with a significantly higher risk for patients with V40 > 340 mL than for the other groups (P<.001).

Discussion

Several previous studies have introduced predictive factors potentially associated with chronic GI complications after RT for gynecologic malignancies employing several types of therapy (3, 10-14). These factors include total RT dose, RT dose per fraction, history of diabetes, acute toxicity, BMI, age, previous abdominopelvic surgery, and smoking. In our study, smoking and low BMI were identified by univariate analysis as predictors of GI complications. Moreover, the V15-V45 volumes and the mean dose of the small bowel loops all showed a significant association with chronic GI complications. In addition, multivariate analysis identified V40 of the small bowel loops and smoking as independent predictors of GI complications. To the best of our knowledge, ours is the first study to show that DVH parameters of the small bowel loops derived with an up-to-date approach are associated with chronic GI complications after postoperative concurrent chemoradiation therapy for cervical cancer.

We believe that our findings are important for the practice of the radiation oncology, because adverse events caused by radiation exposure, such as GI complications, may be relieved by using an appropriate radiation technique or a mechanical device such as a belly-board. Recently, intensity modulated radiation therapy (IMRT) has emerged as a sophisticated technique for treatment of tumor regions or areas at risk of recurrence, while sparing adjacent normal tissue from high-dose irradiation, including in patients with gynecological cancer treated with IMRT after radical hysterectomy (15-18).

Two methods for contouring the small bowel volume have been reported: one uses direct delineation of the individual loops, whereas the other bases delineation on the peritoneal cavity because the bowel may lie within this space at any time throughout the course of treatment (5). Because these methods have not been compared to determine which leads to better predictions of chronic complications of the small bowel, we established separate parameters for the irradiated volume of the small bowel loops and the peritoneal cavity to examine which parameters correlated with

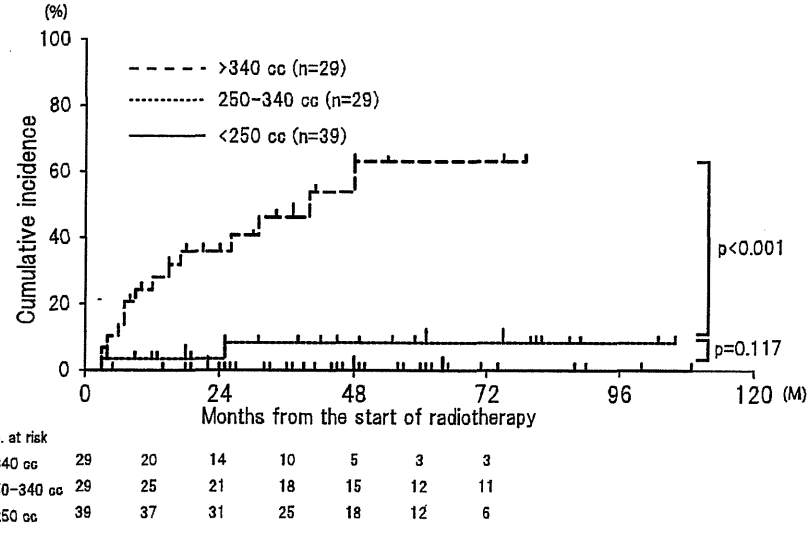

Fig. Kaplan-Meier estimates of cumulative incidence curves for grade 2 or higher chronic gastrointestinal (GI) complications stratified by V40 of the small bowel loops. The 3-year cumulative incidences of grade 2 or higher GI complications were 0%, 8.4%, and 46.2% for patients with V40 values of <250 mL, 250-340 mL, and >340 mL, respectively, with a significantly higher risk for patients with V40 > 340 mL than for the other groups (log-rank test; P<.001).

development of chronic GI complications. Interestingly, patients with grade 2 or higher chronic GI complications featured significantly higher V15-V45 volumes and mean dose to the small bowel loops than did patients without this feature. In contrast, none of the parameters for the peritoneal cavity showed any association with chronic GI complications. Similarly, parameters for the large bowel did not correlate with radiation-induced chronic GI complications. These findings suggest that, compared to the peritoneal cavity, the small bowel loops may constitute a better predictor of chronic GI complications. However, it is also likely that the dose to the peritoneal cavity will be a predictor of acute GI complications (5), and Wedlake et al found that cumulative acute GI symptoms, measured using the questionnaire, are associated with consequential late symptoms (14). Collectively, these results suggest that our finding that parameters for the small bowel loops are better predictors of chronic GI complication, compared with those for the peritoneal cavity, requires verification in larger prospective studies.

The findings in this study should be interpreted with an understanding of the following limitations. First, the heterogeneity in the treatment planning approach over the period of the study (2D vs 3D), the low number of events, and the lack of a prespecified model or protocol are important limitations of the data and analysis. Second, our method resulted in large uniform doses to regions of the small bowel, which differ from the dose patterns produced by techniques such as IMRT, which is becoming more prevalent. Therefore, we cannot exclude the possibility that the optimal DVH parameter predictors found in this study may differ from those for IMRT.

Additionally, we used weekly nedaplatin as concurrent chemotherapy, whereas chemoradiation therapy with 40 mg/m^2 of weekly cisplatin is now accepted as a standard first-line treatment. We therefore cannot exclude the possibility that the optimal DVH parameter predictors found in the study may be chemotherapy-type specific. Furthermore, the small bowel DVH parameters were estimated based on only 1 radiation treatment planning CT before RT, while in fact daily variability of the distention or movement of the small bowels during the treatment course may have affected the dose-volume profile. Also, especially in the 2D era, radiation treatment planning CT performed with 5.0-mm slices without filling the bladder may not reflect the actual dose received. Han et al reported that the dose distribution in the small bowel as observed on CT varies significantly from week to week because of the interfractional variations of small-bowel positions (19). In addition, image guided RT is now widely used in many institutions (20). Therefore, further studies using image guided RT will be necessary to investigate the influence of intra- and interfraction motion of the small bowel loops on chronic GI complications.

Within these limitations, we conclude that DVH parameters of the small bowel loops may serve as predictors of chronic GI complications of grade 2 or higher after postoperative concurrent nedaplatin-based chemoradiation therapy in early-stage cervical cancer patients. For these patients, we recommend that V40 of the small bowel loops should be <340 mL to avoid chronic GI complications using a conventional 2D or 3D technique.

References

1. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group Study. *Gynecol Oncol* 1999;73: 177-183.
2. Fiorica JV, Roberts WS, Greenberg H, Hoffman MS, LaPolla JP, Cavanagh D, et al. Morbidity and survival patterns in patients after radical hysterectomy and postoperative adjuvant pelvic radiotherapy. *Gynecol Oncol* 1990;36:343-347.
3. Chen SW, Liang JA, Yang SN, Hung YC, Yeh LS, Shiau AC, et al. Radiation injury to intestine following hysterectomy and adjuvant radiotherapy for cervical cancer. *Gynecol Oncol* 2004;95: 208-214.
4. Peters WA 3rd, Liu PY, Barrett RJ 2nd, Stock RJ, Monk BJ, Berek JS, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 2000;18:1606-1613.
5. Kavanagh BD, Pan CC, Dawson LA, Das SK, Li XA, Ten Haken RK, et al. Radiation dose-volume effects in the stomach and small bowel. *Int J Radiat Oncol Biol Phys* 2010;76(Suppl. 3):S101-S107.
6. Mabuchi S, Morishige K, Isohashi F, Yoshioka Y, Takeda T, Yamamoto T, et al. Postoperative concurrent nedaplatin-based chemoradiotherapy improves survival in early-stage cervical cancer patients with adverse risk factors. *Gynecol Oncol* 2009;115:482-487.
7. Mabuchi S, Okazawa M, Isohashi F, Ohta Y, Maruoka S, Yoshioka Y, et al. Postoperative whole pelvic radiotherapy plus concurrent chemotherapy versus extended-field irradiation for early-stage cervical cancer patients with multiple pelvic lymph node metastases. *Gynecol Oncol* 2011;120:94-100.
8. Small W Jr., Mell LK, Anderson P, Creutzberg C, De Los Santos J, Gaffney D, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys* 2008;71:428-434.
9. Akobeng AK. Understanding diagnostic tests 3: receiver operating characteristic curves. *Acta Paediatr* 2007;96:644-647.
10. Iraha S, Ogawa K, Moromizato H, Shiraishi M, Nagai Y, Samura H, et al. Radiation enterocolitis requiring surgery in patients with gynecological malignancies. *Int J Radiat Oncol Biol Phys* 2007;68: 1088-1093.
11. Kasuya G, Ogawa K, Iraha S, Nagai Y, Shiraishi M, Hirakawa M, et al. Severe late complications in patients with uterine cancer treated with postoperative radiotherapy. *Anticancer Res* 2011;31: 3527-3533.
12. Eifel PJ, Jhingran A, Bodurka DC, Levenback C, Thames H. Correlation of smoking history and other patient characteristics with major complications of pelvic radiation therapy for cervical cancer. *J Clin Oncol* 2002;20:3651-3657.
13. Kizer NT, Thaker PH, Gao F, Zighelboim I, Powell MA, Rader JS, et al. The effects of body mass index on complications and survival outcomes in patients with cervical carcinoma undergoing curative chemoradiation therapy. *Cancer* 2011;117:948-956.
14. Wedlake LJ, Thomas K, Lalji A, Blake P, Khoo VS, Tait D, et al. Predicting late effects of pelvic radiotherapy: is there a better approach? *Int J Radiat Oncol Biol Phys* 2010;78:1163-1170.
15. Roeske JC, Lujan A, Rotmensch J, Waggoner SE, Yamada D, Mundt AJ. Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2000;48:1613-1621.
16. Jhingran A, Winter K, Portelance L, Miller BE, Salehpour M, Gaur R, et al. A phase II study of intensity modulated radiation therapy (IMRT) to the pelvic for post-operative patients with endometrial carcinoma (RTOG 0418). *Int J Radiat Oncol Biol Phys* 2008;72:S16.
17. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. *Int J Radiat Oncol Biol Phys* 2003;56:1354-1360.
18. Chen MF, Tseng CJ, Tseng CC, Kuo YC, Yu CY, Chen WC. Clinical outcome in posthysterectomy cervical cancer patients treated with

concurrent Cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;67:1438-1444.
19. Han Y, Shin EH, Huh SJ, Lee JE, Park W. Interfractional dose variation during intensity-modulated radiation therapy for cervical cancer assessed by weekly CT evaluation. *Int J Radiat Oncol Biol Phys* 2006; 65:617-623.
20. Simpson DR, Lawson JD, Nath SK, Rose BS, Mundt AJ, Mell LK. A survey of image-guided radiation therapy use in the United States. *Cancer* 2010;116:3953-3960.

Elevated White Blood Cell Count at the Time of Recurrence Diagnosis Is an Indicator of Short Survival in Patients With Recurrent Cervical Cancer

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Objectives: The aim of this study was to investigate the prognostic significance of elevated white blood cell (WBC) count at the time of the diagnosis of cervical cancer recurrence.

Methods: The baseline characteristics and outcome data of 219 patients who had a diagnosis of recurrent cervical cancer between April 1996 and September 2010 were collected and reviewed. Survival after recurrence was compared between the leukocytosis group (WBC ≥9000/μL) and the nonleukocytosis group (WBC <9000/μL). A Cox proportional hazards regression model was used to investigate the prognostic significance of elevated WBC count in patients with recurrent cervical cancer.

Results: The patients in the leukocytosis group showed significantly shorter disease-free interval ($P = 0.0005$) and more frequently had multiple recurrences ($P = 0.0101$) than those in the nonleukocytosis group. The median survival after recurrence of the patients with elevated WBC count was 9 months, which was significantly shorter than the 21 months observed in the patients without normal WBC count (log rank; $P < 0.0001$). Multivariate analyses revealed that clinical stage, tumor diameter, histology, an elevated WBC count (≥9000/μL), and an elevated neutrophil count (≥6500/μL) were significant prognostic factors in survival after recurrence.

Conclusion: The elevated WBC count at the time of the diagnosis of recurrence is an independent prognostic factor in patients with recurrent cervical cancer.

Key Words: Leukocytosis, WBC, Neutrophilia, Recurrent cervical cancer, Survival

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Cervical cancer is still one of the most common malignancies in women worldwide. It is estimated that 12,200 new cases and 4210 deaths occurred in the United States in 2010.[1] In Japan, 6000 to 7000 new cases are reported annually.[2]

Despite recent advances in surgery,[3] the introduction of new radiotherapy techniques including intensity-modulated radiotherapy and image-guided radiotherapy,[4,5] and the development of cisplatin-based combination chemotherapy,[6] patients

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with cervical cancer who have recurrence still have a very poor prognosis with a 1-year survival rate of between 15% and 20%.[7]

Owing to the short life expectancy of patients with recurrent cervical cancer, we believe that it is of great importance to identify the predictors of survival after recurrence to enable physicians and patients to choose the optimal treatment for recurrent disease. In addition, identifying patients who would not derive clinical benefit from the current treatment modalities would allow physicians to offer them the opportunity to receive other types of treatment including best supportive care.

The prognostic factors in patients with recurrent cervical cancer have been investigated in several studies.[8–10] With regard to recurrence within the previously irradiated area, being young, a poor performance status, and a short time to progression from the initial diagnosis were reported to be significant predictors of shorter survival.[8–10]

Tumor-related leukocytosis (TRL) is a paraneoplastic syndrome that is occasionally encountered in patients with malignant tumors either at diagnosis or during the course of the disease. Tumor-related leukocytosis is mainly caused by the unregulated production of hematopoietic cytokines.[11,12] As marked leukocytosis can be caused by infection, bone marrow metastasis, the administration of corticosteroids or hematopoietic growth factors, severe hemorrhaging, or newly developed hematological malignancies, TRL is diagnosed by exclusion. Some reports have indicated that TRL occurs in 1% to 10% of patients with nonhematopoietic malignancies and is associated with a poor prognosis.[11,12] However, in uterine cervical cancer, information regarding the incidence and the prognostic significance of TRL is limited. Recently, it has been reported that pretreatment leukocytosis is observed in 9.4% of patients with cervical cancer and is a poor prognostic indicator in untreated patients with cervical cancer.[13–15] However, the prognostic significance of TRL in patients with recurrent cervical cancer has never been investigated.

We hypothesized that the presence of leukocytosis at the time of recurrence diagnosis is a poor prognostic indicator in patients with recurrent cervical cancer. The incidence and prognostic significance of TRL in patients with recurrent cervical cancer were evaluated in a retrospective review of the clinical records of 219 patients.

MATERIALS AND METHODS

Patients

Permission to proceed with the data acquisition and analysis was obtained from Osaka University Hospital's institutional review board (IRB). A list of patients who had a diagnosis of recurrent cervical cancer at Osaka University Hospital from April 1996 to September 2010 was generated from our institutional tumor registry information. Of the 262 patients who were considered for inclusion in this retrospective study, 36 patients were excluded owing to persistent disease, which was defined as the presence of disease at less than 3 months after the completion of treatment. In addition, 7 patients were excluded because their primary treatments were performed at a facility other than Osaka University. The remaining 219 patients with recurrent cervical cancer were included in this study. As 797 patients with newly diagnosed invasive cervical cancer were treated in our institution during the study period, the recurrence rate was 27.5%.

The follow-up examinations after the initial treatment were conducted by gynecological oncologists with or without radiation oncologists in an outpatient clinic, as reported previously.[10,16] Suspected recurrence lesions were confirmed by histological or cytological diagnosis whenever possible. Recurrence was defined as the presence of disease after more than a 3-month disease-free interval after the end of the primary treatment. The date of recurrence diagnosis, the presence or absence of symptoms, the site of the recurrent cancer, the treatment of the recurrence, and the date of death or the last visit were recorded. The disease-free interval (DFI) was defined as the time from the end of primary treatment until the detection of recurrence.

Recurrent disease was treated in accordance with the institutional treatment guidelines: Single distant recurrent tumors were treated with salvage external beam radiotherapy or salvage surgery. Patients that suffered recurrence in the central pelvis were treated with salvage surgery or, when possible, with interstitial brachytherapy. Patients with pelvic sidewall disease or multiple recurrences were treated with platinum-based chemotherapy. Patients with a single distant tumor that could not be salvaged by either surgery or radiotherapy were also treated with platinum-based chemotherapy. Patients who refused salvage chemotherapy or radiotherapy were treated with palliative care alone. Survival after recurrence was defined as the time from the diagnosis of recurrence to death or the last observation.

Definitions of Leukocytosis and Neutrophilia

During the period between the diagnosis of recurrence and the start of salvage treatment, all patients underwent at least 2 blood tests including a complete blood count. Leukocytosis was defined as a persistent white blood cell (WBC) count exceeding 9000/μL that was detected on at least 2 separate occasions. Neutrophilia was defined as a persistent neutrophil count exceeding 6500/μL that was detected on at least 2 separate occasions.

Patients with coexisting hematologic malignancies, patients with severe hemorrhage, patients who had received corticosteroids or recombinant granulocyte colony-stimulating factor (G-CSF), and patients who had acute or chronic infection were excluded. No human immunodeficiency virus–infected patients were included in the current study.

Statistical Analysis

Continuous data such as age and DFI are shown as mean ± SD or interquartile range, and comparison of such data between groups were performed using the Student *t* test or the Kolmogorov-Smirov test. Frequency counts and proportions were calculated for categorical data such as stage and histological data and compared between groups using the χ^2 test or the Fisher exact test. Spearman correlation coefficient and the associated confidence interval (CI) were calculated to assess the relationship among the patients' WBC counts and neutrophil counts. We performed univariate analysis by

comparing the Kaplan-Meier curves of each group using the log-rank test. Cox proportional hazards regression analysis with stepwise variable selection was performed to identify significant independent prognostic factors for survival after recurrence. All P values were two sided, and $P < 0.05$ were considered statistically significant. All analyses were performed with SAS version 9.1 for Windows (SAS Institute Inc, Cary, NC).

RESULTS

Patients

The clinicopathological characteristics of the patients included in the current study are summarized in Table 1. The mean age of the patients was 57.2 years. Of the 219 patients, 125 patients (57.1%) had stage IA to stage IIB disease, 64 patients (29.2%) had stage IIIA to stage IVA disease, and 30 patients (13.7%) had stage IVB disease. Histologically, 173 patients (79.0%) had squamous cell carcinoma, and 46 patients (21.0%) had nonsquamous histology. The initial treatment for primary cervical cancer was surgery alone in 17 patients, surgery followed by adjuvant radiotherapy in 71 patients, and definitive radiotherapy in 131 patients. Therefore, 202 patients (92.2%) received radiotherapy as a part of their initial treatment. One hundred and ninety-seven recurrences (90%) were diagnosed within 3 years of the primary treatment. The median DFI was 12 months. Seventy-five patients (34.2%) developed a single pelvic recurrence, 43 patients (19.6%) developed a single distant recurrence, and 101 patients (46.1%) developed both pelvic and distant or multiple recurrences. Recurrent disease was treated with palliative care alone in 68 patients, platinum-based chemotherapy in 74 patients, radiotherapy in 68 patients, and surgery in 9 patients. The salvage surgery performed was total abdominal hysterectomy in 5 patients, para-aortic lymphadenectomy in 1 patient, lung lobectomy in 1 patient, and partial hepatectomy in 1 patient. The median survival after recurrence of these patients was 16 months.

Patients With Leukocytosis

As shown in Table 1, of a total of 219 patients, leukocytosis was observed in 33 patients (15.1%) at the time of

TABLE 1. Patients' characteristics (patients with leukocytosis or neutrophilia vs those without)

	All Patients (N = 219)	Leukocytosis (n = 33)	Nonleukocytosis (n = 186)		Neutrophilia (n = 38)	Nonneutrophilia (n = 181)	
	n (%)	n (%)		P	n (%)		P
Age, yrs							
≤50	68 (31.1)	13 (39.4)	55 (29.6)	0.6496	14 (36.8)	54 (29.8)	0.8970
51–70	108 (49.3)	14 (42.4)	94 (50.5)		16 (42.1)	92 (50.8)	
≥71	43 (19.6)	6 (18.2)	37 (19.9)		8 (21.1)	35 (19.4)	
FIGO stage							
IA2–IIB	125 (57.1)	16 (48.5)	109 (58.6)	0.3288	15 (39.5)	110 (60.8)	0.0153
IIIA–IVA	64 (29.2)	12 (36.4)	52 (28.0)		15 (39.5)	49 (27.1)	
IVB	30 (13.7)	5 (15.1)	25 (13.4)		8 (21.0)	22 (12.1)	
Histology							
SCC	173 (79.0)	29 (87.9)	144 (77.4)	0.3758	33 (86.9)	140 (77.3)	0.4223
A or AS	38 (17.3)	3 (9.1)	35 (18.8)		4 (10.5)	34 (18.8)	
Others	8 (3.7)	1 (3.0)	7 (3.8)		1 (2.6)	7 (3.9)	
DFI, mos							
≤11	109 (49.8)	27 (81.8)	82 (44.1)	0.0005	30 (79.0)	79 (43.6)	0.0030
12–35	88 (40.2)	5 (15.2)	83 (44.6)		7 (18.4)	81 (44.8)	
≥36	22 (10.0)	1 (3.0)	21 (11.3)		1 (2.6)	21 (11.6)	
Site of recurrences							
Pelvis	75 (34.3)	10 (30.3)	65 (34.9)	0.0101	9 (23.7)	66 (36.4)	0.0019
Distant	43 (19.6)	1 (3.0)	42 (22.6)		2 (5.3)	41 (22.7)	
Pelvis + distant or multiple	101 (46.1)	22 (66.7)	79 (42.5)		27 (71.0)	74 (40.9)	
Prior RT							
Yes	202 (92.2)	29 (87.9)	173 (93.0)	0.4796	33 (86.8)	169 (93.4)	0.1843
No	17 (7.8)	4 (12.1)	13 (7.0)		5 (13.2)	12 (6.6)	

A, adenocarcinoma; AS, adenosquamous carcinoma; DFI, disease free interval; RT, radiotherapy; SCC, squamous cell carcinoma.

recurrence diagnosis (leukocytosis group). The WBC counts of these patients ranged from 9140 to 41,300/μL. The WBC counts of the remaining 186 patients (nonleukocytosis group) ranged from 1860 to 8980/μL. In a comparison between the leukocytosis and the nonleukocytosis groups, there was no significant difference in age, clinical stage, histological distribution, or the proportion of patients that had previously been treated with radiotherapy. However, the patients with leukocytosis presented with a significantly shorter DFI than the patients without leukocytosis (P = 0.0005). Moreover, multiple recurrences were more common in the patients with leukocytosis than in the patients without leukocytosis (P = 0.0101).

Leukocytosis Is an Independent Prognostic Factor for Survival After Recurrence

To investigate the prognostic significance of the WBC count in the patients with recurrent cervical cancer, we first conducted univariate analyses. As shown in Figure 1A and Supplemental Table 1, (http://links.lww.com/IGC/A137), a statistically significant difference in survival after recurrence was observed between the patients with leukocytosis and those without leukocytosis: the median survival after recurrence for those with and without leukocytosis was 9 and 21 months, respectively (log-rank test; $P < 0.0001$).

To investigate the mechanism responsible for the leukocytosis observed in our patients with recurrent cervical cancer, we next examined the leukocyte subtype in these patients. We found that 32 of 33 patients in the leukocytosis group had an elevated neutrophil count at the time of recurrence diagnosis (30 patients had neutrophilia alone, and 2 patients had both neutrophilia and eosinophilia). None of the patients had basophilia, lymphocytosis, or monocytosis. Thus, we next examined the relationship between the WBC count and neutrophil count using the data obtained at the time of recurrence diagnosis (Fig. 1B). As shown, a positive correlation was demonstrated between the WBC and neutrophil count. Collectively, these results strongly indicate that the leukocytosis observed in these patients was caused by an elevated neutrophil count.

We next determined whether an elevated neutrophil count is also an indicator of short survival after recurrence. As shown in Table 1, neutrophilia was observed in 38 of 219 patients at the time of recurrence diagnosis (17.4%). The neutrophil counts of these patients ranged from 6603 to 38,822/μL. In a comparison between the neutrophilia and

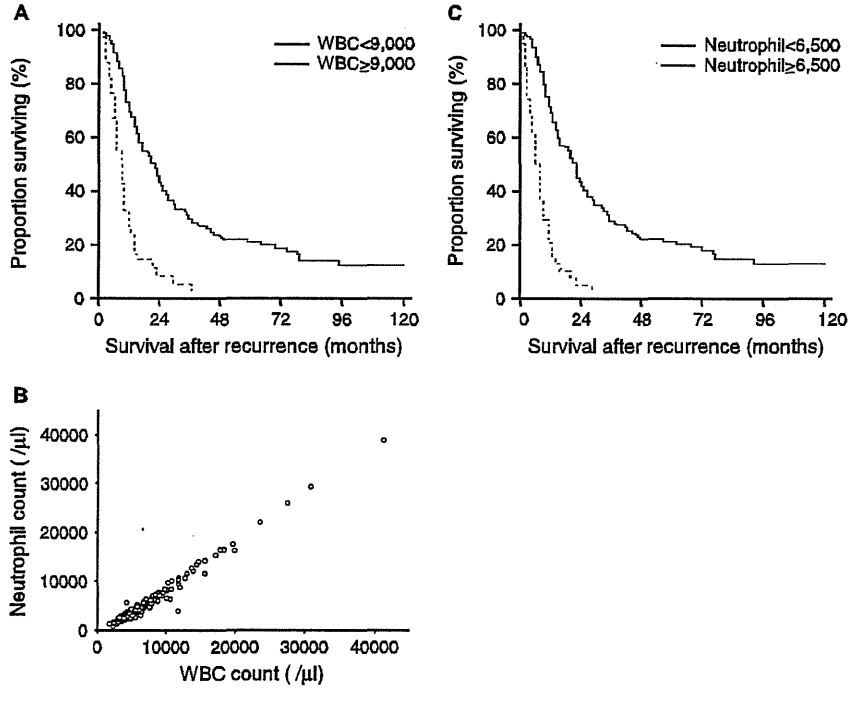

FIGURE 1. A, Kaplan-Meier estimates of survival after recurrence according to the WBC count at the time of recurrence diagnosis. The patients with leukocytosis showed significantly shorter survival after recurrence than those without leukocytosis ($P < 0.0001$). B, Correlation between the WBC count and neutrophil count. A positive correlation was demonstrated between the WBC and neutrophil count (Spearman correlation coefficient, $r = 0.938$; $P < 0.0001$). C, Kaplan-Meier estimates of survival after recurrence according to the neutrophil count at the time of recurrence diagnosis. The patients with neutrophilia showed significantly shorter survival after recurrence than those without leukocytosis ($P < 0.0001$).

TABLE 2. Multivariate Cox-proportional hazards regression analysis of prognostic factors for survival after recurrence

	Stepwise Multivariate Analysis (Excluding Neutrophil Count)*			Stepwise Multivariate Analysis (Excluding WBC Count)†		
	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Age, yrs						
<51	1					
≥51	0.72	0.52–1.00	0.0469			
FIGO stage						
IA2–IIB	1					
IIIA–IVA	1.54	1.09–2.17	0.0145			
IVB	1.56	1.00–2.43	0.0517			
DFI, mos						
<12	1.00			1.00		
≥12	0.63	0.45–0.88	0.0061	0.62	0.45–0.75	0.0037
Site of recurrences						
Pelvis	1			1.00		
Distant	0.67	0.42–1.07	0.0939	0.65	0.41–1.03	0.0679
Pelvis + distant or multiple	2.66	1.84–3.83	<0.0001	2.47	1.73–3.53	<0.0001
WBC count, /μL						
≤6499	1					
6500–8999	1.12	0.73–1.72	0.5902			
≥9000	1.98	1.26–3.11	0.0031			
Neutrophil count, /μL						
≤4499				1.00		
4500–6499				0.92	0.61–1.40	0.6979
≥6500				2.70	1.77–4.11	<0.0001

*The multivariate Cox regression analysis in which WBC was included but neutrophil count was excluded as a prognostic variable.
†The multivariate Cox regression analysis in which neutrophil count was included but WBC was excluded as a prognostic variable.

nonneutrophilia groups, we detected significant differences in clinical stage, DFI, and the site of recurrence, which was consistent with the results shown in Table 1. As shown in Figure 1C and Supplemental Table 1, (http://links.lww.com/IGC/A137), a statistically significant difference in survival after recurrence was observed between the patients with neutrophilia and those without neutrophilia: the median survival after recurrence for those with and without neutrophilia was 7 and 22 months, respectively (log-rank test; $P < 0.0001$).

Thus, we next determined whether leukocytosis or neutrophilia is an independent prognostic factor for survival after recurrence using Cox proportional hazards analyses (Table 2). In a multivariate analysis in which neutrophil count was not included as a prognostic variable, in addition to age, clinical stage, DFI, and site of recurrence, a WBC count greater than 9000/μL was shown to be an independent prognostic factor for survival after recurrence (hazards ratio [HR], 1.98; 95% CI, 1.26–3.11; $P = 0.0031$). In a separate multivariate analysis in which WBC count was not included as a prognostic variable, in addition to DFI and the site of recurrence, a neutrophil count greater than 6500/μL was also shown to be a significant prognostic factor for survival after recurrence (HR, 2.70; 95% CI, 1.77 to 4.11; $P < 0.0001$).

DISCUSSION

This study shows that elevated WBC (≥9000/μL) and neutrophil counts (≥6500/μL) at the time of recurrence diagnosis are correlated with shorter survival after recurrence.

In our investigation, we found 33 patients with recurrent cervical cancer with leukocytosis. The incidence of leukocytosis (≥9000/μL) at the time of recurrence diagnosis was 15.1%. The median survival after recurrence of patients with leukocytosis was 9 months, which was significantly shorter than 21 months observed in those without leukocytosis (log-rank test; $P < 0.0001$). Multivariate analysis showed that the presence of leukocytosis at the time of recurrence diagnosis was associated with shorter survival after recurrence (HR, 1.98; 95% CI, 1.26–3.11; $P = 0.0031$).

Importantly, among the 33 patients with leukocytosis, 32 patients had significantly elevated neutrophil counts

(≥6500/μL). Moreover, multivariate analysis showed that the presence of neutrophilia at the time of recurrence diagnosis was associated with short survival after recurrence (Table 2). This finding indicates that the observed increased WBC counts had been caused by the up-regulated neutrophilic differentiation of hematopoietic progenitor cells.

The mechanisms responsible for the elevated WBC and neutrophil counts observed in this study are unknown. However, as the patients' WBC and/or neutrophil counts transiently decreased in response to salvage treatment and markedly elevated during the regrowth of the recurrent tumor (data not shown), we consider that the leukocytosis observed in our patients with recurrent cervical cancer was caused by the tumor cells themselves.

It has been hypothesized that TRL is caused by the up-regulated production of hematopoietic growth factors, including G-CSF, granulocyte macrophage colony-stimulating factor, IL-1, IL-6, and tumor necrosis factor α.[11,12] Among these cytokines, G-CSF plays a crucial role in granulopoiesis. The first case of a G-CSF-producing malignant tumor was reported in 1977, which involved a patient with lung cancer.[17] Since then, an increasing number of G-CSF-producing non-hematopoietic malignancies including uterine cervical cancer have been reported,[18–21] most of which have been associated with a poor clinical outcome.

In the present study, as biopsy samples could not be obtained from most recurrent cases, we did not perform an immunohistochemical analysis to investigate the expression of G-CSF in the recurrent tumors. However, all 33 primary tumors obtained at the initial diagnosis of cervical cancer displayed moderate to strong G-CSF expression in the leukocytosis group (data not shown). Therefore, the G-CSF produced by recurrent tumors might have, at least in part, been responsible for the leukocytosis observed in the patients enrolled in the current study. To draw a definitive conclusion concerning the association between G-CSF expression and leukocytosis in patients with recurrent cervical cancer, further investigations in preclinical and clinical settings are needed.

Despite intensive salvage treatment for recurrent disease, most patients in the leukocytosis group died within a short period of time (median survival after recurrence was 9 months), indicating that conventional salvage treatments are not effective in this patient population. To improve the prognosis of these patients, understanding the mechanisms responsible for the aggressiveness of this type of recurrent cervical cancer, as well as the development of novel treatments, is necessary. It has been reported that G-CSF might serve as both an autocrine and paracrine stimulator of cancer cells.[22–25] Thus, a novel treatment strategy that targets G- CSF, its receptor, or downstream effectors could be effective against recurrent cervical cancer involving leukocytosis or neutrophilia.

The limitations of our study need to be addressed. One is the relatively small sample size. Moreover, owing to its retrospective nature, potential confounding biases might have been missed in the analysis, such as the selection bias introduced by the fact that the physicians chose the salvage treatments. In addition, the choice of salvage treatment might have been influenced by the educational level and/or the socioeconomic status of the patient. To eliminate these potential biases, further prospective studies are necessary.

In conclusion, we have shown that the presence of leukocytosis at the time of recurrent cervical cancer diagnosis is an indicator of short survival. We believe that our results suggest that it is possible to identify high-risk patients who would not derive clinical benefit from conventional salvage treatments by performing a simple blood test, which would give the physician the opportunity to offer patients other types of treatment, that is, the best supportive care for those with a poor performance status or entry into a novel clinical trial for patients with a good performance status. The development of a novel treatment strategy for this type of aggressive recurrent tumor is urgently needed.

REFERENCES

1. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. *CA Cancer J Clin.* 2010;60:277–300.
2. Ajiki W, Tsukuma H, Oshima A. Research group for population-based cancer registration in Japan. Cancer incidence and incidence rates in Japan in 1999: estimates based on data from 11 population-based cancer registries. *Jpn J Clin Oncol.* 2004;34:352–356.
3. Höckel M, Dornhöfer N. Pelvic exenteration for gynaecological tumours: achievements and unanswered questions. *Lancet Oncol.* 2006;7:837–847.
4. Fokdal L, Tanderup K, Nielsen SK, et al. Image and laparoscopic guided interstitial brachytherapy for locally advanced primary or recurrent gynaecological cancer using the adaptive GEC ESTRO target concept. *Radiother Oncol.* 2011;100:473–479.
5. Powell ME. Modern radiotherapy and cervical cancer. *Int J Gynecol Cancer.* 2010;20:S49–S51.
6. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol.* 2009;27:4649–4655.
7. Long HJ 3rd. Management of metastatic cervical cancer: review of the literature. *J Clin Oncol.* 2007;25:2966–2974.
8. Omura GA, Blessing JA, Vaccarello L, et al. Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol.* 1997;15:165–171.
9. Vermorken JB, Zanetta G, De Oliveira CF, et al. Randomized phase III trial of bleomycin, vindesine, mitomycin-C, and cisplatin (BEMP) versus cisplatin (P) in disseminated squamous-cell carcinoma of the uterine cervix: an EORTC Gynecological Cancer Cooperative Group study. *Ann Oncol.* 2001;12:967–974.
10. Mabuchi S, Isohashi F, Yoshioka Y, et al. Prognostic factors for survival in patients with recurrent cervical cancer previously treated with radiotherapy. *Int J Gynecol Cancer.* 2010;20:834–840.
11. Granger JM, Kontoyiannis DP. Etiology and outcome of extreme leukocytosis in 758 nonhematologic cancer patients: a retrospective, single-institution study. *Cancer.* 2009;115:3919–3923.
12. Sakka V, Tsiodras S, Giamarellos-Bourboulis EJ, et al. An update on the etiology and diagnostic evaluation of a leukemoid reaction. *Eur J Intern Med.* 2006;17:394–398.

13. Mabuchi S, Matsumoto Y, Isohashi F, et al. Pretreatment leukocytosis is an indicator of poor prognosis in patients with cervical cancer. *Gynecol Oncol.* 2011;122:25–32.
14. Tavares-Murta BM, Mendonça MA, Duarte NL, et al. Systemic leukocyte alterations are associated with invasive uterine cervical cancer. *Int J Gynecol Cancer.* 2010;20:1154–1159.
15. Garcia-Arias A, Cetina L, Candelaria M, et al. The prognostic significance of leukocytosis in cervical cancer. *Int J Gynecol Cancer.* 2007;17:465–470.
16. Mabuchi S, Okazawa M, Isohashi F, et al. Radical hysterectomy with adjuvant radiotherapy versus definitive radiotherapy alone for FIGO stage IIB cervical cancer. *Gynecol Oncol.* 2011;123:241–247.
17. Asano S, Urabe A, Okabe T, et al. Demonstration of granulopoietic factor(s) in the plasma of nude mice transplanted with a human lung cancer and in the tumor tissue. *Blood.* 1977;49:845–852.
18. Hirasawa K, Kitamura T, Oka T, et al. Bladder tumor producing granulocyte colony-stimulating factor and parathyroid hormone related protein. *J Urol.* 2002; 167:2130.
19. Takahashi H, Yasuda A, Ochi N, et al. Granulocyte-colony stimulating factor producing rectal cancer. *World J Surg Oncol.* 2008;6:70.
20. Mabuchi S, Matsumoto Y, Morii E, et al. The first 2 cases of granulocyte colony-stimulating factor producing adenocarcinoma of the uterine cervix. *Int J Gynecol Pathol.* 2010;29:483–487.
21. Matsumoto Y, Mabuchi S, Muraji M, et al. Squamous cell carcinoma of the uterine cervix producing granulocyte colony-stimulating factor: a report of 4 cases and a review of the literature. *Int J Gynecol Cancer.* 2010;20: 417–421.
22. Connor JP. Aggressive carcinosarcoma of the uterine cervix associated with high levels of granulocyte colony stimulating factor: case report and laboratory correlates. *Gynecol Oncol.* 2006;103:349–353.
23. Shameem IA, Kurisu H, Matsuyama H, et al. Direct and indirect effects of recombinant human granulocyte-colony stimulating factor on in vitro colony formation of human bladder cancer cells. *Cancer Immunol Immunother.* 1994;38:353–357.
24. Tachibana M, Miyakawa A, Uchida A, et al. Granulocyte colony-stimulating factor receptor expression on human transitional cell carcinoma of the bladder. *Br J Cancer.* 1997;75:1489–1496.
25. Shojaei F, Wu X, Qu X, et al. G-CSF–initiated myeloid cell mobilization and angiogenesis mediate tumor refractoriness to anti-VEGF therapy in mouse models. *Proc Natl Acad Sci U S A.* 2009;106:6742–6747.