Table 6. Univariate analyses of the clinical outcome according to predictive variables: 5-year rate calculated by the Kaplan-Meier method

Predictive variable	Patient number	OAS	DFS	PC	DMFS
Tumor diameters					
Anteroposterior (D_{ap})					
≤50 mm	145	$p = 0.0032$	$p = 0.0007$	$p = 0.0027$	$p = 0.0002$
>50 mm	19				
Lateral (D_l)					
≤50 mm	124	$p = 0.001$	$p = 0.0026$	$p = 0.043$	$p = 0.014$
>50 mm	40				
Craniocaudal (D_{cc})					
≤50 mm	115	$p = 0.023$	$p = 0.0041$	$p = 0.075$	$p < 0.0001$
>50 mm	49				
Maximum (D_{max})					
≤50 mm	95	$p = 0.0007$	$p = 0.0003$	$p = 0.018$	$p < 0.0001$
>50 mm	69				
Tumor volume					
≤50 cc	112	$p = 0.0007$	$p < 0.0001$	$p = 0.0043$	$p < 0.0001$
>50 cc	52				
Lymph node					
Negative	121	$p = 0.0004$	$p < 0.0001$	$p = 0.0007$	$p < 0.0001$
Positive	43				
Patient age (years)					
≤50	15	$p = 0.054$	$p = 0.072$	$p = 0.027$	$p = 0.27$
>50	149				
Stage					
II	84	$p = 0.014$	$p = 0.0072$	$p = 0.2$	$p = 0.044$
III	80				
SCC					
Elevated	97	$p = 0.61$	$p = 0.66$	$p = 0.51$	$p = 0.73$
Normal	35				
CEA					
Elevated	22	$p = 0.018$	$p = 0.15$	$p = 0.066$	$p = 0.42$
Normal	56				
OTT					
≤55 days	120	$p = 0.95$	$p = 0.7$	$p = 0.32$	$p = 0.46$
>55 days	44				

* Defined by physical examination.
Abbreviations: OAS = overall survival; DFS = disease-free survival; PC = pelvic control; DMFS = distant metastasis-free survival; SCC = squamous cell carcinoma antigen; CEA = carcinoembryonic antigen; OTT = overall treatment time.

efficacious, and did not use these results in the following analysis.

At last follow-up, 32 patients had developed local recurrence, of which 9 were accompanied by pelvic failures. Recurrence within the pelvic region developed in 11 patients. Forty-two patients developed distant metastases. The most frequent site was the paraaortic lymph node ($n = 21$), followed by Virchow's node ($n = 10$), the lung ($n = 8$), liver ($n = 7$), and bone metastasis ($n = 7$). Nineteen patients experienced both locoregional and distant failure.

Univariate analysis

Survival: Every parameter derived from pretreatment MRI study showed a strong impact on both OAS and DFS (Table 6). Larger size (D_{ap}, D_l, D_{cc}, and D_{max}) or volume proved to be a significantly unfavorable factor of OAS ($p <$ 0.05). For example, patients with D_{max} >50 mm had a significantly worse OAS (5 years, 54.0%; 95% CI 41.5–66.5%) compared with those with D_{max} ≤50 mm (79.0%; 95% CI 70.0–88.2%, $p = 0.0007$). The same results were also observed as a function of DFS. The DFS of patients with large volume disease (>50 cc; 5 years, 40.9%; 95%CI 27.0–54.8%) proved to be significantly lower than that of patients with a smaller volume (≤50 cc; 69.4%; 95% CI 60.4–78.4% $p < 0.0001$; Fig. 1). Patients with positive lymph node enlargement had a significantly poorer OAS (47.9%; 95% CI 31.0–64.8% vs. 75.9%; 95% CI 67.7–84.1%, $p = 0.0004$) and DFS (38.6%; 95% CI 23.7–53.5% vs. 68.3%; 95% CI 59.5–77.1%, $p < 0.0001$; Fig. 2) compared with those without lymph node enlargement. Patients aged ≤50 years tended to have an unfavorable OAS (p = 0.054) and DFS ($p = 0.072$) compared with those aged >50 years, but this did not reach statistical significance. Patients with Stage II disease had a significantly favorable survival estimate compared with those with Stage III disease as a function of OAS (76.8%; 95% CI 67.2–86.4% vs. 59.5%; 95% CI 47.3–71.7%, $p = 0.014$) and DFS (70.7%; 95% CI 60.7–80.7% vs. 48.7%; 95% CI 36.5–60.9%, $p = 0.0072$). OTT, histopathologic subtype, and serum level of SCC antigen showed no apparent correlation with survival ($p >$

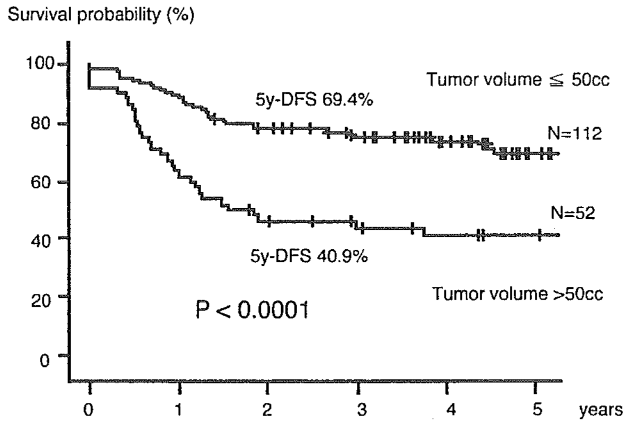

Fig. 1. Disease-free survival curves of the groups divided by tumor volume.

0.05). A higher serum level of CEA proved to be a significantly worse prognostic factor for OAS ($p = 0.018$), but not for DFS ($p > 0.05$).

Patterns of failure

The same results were obtained from the analyses of survival: patients with larger size/volume tumors had a significantly worse PC and DMFS compared with those with smaller tumors (Table 6). At several dividing points of tumor size/volume, each pair of groups showed statistical significance as a function of DMFS. Size/volume also proved to be a significant prognostic factor of PC, although it showed only a tendency as a prognostic factor of PC at some dividing points. Positive lymph node swelling proved to be a significantly unfavorable factor of PC ($p = 0.0007$) and DMFS ($p < 0.0001$). Patients with Stage III disease had a significantly poorer DMFS ($p = 0.044$) compared with those with Stage II disease, although there was no significant relationship between disease Stage and PC ($p > 0.05$).

Patients aged ≤50 years proved to be a unfavorable factor of PC ($p = 0.027$), but not for DMFS ($p > 0.05$). OTT, histopathologic subtype, and serum level of SCC antigen again

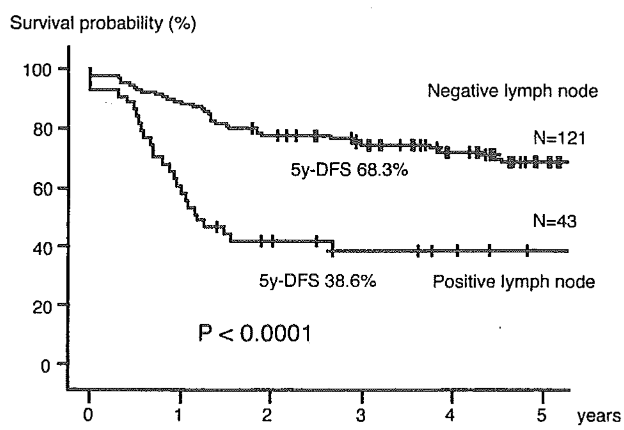

Fig. 2. Disease-free survival curves of the groups divided by lymph nodes.

showed no apparent correlation with local or distant failures ($p > 0.05$). An elevated level of CEA ($p = 0.066$) showed a tendency to be a prognostic factor of PC, although it revealed no apparent relationship with DMFS ($p > 0.05$).

Multivariate analysis

Generally, size/volume proved to be a significant prognostic factor in multivariate analyses. However, the tumor volume divided at 50 cc showed the most appropriate results within all combinations of variables (Table 7). Thus, we provided the outcome using this criteria for the following multivariate analysis. Large calculated volume (>50 cc; $p = 0.0025$, relative risk [RR] =2.207, 95% CI 1.321–3.689) and lymph node enlargement ($p = 0.0008$, RR = 2.439, 95% CI 1.445–4.132) were revealed to be significant prognostic factors for DFS in the multivariate model (Table 7). As a function of OAS, significant prognostic factors were large volume ($p = 0.012$, RR = 2.15, 95% CI 1.18–3.917) and positive lymph node enlargement ($p = 0.0089$, RR = 2.247, 95% CI 1.225–4.115). CEA was excluded from this analysis because almost half of the patients lacked records. FIGO stage failed to be significant prognosticator of either DFS or OAS in multivariate analysis.

In the analysis of PC, these two factors again proved to be significant (volume >50 cc; $p = 0.048$, RR = 2.034, 95% CI 1.006–4.113, positive lymph node enlargement; $p = 0.011$, RR = 2.494, 95% CI = 1.23–5.051). They were also significant prognostic factors of DMFS (volume >50 cc; $p = 0.0006$, RR = 3.042, 95% CI 1.61–5.746, positive lymph node enlargement; $p = 0.0012$, RR = 2.849, 95% CI 1.511–5.348). Again, FIGO stage showed no apparent influence on either PC or DMFS using multivariate analysis.

Predictive model using prognostic factors

Using the results of multivariate analyses, we devised a predictive model for DFS. Patients were scored as being at risk with tumors with volume >50 mm or positive lymph node enlargement, and were classified into three groups with zero, one, and two risk factors. The differences in DFS among the three groups of the proposed model were statistically significant ($p < 0.0001$; Fig. 3). The 5-year DFS rates of patients scored as zero, one, and two risks were 72.9% (95% CI 63.3–82.5%), 53.3% (95% CI 38.8–67.8%), and 26.1% (95% CI 8.1–44.1%), respectively.

Relationship between FIGO stage and size/volume derived from MRI

To evaluate the relationship between disease stage and tumor volume, we compared the survival estimates and failure patterns among these groups (Table 8). Within patients with smaller volume disease (≤50 cc), disease stage showed a significant influence on OAS ($p = 0.0023$), DFS ($p = 0.0044$), and PC ($p = 0.042$). In contrast with these analyses, advanced-stage disease showed no apparent influence on survival or local control ($p > 0.05$) in cases with large volume disease. Interestingly, disease stage showed no apparent relationship with distant failure in either group divided by

Table 7. Multivariate analyses of prognostic factors according to disease-free survival (final stepwise-regression model)

Factors	Initial model			Final model		
	RR	95% CI	*p* value	RR	95% CI	*p* value
Volume (≤50 cc)*	2.036	1.2–3.456	0.0084	2.207	1.321–3.689	0.0025
LN (negative)*	2.315	1.362–3.937	0.0019	2.439	1.445–4.132	0.0008
Stage (Stage II)*	1.369	0.8–2.347	0.2512			

* Control group.
Abbreviations: RR = relative risk; CI = confidential interval; LN = lymph node enlargement.

tumor volume ($p > 0.05$). We observed only a slight difference in DMFS between patients with Stage II and III disease within each group divided by tumor volume (Table 8).

Toxicity

Seventeen patients (10.4%) developed late bladder adverse effects 211 to 2,592 days (median 657 days) after the initial treatment. The grades decided by Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) score (17) were 9 with Grade 1 and 8 with Grade 2. Twenty-nine patients (17.7%) developed late rectal adverse effects 136 to 1,591 days (median 412 days) after the initial treatment. The RTOG/EORTC scores of the late rectal adverse effects of Grade 1, 2, 3, and 4 were 12, 15, 1, and 1 patient, respectively. Two patients developed radionecrosis at the pubic bone and femoral head 73.1 months and 31.0 months after the initial treatment, respectively.

DISCUSSION

Radiotherapy plays an important role in the treatment of patients with cervical carcinoma. Patients with Stage I disease usually undergo operations, hence Stage II or a more advanced stage patients are thought to be candidates for definitive radiotherapy (18). To date, the outcome from Stage IV disease patients has been poor, and as a group it is relatively small. Considering these backgrounds, we intended to emphasize the outcome from Stage II–III disease patients who were regarded as the majority of cases in these groups.

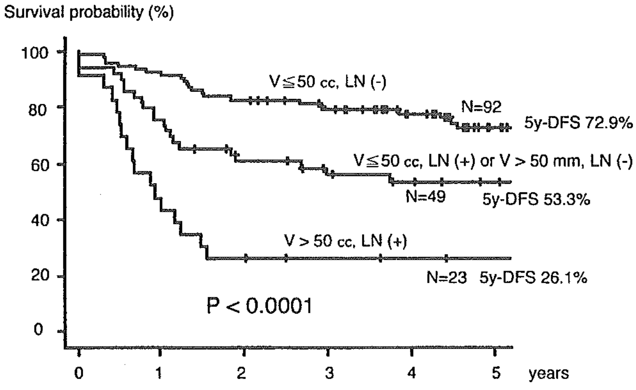

Fig. 3. Disease-free survival curves of the groups divided by the predictive prognostic model.

FIGO stage is reported to be a convincing predictor of outcome among patients treated with definitive radiotherapy. However, several factors such as size/volume and lymph node status, which are not assessed by this system, are also reported to be meaningful factors (2–4, 6–8). For patients treated with radiotherapy, these parameters are usually evaluated by noninvasive workups such as CT, US, and MRI; however, diagnostic imaging has distinct limitations compared to surgical confirmation.

Tumor volume is a well-known prognostic factor influencing tumor control and disease-free survival for cervical cancer (2, 3, 6, 8). Classically, tumor size has been evaluated by physical pelvic examination. Although this is convenient and cost-effective, the accuracy of tumor size/volume estimation is not satisfactory (19). In addition, this method is not reproducible and depends greatly on interphysician variability. To acquire objective information regarding tumor status, MRI has great advantages in terms of excellent soft tissue contrast resolution, capability of three-dimensional measurement, and accurate judgment of invasion surrounding normal tissue. Several reports have noted that surgical confirmation proved to correlate well with the findings obtained by MRI in cervical cancer (20, 21). Lymph node enlargement was also reported to be a significant prognostic factor in the reported data (6–8). As for the diagnostic quality for lymph node status, MRI is considered to be equal to that of CT scans (9). Considering these encouraging diagnostic factors of MRI, we tried to establish whether FIGO stage or these parameters were more representative.

In uni- and multivariate analyses, size/volume and lymph node enlargement proved to be significantly strong predictors of survival and local and distant failure. On the contrary, the FIGO system proved to be a prognosticator in univariate analysis, but not in multivariate analysis. One reason for this is that it is influenced by the staging procedure. The majority of this cohort (144/164; 87.8%) was Stage IIB or IIIB patients. The difference between these groups is defined by the presence or absence of pelvic fixation, which was decided by physical examination or hydronephrosis. Only 18 (24.3%) of 74 patients with Stage IIIB disease were diagnosed as having hydronephrosis. Thus the majority of these groups were diagnosed by *subjective* and *nonreproducible* methods. We believe the evaluation using MRI is more applicable and objective compared with the FIGO system.

Table 8. Comparison of several clinical outcomes among subgroups divided by disease stage and volume determined with MRI

	V ≤ 50 cc		V > 50 cc	
Outcome	5-y rate (%)	p value	5-y rate (%)	p value
Overal survival				
Stage II	86.1	0.0023	41.2	0.4
Stage III	61.1		56.9	
Disease-free survival				
Stage II	79.8	0.0044	35.3	0.6
Stage III	51.9		44.0	
Pelvic control				
Stage II	88.1	0.042	51.5	0.22
Stage III	74.6		73.3	
Distant metastasis-free survival				
Stage II	84.6	0.38	56.6	0.7
Stage III	80.3		47.8	

We further evaluated the correlation of tumor size/volume with FIGO stage in subset analysis. Generally, size/volume proved to be a significant prognostic factor in multivariate analyses. However, the tumor volume divided at 50 cc showed the most appropriate results within all combinations of variables. Thus, we provided the outcome using these criteria for the following analysis. Stratification by volume derived from MRI, the FIGO stage remained meaningful predictor for locoregional control and survival within groups with smaller volume (≤50 cc). Among these patients, the estimates of distant failures of groups with Stage II and III disease seemed to be invariable ($p > 0.05$), so the effort to improve locoregional control might lead to favorable outcome. On the contrary, this result might represent MRI failing to identify parametrial involvement among patients with smaller size/volume. Indeed, we noted that 112 of 164 patients (68.3%) were included in this definition. Thus, the FIGO system retained prognostic value in these patients.

Conversely, the difference between two groups became obscure among a cohort with bulky disease (>50 cc). One reason for this is the higher incidence of distant failure (43.4–52.2%) compared with that of locoregional sites (26.7–48.5%; Table 8). A larger size/volume disease had an increasing probability of lymphatic metastasis, which also led to unfavorable clinical outcome. The same result was reported by Eifel *et al.* (2). Poorer pelvic control was another reason for unsatisfactory outcome in patients with bulky lesions. We suspected that an unfavorable outcome from Stage III disease chiefly depended on the large proportion of patients with bulky disease.

With these two prognostic variables, we adapted the predictive model for DFS. Three subgroups showed significant differences in DFS. With the aid of MRI, Stage II–III patients, thought to be the majority of patients treated with radiotherapy, could be classified according to clinical risk factors. In our previous report, similar results were acquired in the group with Stage II disease. Again in this analysis, the benefit of the proposed model could be easily extended to the group with Stage II–III disease. Using MRI, noninvasive, accurate, and useful information could be obtained before treatment, and we believe application of this model to clinical trials would be advantageous and meaningful. However, we should carefully consider the considerable variations such as treatment content (radiation technique and type of brachytherapy), MRI procedure (imaging protocol, apparatus, and diagnostic method), and patient selection (excluding patients treated with chemoradiotherapy). Although we found no significant difference in treatment outcome and tumor volume among three institutes, we were encouraged by our results using MRI. There are few reports of MRI for cervical cancer with such large patient numbers (n = 164) and longer follow-up, so we believe our results are quite meaningful and applicable for clinical studies.

Recently, concurrent chemoradiotherapy has been the standard treatment for Stage II–IVA cervical carcinoma (22–27). We previously reported the efficacy of MRI among patients with Stage II disease (8). In this report, low-risk patients provided an excellent DFS (93.2%), and chemoradiotherapy would have been overtreatment for this group. Using MRI, one could obtain useful information about disease severity. According to these findings, chemoradiotherapy could be adapted according to the criteria for using MRI in Aichi Cancer Center. MRI could greatly contribute to both optimal adaptation for chemoradiotherapy and common stratification in clinical studies.

Finally, we also evaluated other clinical parameters such as patient age, histopathologic differentiation, tumor markers, and radiation treatment contents; none was a significantly prognostic factor. Efficacy of tumor markers as predictors for clinical outcome was limited in this analysis. This is different from the results reported by Pras (28). Histology of adenocarcinoma is believed to be a more unfavorable factor compared with SCC histology (29), so we excluded these patients from the present analysis. Adenocarcinoma is thought to have poor radiosensitivity compared with that of squamous cell carcinoma. As for histologic subtype, we could not find any significant influence in our analysis. Overall treatment time was reported to be a significant prognostic factor among patients treated with definitive radiotherapy (30), although we failed to show any apparent influence in this analysis. This result could be explained by the lack of serious prolongation of treatment contents among our analyzed patients.

CONCLUSION

Size/volume analysis derived from MRI will add meaningful information for clinical outcome for extremely bulky disease. Lymphatic involvement diagnosed by MRI also proved to be a significant prognostic factor. Using these two parameters from MRI, we devised a practical and effective model to predict DFS. In the future, we believe clinical application of this model would be beneficial in the management of definitive (chemo-) radiotherapy for cervical carcinoma.

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ORIGINAL ARTICLE

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Weekly 1-h paclitaxel infusion in patients with recurrent endometrial cancer: a preliminary study

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Abstract
Background. The aim of this study was to evaluate the toxicity and efficacy of weekly paclitaxel in patients with recurrent endometrial cancer.
Methods. Nine patients with recurrent endometrial cancer who had previously received chemotherapy or radiotherapy participated in the study, between May 1999 and August 2001. Paclitaxel was given at a dose of $70 mg/m^2$ as a 1-h infusion every week for at least 20 consecutive weeks unless lesions became progressive. Intravenous dexamethasone and cimetidine and oral diphenhydramine were administered 30min before paclitaxel infusion.
Results. The nine patients received a total of 149 cycles of therapy. No hypersensitivity reactions were elicited. Grade 3 leukopenia, neutropenia, and anemia occurred in 22%, 33%, and 33% of the patients, respectively. Granulocyte colony-stimulating factor was required for two patients and no patients experienced febrile neutropenia. Neurotoxicity was commonly observed. Grade 1 peripheral neuropathy and myalgias were observed in 78% and 11% of the patients, respectively. No grade 3 or higher nonhematological toxicities were observed. Partial responses were seen in six of the nine patients (67%). The median progression-free interval was 8 months (range, 0–12 months) and the median overall survival was 10 months (range, 4–24 months).
Conclusion. Weekly 1-h paclitaxel administration is considered safe and effective as a salvage therapy for recurrent endometrial cancer, with this schedule and delivery making its use more convenient and easier in the outpatient setting. The current results support further evaluation.

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Key words Recurrent endometrial cancer · Paclitaxel · Weekly 1-h infusion

Introduction

Endometrial cancer is one of the common gynecologic malignancies. Nearly 80% of the patients have disease confined to the uterus at diagnosis and have a good prognosis.[1] For patients with risk factors for recurrence, postoperative radiotherapy and/or chemotherapy is generally given. Patients with recurrent or advanced disease, however, will rarely be cured with second-line treatment. Cisplatin and doxorubicin have been effective for advanced and recurrent endometrial cancer, respectively, and the combination of cisplatin and doxorubicin with or without cyclophosphamide (AP or CAP) has been considered to be an adjuvant or salvage regimen.[2–5] One possible way to decrease the toxicity of treatment without compromising efficacy is to give lower doses more frequently.

Recently, paclitaxel (Taxol; Bristol Myers Squibb, Princeton, NJ, USA) has also been used as an active agent against endometrial cancer.[6–8] Clinical trials of the drug have been performed with different administration schedules of 1 to 3-h and 24-h infusions, with doses ranging from 135 to $250 mg/m^2$, every 3 weeks.[9–13] These trials suggested that the observed toxicity profile seemed to depend on dose and schedule. Therefore, the efficacy of shorter infusion schedules of paclitaxel (TXL) has been investigated, and some phase I/II studies have reported that 1-h infusion of TXL at doses of 60 to $90 mg/m^2$ weekly yielded low toxicity profiles.[14–19] The decreased leukocyte toxicity associated with short infusion times allows for reduced intertreatment periods, from the standard 3-week to a 1-week interval. Moreover, the response rate with weekly TXL administration appears to be comparable to that of the 3-week schedule.[14–19]

This short-infusion time weekly strategy supports more frequent and prolonged formation of stable cellular microtubules with subsequent mitotic arrest, which forms the pharmacological basis for TXL's antitumor activity.

This preliminary study was carried out to evaluate the safety and efficacy of weekly TXL administration by 1-h infusion for recurrent endometrial cancer, in the outpatient setting.

Patients and methods

Patients with recurrent endometrial cancer that developed after chemotherapy and/or radiotherapy were eligible for the preliminary study. All patients had at least one measurable lesion which had been documented radiographically. The eligibility criteria were as follows: performance status (PS; World Health Organization; WHO), less than 2, good general health with no history of cardiac disorder or congestive heart failure, and an expected survival of least 3 months. Before patients received treatment, laboratory tests showed that all patients conformed to the following criteria: white blood cell count, 4000–12 000/μl; platelet count, more than 100 000/μl; hemoglobin, more than 9.5 g/dl; aspartate amino-transferase (AST) and alanine amino transferase (ALT), less than twice the normal upper limit; total serum bilirubin, less than 1.5 mg/dl; serum creatinine, less than 1.5 mg/dl; creatinine clearance, more than 60 mg/min; and blood urea nitrogen (BUN), less than 25 mg/dl.

This study was approved by the Ethics Committee of Kurume University School of Medicine, and all patients signed an informed consent document that described the investigational nature of the proposed treatment.

The treatment schedule was designed on the basis of previous reports describing weekly administrations of TXL.[14–19] Chemotherapy consisted of TXL (70 mg/m^2) in 250 ml of 5% glucose, given in 1-h infusions. Infusions were repeated each week with no planned pause during the treatment period of at least 20 weeks, unless progressive disease was detected or intolerable nonhematological toxicity was observed. All patients were premedicated with dexamethasone (10 mg) i.v., cimetidine (50 mg) i.v., and diphenhydramine (50 mg) orally, 30 min prior to each weekly administration.[20]

All patients were treated on an outpatient basis unless they had been hospitalized for other reasons before TXL therapy was initiated. A physician was present during the first 15 min of therapy. Blood pressure was monitored after the first 15 min of infusion.

Total blood cell counts were examined at least twice weekly and serum chemistry and liver function tests were monitored weekly. Before the next cycle was initiated, leukocyte counts were confirmed to be more than 2000/μl and platelets more than 100 000/μl, with liver and renal functions within the eligibility criteria. No premedication was given for neutropenia. Patients were evaluated for response to treatment. Patients who progressed were considered treatment failures and the therapy was stopped. Those with stable disease or objective tumor responses continued the therapy.

Toxicity evaluations were based on WHO criteria. Although the determination of antitumor activity was not the primary objective of this study, all patients were assessed for responses by computed tomography and/or ultrasonography at least every four to six cycles.

The criteria for tumor responses were as follows: complete response (CR) was defined as the complete disappearance of all known disease for a minimum of 4 weeks; partial response (PR) was defined as a more than 50% reduction in the sum of the length-width products of measurable lesions for a minimum of 4 weeks; progressive disease (PD) was defined as a more than 25% increase in the sum of products of all indicator lesions, reappearance of any lesion that had disappeared, or appearance of any new lesion; and stable disease (SD) was defined as any situation that did not qualify as a response or progression. The time to response was recorded from the beginning of treatment until the first objective response was detected. The progression-free interval was determined from the first cycle of treatment until PD was elicited.

Results

The patients' characteristics are listed in Table 1. Between May 1999 and August 2001, nine patients entered the study. The median age was 68 years (range, 40–79 years) and the median performance status was 1 (range, 0–2). Seven of the

Table 1. Patients' characteristics (n = 9)

No. of patients	Primary stage (FIGO)	Histology	PS (WHO)	Measurable lesions	Postoperative treatment	Treatment-free interval (months)
1	Ic	Endometrioid (G1)	0	Lung	Radiotherapy	12
2	Ic	Endometrioid (G2)	0	Lung	CAP	63
3	Ic	Endometrioid (G3)	0	Lung	CAP	11
4	IIb	Endometrioid (G3)	0	Lung, pelvic cavity	CAP, 5-FU	21
5	IIIa	Endometrioid (G1)	1	Lung	Radiotherapy	160
6	IIIa	Endometrioid (G3)	1	Lung, pelvic cavity	AP, CDDP	4
7	IIIa	Endometrioid (G3)	0	Pelvic cavity	AP, CDDP	7
8	IIIc	Endometrioid (G2)	2	Lung, pelvic cavity	CAP	38
9	IIIc	Endometrioid (G2)	2	Pelvic cavity	AP, CBDCA	35

PS, Performance status; FIGO, International Federation of Gynecology and Obstertrics; WHO, World Health Organization; CAP, cyclophosphamide, doxorubicin, cisplatin; AP, doxorubicin, cisplatin; CDDP, cisplatin; CBDCA, carboplatin; 5-FU, 5-fluorouracil nine patients had previously received heavy treatment with one or more platinum-based chemotherapies, and two of the patients had undergone radiotherapy. The nine patients received a total of 149 cycles of therapy, with an average of 16.6 cycles (range, 4–30 cycles) per patient. All patients received 70 mg/m^2 per week. One of the nine patients had a treatment delay. The median duration of the treatment-free interval was 21 months (range, 14–160 months). All patients were evaluated for toxicity and response.

Toxicity

No treatment-related deaths occurred in this study. Table 2 lists the nonhematological toxicities encountered during treatment. No hypersensitivity reactions to TXL were exhibited. Neurotoxicity was commonly observed. Grade 1 peripheral neuropathy and myalgias were observed in 78% and 11% of the patients, respectively. Nausea/emesis, diarrhea, and mucositis were uncommon, and none of the patients needed antiemetic support. Alopecia was of moderate intensity. Although significant nail discoloration and onychorrexis were noted in one patient after the tenth cycle of TXL, the nails grew back completely after completion of the treatment.

Table 3 shows the hematological toxicities manifested in the patients. Myelosuppression was commonly observed, but was mild to moderate in most patients. Grade 3 leukopenia and neutropenia occurred in two (22%) and three (33%) of the patients, respectively, and there were no episodes of febrile neutropenia. Granulocyte colony-stimulating factor (G-CSF) was required for two patients. Thrombocytopenia was not observed. Grade 3 anemia was noted in three patients (33%), but they did not require red blood cell transfusion. There was no evidence or cumulative hematological toxicity.

Response

Table 4 lists the response to weekly TXL in the patients. The clinical response rate was 67%, with six partial responses (67%). Stable disease was seen in one patient (11%) and the remaining two (22%) manifested PD. The median progression-free interval was 8 months (range, 0–12 months) and the median overall survival was 10 months (range, 4–24 months).

Table 2. Nonhematologic toxicity (per patient; n = 9)

Toxicities	Grade (WHO)				
	0	1	2	3	4
Peripheral neuropathy	0	9	0	0	0
Myalgias	8	1	0	0	0
Fatigue/weakness	7	2	0	0	0
Alopecia	0	6	3	–	–
Nausea/emesis	9	0	0	0	–
Diarrhea	9	0	0	0	0

Discussion

Single-agent (such as cisplatin or doxorubicin) and combination chemotherapy regimens (AP or CAP) are associated with substantial response rates in patients with metastatic or recurrent endometrial cancer, but the responses have not been durable and appear to have little impact on survival.[2–5] Because treatment for patients with recurrent

Table 3. Hematologic toxicity (per patient; n = 9)

Toxicities	Grade					≥Grade 3	
	0	1	2	3	4	No. of patients	Percentage
Leukopenia	3	1	3	2	0	2	22
Neutropenia	3	2	1	3	0	3	33
Thrombocytopenia	9	0	0	0	0	0	0
Anemia	1	4	1	3	0	3	33

Table 4. Response to weekly paclitaxel

No. of patients	No. of cycles	Response	Progression-free interval (months)
1	20	PR	5+
2	12	PR	4
3	20	PR	9+
4	30	SD	12
5	20	PR	8
6	14	PR	9
7	24	PR	8+
8	5	PD	0
9	4	PD	0

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease gynecological tumors is mostly palliative, it is very important to maintain good quality of life (QOL) during the treatment period. Three phase II studies of TXL in advanced or recurrent endometrial cancer have shown overall response rates of up to 30%.[6–8] Lissoni et al.[8] reported that TXL was active in patients with endometrial cancer pretreated with CAP. Woo et al.[7] reported that TXL had activity for platinum-resistant endometrial cancer.

The choice of a second-line drug in this situation is dependent on toxicity and QOL considerations, in addition to efficacy. Weekly administration of TXL by 1-h infusion has been reported to have less toxicity than other schedules and a promising effect in patients with pretreated gynecological cancers.[14–18] Greco and Hainsworth[12] demonstrated that the 1-h infusion schedule was feasible. Actually, the 1-h weekly infusion of TXL seems to have promising activity in a variety of pretreated solid tumors, including those of recurrent ovarian cancer.[11,14] Using this 1-h infusion, we can anticipate the advantage of the limited hematologic toxicity associated with the shorter TXL infusion schedule, and the use of a weekly schedule will increase the intensity of TXL exposure. Previous reports have demonstrated that weekly i.v. TXL administration in a 1-h infusion at doses of 60–90 mg/m^2 is an acceptable salvage regimen.[14–18] In the present study, we administered 70 mg/m^2 of TXL without dose escalation in order to maintain dose density and to avoid adverse effects. All patients underwent this therapy. One patient suffered treatment delays due to neutropenia. Grade 3 or higher neutropenia was observed in 33% of patients, and two patients with grade 3 neutropenia required G-CSF support for long-term neutropenia (2 weeks).

Hematologic toxicity was uncommon and mild with the weekly administration of TXL 70 mg/m^2, despite the fact that the overall dose intensity was increased compared with standard TXL treatment at 175 mg/m^2 every 3 weeks. The intravenous premedication given immediately before TXL administration was effective in preventing hypersensitivity reactions.

In conclusion, weekly 1-h TXL administration is considered safe and effective as a salvage therapy for endometrial cancer. This low toxicity profile and the short duration of therapy is advantageous for outpatient treatment and is favorable for maintaining or improving the patient's quality of life during treatment.

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Use of small pelvic field instead of whole pelvic field in postoperative radiotherapy for node-negative, high-risk stages I and II cervical squamous cell carcinoma

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Abstract. Ohara K. Tsunoda H, Nishida M, Sugahara S, Hashimoto T, Shioyama Y, Hashimoto T, Shioyama Y, Hasezawa K, Yoshikawa H, Akine Y, Itai Y. Use of small pelvic field instead of whole pelvic field in post-operative radiotherapy for node-negative, high-risk stages I and II cevical squamous cell carcinoma. *Int J Gynecol Cancer* 2003;**13**:170–176.

We investigated whether a small pelvic (SP) field that covers primarily the pericervical regions in postoperative radiotherapy for cervical squamous cell carcinoma is adequate for a subgroup of node-negative patients. Of 84 patients with stage I–II disease treated with postoperative radiotherapy due to pathologic risk factors, 42 node-negative patients received SP-field radiotherapy, whereas remaining 42 node-positive patients were treated with a conventional whole pelvic (WP) field that also covered pelvic lymph nodes, both with 50.0–50.4 Gy/25–28 fractions. The pathologic risk factors included positive nodes, deep stromal invasion (≥2/3 thickness), parametrial extension, and positive or close surgical margin. Recurrence was identified for 20 patients: three in the SP group and 17 in the WP group. Intrapelvic recurrence accounted for all three recurrences in the SP group and for four in the WP group; 5-year pelvic-control rate did not differ significantly between the SP (93%) and WP (90%) groups. Extrapelvic recurrence ($n = 11$) was identified exclusively in the WP group. Patterns of recurrence indicate that use of an SP field instead of a WP field may be adequate in postoperative radiotherapy for a subgroup of node-negative, high-risk patients.

KEYWORDS: complication, lymph node metastasis, pelvic failure, prognostic factor.

Postoperative radiotherapy (RT) has been used in an attempt to improve survival by reducing pelvic recurrence for stage I and stage II (the stages of International Federation of Gynecologists and Obstetricians) cervical cancer patients treated by surgery who showed pathologic risk factors. Major pathologic risk factors identified included positive lymph nodes, tumor size, stromal invasion, parametrial extension, and lymph-vascular space invasion[1-10]. Apart from these factors, clinical risk factors assessible before

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treatment, such as histologic type and grade, clinical stage, and clinical tumor diameter, were also considered important. Among these pathologic risk factors, node-positive status was a factor that differed from others in its prognostic implications[2,5–8,10–12], although it was relevant to the other factors[2,3]. A node-positive status indicated the possibility of both regional microscopic cancer deposits left behind along pelvic lymphatic channels and development of extrapelvic diseases. In contrast, the other four factors related to contiguous local extension of disease implied the possibility of localized microscopic cancer-invasion foci left behind at pericervical tissues or organs. Irrespective of these different implications, a whole pelvic (WP) field has traditionally been used for postoperative RT, even in recent clinical practice[7,10,13–15]. The WP field, which covered both the primary disease and the regional pelvic lymphatic channels, was primarily used as a standard field in definitive radiotherapy where nodal metastasis was possible but unproven. Therefore, for patients pathologically proven to have had negative nodes through surgical findings, the WP field was unnecessarily large, and a small field that covered only the pericervical region was logically sufficient. It was essential for RT planning to include the volume where tumors certainly or possibly existed and to exclude the volume where tumors did not exist. A reduced field could decrease adverse effects of treatments. With this rationale in minds, we have been carefully using a small pelvic (SP) field for the subgroup of node-negative patients since October 1993. In this preliminary study, we investigated patterns of treatment failure and survival to study the adequacy of using an SP field instead of a WP field.

Patients and methods

Eighty-four patients were the subjects of this study: 42 node-positive patients and 42 node-negative patients. Pathologic risk factors included in our postoperative RT indication criteria were positive nodes, deep stromal invasion ($\geq$ 2/3 of the stromal thickness), parametrial extension, and positive or close (<5 mm) surgical margin. Tumor size and lymph-vascular space invasion were not included. Patients included had stage I or II squamous cell carcinoma and underwent postoperative RT after hysterectomy and bilateral pelvic lymph-node dissection. They were selected from 134 consecutive patients with cervical cancer treated primarily by surgery and postoperative RT between January 1990 and December 1998. To match the sample size of the node-positive patients to that of the node-negative patients, some patients treated before we began using the SP field were included. The treatment protocol, except field type (the SP field or the WP field), was consistent throughout the period. Excluded patients were those who had cancers of nonsquamous cell carcinoma histology, node-negative patients who were treated with the WP field before October 1993, those who did not undergo lymph-node dissection, those who had para-aortic

Table 1. Patient characteristics according to field type

	Whole pelvic field	Small pelvic field	*P*-value
Total number	42	42	
Age range (median)	23–74 (46.9)	27–71 (47.5)	0.8527
Pathologic T category			0.0007
T1b1	6	14	
T1b2	11	19	
T2a	6	6	
T2b: parametrial invasion	19	3	
Stromal invasion ($\geq$2/3 thickness)			0.0778
Negative	3	0	
Positive	39	42	
Surgical margin			0.1543
Negative	32	37	
Close (to vagina)	6 (4)	1 (1)	
Positive (to vagina)	4 (1)	4 (2)	
Number of local risk factors[a]			0.0002
0	2	0	
1	18	36	
2	16	4	
3	6	2	

[a]Local risk factors: parametrial invasion (T2b), stromal deep invasion, and close or positive surgical margin.

lymph-node metastasis, those whose postoperative RT was discontinued, those who had macroscopic residual diseases, and those who underwent neoadjuvant chemotherapy before surgery.

Patient characteristics including age, pathologic T category (the UICC TNM Classification, 1997), deep stromal invasion, status of surgical margin, and number of risk factors for local extension were shown according to the field type (Table 1). Most patients underwent radical hysterectomy, but some had modified radical hysterectomy, depending on the gynecologist's discretion. Pathologic T2b matched up with the risk factor of parametrial extension. The number of pathologically examined lymph nodes in each patient ranged from eight to 70 (median, 27); the number was less than 10 for one node-positive patient. The site of positive nodes was the parametrium for nine patients, obturator for 24, external iliac for five, internal iliac for 22, common iliac for four, and others, such as sacral, for three. The number of positive nodes in each patient ranged from 1 to 18 and was four or more in nine patients. Among these patients, four had metastasis to the common iliac node. The time from surgery to the start of postoperative RT ranged from 14 to 44 days (median, 22 days).

We introduced the SP field very carefully, considering a possibility of false-negative nodal status. The SP field was set not only to include the pericervical regions of the upper half or third of the vagina, the pelvic walls of the parametrial stump, and the rectum and bladder, but also to cover the major part of upper stream echelons of the internal and external iliac lymphatic channels (Fig. 1). The WP field encompassed the pericervical regions that were included in the SP field and the internal, external, and common iliac lymphatic channels up to the spinal bone level of L4–5 (Fig. 2). The field size was normally around 14×10 cm for SP and 16×18 cm for WP. Patients were treated with 10 MV X-ray through anteroposteriorly opposing portals with 1.8 or 2.0 Gy per fraction at five fractions per week for a total of 50.4 or 50.0 Gy. Boost irradiation was given to 15 patients with close or positive surgical margins to the pericervical tissues by external irradiation ($n = 7$; 6.0–16.0 Gy) and to the vagina by high-dose-rate intracavitary irradiation ($n = 6$; 5–10 Gy at 5 mm submucosa) or by external irradiation ($n = 2$; 10.0 or 16.0 Gy). All four patients who had metastasis to the common iliac node(s) also were treated concurrently or sequentially with prophylactic para-aortic lymph node irradiation up to the spinal bone level of D12–L1 with 43.2–50.4 Gy.

The patterns of recurrence in terms of overall disease-control rate (DCR), pelvic-control rate (PCR), and overall survival rate (OSR) were determined. The site of recurrence was categorized as intrapelvis, extrapelvis, or vagina. The intrapelvis was defined as the sites covered by the WP field. In the estimation of rates, all the recurrence were counted in DCR, and only the

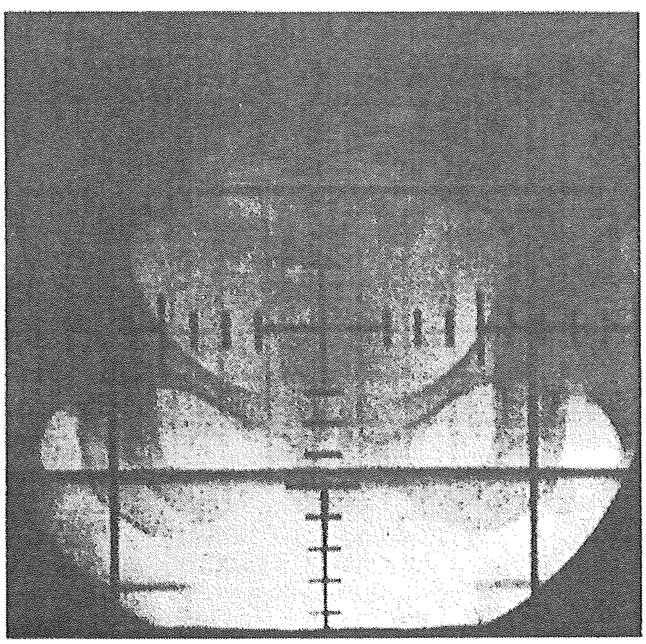

Fig. 1. A small pelvic field that covers the pericervical regions and the major part of the internal and external iliac lymphatic nodes.

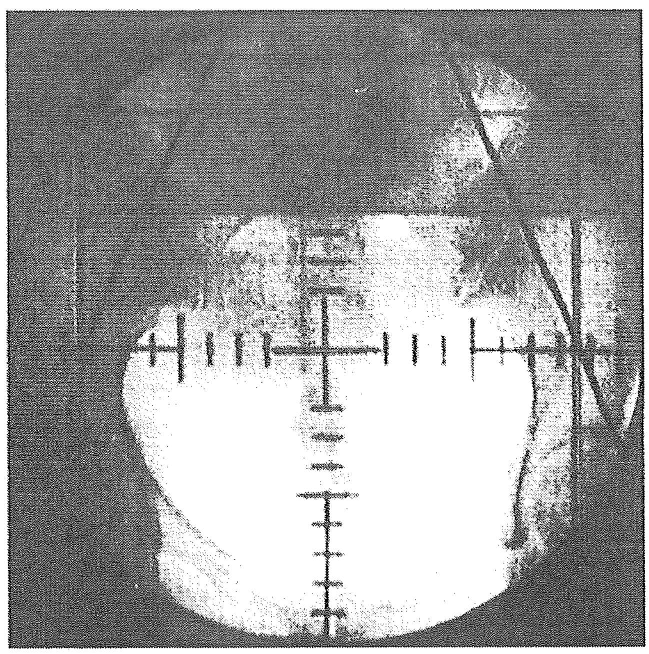

Fig. 2. A whole pelvic field that covers the pericervical regions and lymphatic channels of the internal, external, and common iliac nodes.

pelvic recurrence was counted in PCR, censoring survival without recurrence at the time of the last follow-up. The time to recurrence and the survival time were computed from the day of surgery. Estimates were computed by the Kaplan-Meier method. Differences in the T category and risk factors between the node-negative patient group and the node-positive patient group were tested by chi-square test. The estimates were analyzed by the log rank test. StatView 5.0 (SAS Institute Inc., Cary, NC) was used for all statistical analyses. *P*-values of less than 0.05 were considered statistically significant.

Results

Age, stromal invasion, and surgical-margin status did not differ significantly between the two field-type groups (Table 1). T2b category and the presence of two or more local risk factors, however, were found significantly more often in the WP group of node-positive patients than in the SP group of node-negative patients.

Recurrence was identified for 20 patients (23.8%) in the entire group, of whom 14 have died of disease. The follow-up time of the 70 living patients ranged from 12.3 to 122 months (median, 58.5 months) after surgery. Of these 70 patients, three were lost to follow-up within 2 years; one with recurrence and two without evidence of recurrence. In the node-negative group, recurrence was identified in three patients (7.1%) between 6.5 and 12.5 months after surgery. All three recurrences were intrapelvic recurrence: two in-field recurrences at the lateral or central region and one out-field recurrence at the common iliac node. The patient presenting out-field recurrence had T1b1 disease with a risk factor of deep stromal invasion. In the node-positive group, recurrence was identified for 17 patients (40.4%) between 2.0 and 75.0 months after surgery; 13 within a year and four after 2 years. Of the 17 recurrences, four were intrapelvic recurrence (23.5%), 11 were extrapelvic (64.7%), and two were vaginal (11.8%). The site of intrapelvic recurrence included the pelvic node ($n=1$) and the lateral or central pericervical regions ($n=3$). The site of extrapelvic recurrence included the para-aortic node ($n=3$), the supraclavicular node ($n=2$), distant organs such as skin and bone ($n=5$), and the ovary, which had been transposed outside the treatment field ($n=1$). The two vaginal recurrences appeared at the lower third as out-field recurrence, and were successfully treated by interstitial radiotherapy. Therefore, vaginal recurrence was excluded from the analysis of PCR.

The PCR, DCR, and OSR according to the field type and the pathologic T category (T1 vs. T2) were shown in Table 2 as a 5-year rate. The DCR (Fig. 3) and OSR were significantly higher for the node-negative group than for the node-positive group. The DCR was also significantly higher for the T1 group than for the T2 group. The PCR, however, did not differ between the node-negative group and the node-positive group, even when the transposed-ovary recurrence was excluded (Fig. 4).

Discussion

The utility of postoperative RT for cervical cancer remains controversial[2,4,11,16,17]. The benefits of postoperative RT depend on the surgical findings: whether intrapelvic or extrapelvic microscopic residual disease that will cause recurrence exists. The probability of residual disease will naturally be lower for stage I disease than for stage II disease. Also, the probability will be lower under certain more inclusive indication criteria of postoperative RT (e.g. > 1/3 stromal invasion) than under less inclusive indication criteria (e.g. ≥ 2/3 stromal invasion). When probability of residual disease is low, the benefit of postoperative RT will appear only modestly as a group, or even may be offset by adverse effects of treatment[14,16,18]. Also, if diseases exist outside the RT field, overall disease control will not be assured.

Table 2. Five-year rates (%) of disease-control rate and survival rate according to nodal status and T category[a]

	PCR	*P*-value	DCR	*P*-value	OSR	*P*-value
Entire group ($n=84$)	91.6		77.1		81.3	
Nodal status						
Negative ($n=42$)	92.8	0.652	92.8	0.0005	95.1	0.005
Positive ($n=42$)	90.3		61.2		68.7	
Pathologic T category						
T1 ($n=50$)	91.9	0.882	86.0	0.013	85.2	0.467
T2 ($n=34$)	91.1		63.9		76.6	

[a]PCR: pelvic-control rate, DCR: overall disease-control rate, OSR: overall survival rate.

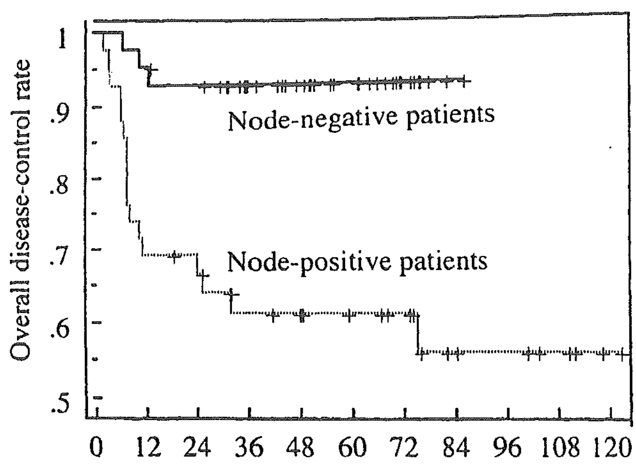

Fig. 3. The overall disease-control rate for node-negative patients treated by a small pelvic field ($n = 42$) and for node-positive patients treated by a whole pelvic field ($n = 42$).

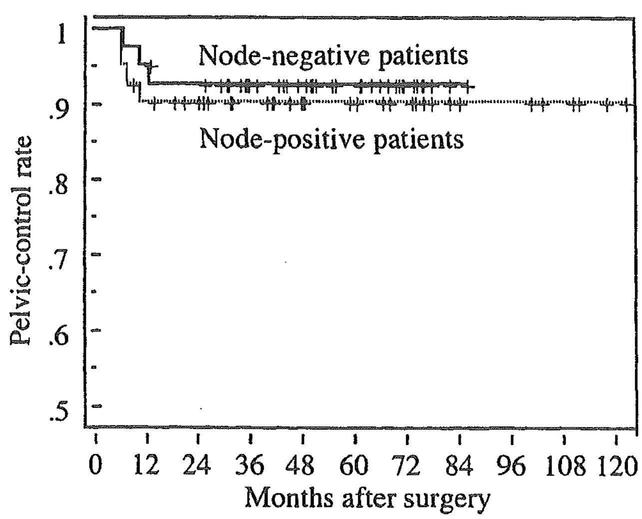

Fig. 4. The pelvic-control rate for node-negative patients treated by a small pelvic field ($n = 42$) and for node-positive patients treated by a whole pelvic field ($n = 42$).

Therefore, thorough analysis of pathologic findings is of great importance in verifying the effectiveness of postoperative RT.

To estimate the probability of postoperative recurrence in node-negative patients, a large-scale study that could test the significance of each individual risk factor would be useful. A report from a Gynecologic Oncology Group study showed that 84 of 545 (15.4%) patients with node-negative, stage IB squamous cell carcinoma treated by surgery alone experienced recurrence; the site of recurrence was not listed[1]. In that prior group study, three risk factors, stromal invasion, clinical tumor size, and lymph-vascular space invasion, were examined, and relative risk for each risk factor was estimated by a proportional hazard model. In an analysis of a subset of 201 high-risk patients with node-negative, stage IB or II disease, Lai *et al.* found that the 5-year RFR was 63.3% without postoperative RT and 84.3% with postoperative RT ($P = 0.015$)[9]. These 201 high-risk patients were identified by relative-risk scores estimated by a multivariate regression analysis of five risk factors: 1) clinical stage II plus stromal invasion (>2/3 thickness) plus DNA index (> 1.3); 2) stromal invasion of full thickness; 3) parametrial extension; 4) large tumor size (>4 cm); and 5) positive vaginal margin. In their study, however, nonsquamous cell carcinomas were also included, and the site of recurrence was not noted. Snijders-Keilholz *et al.* reported 12 recurrences in 156 (7.7%) patients with node-negative, stage I or IIA disease treated by surgery alone, and all the recurrences were intrapelvic[19]. Of the 156 patients, 69.2% had squamous cell carcinoma, 3.2% had a large-sized tumor (>40 mm), and 3.3% showed deep invasion (>15 mm). According to the results of these representative studies, node-negative stage I and II diseases are likely to recur without postoperative RT in a range from 8% to 37% depending on the histologic type, stage, risk factors concerned, and postoperative RT criteria.

In our present study, PCR was almost satisfactorily high for both the node-negative and node-positive groups. This implies that postoperative RT was quite effective in sterilization of the intrapelvic residual disease. The probability of intrapelvic residual disease would have been no less than the rates of recurrence cited above because our patient series included those with stage IIB disease, which was found in 7% of the node-negative group and 45% of the node-positive group. In addition, the patients with compromised surgical margin accounted for 12% of the node-negative group and 24% of the node-positive group. Therefore, we consider postoperative RT beneficial in pelvic disease control.

The DCR was identical to the PCR for the node-negative group, whereas the DCR was substantially lower than the PCR for the node-positive group. In addition, our DCR (92.8%) for the node-negative group was consistent with the previously reported DCRs or disease-free survival rates (range, 83% –92%)[7–9,11,12] for the node-negative patients treated with a WP field. This implies that node-negative status strongly suggests that the disease be localized. Kridelka *et al.*[20], who pioneered in the use of the SP field, reported that only one of 25 (4%) patients with node-negative, stage IB disease treated with the SP field experienced recurrence both intrapelvically and extrapelvically. In addition, 58 of 141 (41%) patients with comparable risk factors treated by surgery alone experienced recurrence. Their risk factors included clinical tumor size, depth of stromal invasion, and lymph-vascular space invasion, and the factors were scored individually under the scoring system proposed by Delgado[1].

The DCR or OSR for node-negative patients treated with an SP field and that for node-positive patients treated with a WP field are both no way inferior to those conducted by recent studies, in which a WP field was customarily used. Yeh *et al.*[11] reported that 5-year disease-free survival and OSR were 81% and 83% for node-negative patients and 53% and 57% for node-positive patients, respectively, after post-operative RT for stage IB-IIA diseases. Uno *et al.*[12] reported that 5-year OSR was 89% for node-negative patients and 62% for node-positive patients after post-operative RT for stage IB-IIB diseases. That these rates were almost identical to ours suggests that use of an SP field for node-negative patients is adequate from the viewpoint of survival.

Although study is confined to the small-scale studies by Kridelka[20] and our current effort, the use of an SP field for high risk, node-negative patients may be justified from the viewpoint of pelvic disease control. One of our patients treated by the SP field, however, developed intrapelvic, out-field lymph node metastasis. It is not known with this patient whether the pathologic examination on nodal status had not been thorough or whether an unexpected course of metastasis had occurred. The adequacy of using a reduced field must be proven carefully by a large-scale study that directly compares node-negative patients treated with an SP field with those patients treated with a WP field. When the adequacy of a SP field is proven, the next step will be the use of a reasonably reduced field that covers the pericervical regions only for patients without parametrial extension that extends lateral to lymphatic channels. Exclusion of the lymphatic channels from the radiation field could avoid the induction of leg edema.

We are currently reviewing a possible difference in treatment toxicity between the two groups of this study. Preliminary results show that severe late toxicity was rare in both groups. Our new study, now underway, may show a subjective benefit of using an SP field instead of the WP field in relation to reducing the frequency and severity of acute adverse effects such as lethargy, appetite loss, and diarrhea. Even if the difference is not clearly shown, use of an SP field ensures reduction of the normal tissue volume unnecessarily treated by RT.

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Clinical Evaluation Using Magnetic Resonance Imaging for Patients With Stage III Cervical Carcinoma Treated by Radiation Alone in Multicenter Analysis

Its Usefulness and Limitations in Clinical Practice

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Abstract: To evaluate the ability of magnetic resonance imaging (MRI) to predict the clinical outcome, we perform retrospective multicenter analysis of patients with stage III disease treated with radiation alone. From three institutions, 80 patients with stage III disease diagnosed with MRI were entered in the study. Seventy-eight patients received intracavitary brachytherapy with external beam radiotherapy. Univariate and multivariate analyses were performed to identify the prognostic factors for overall survival (OAS), disease-free survival (DFS), pelvic control (PC), and distant metastasis-free survival (DMFS). The 5-year OAS, DFS, PC, and DMFS rates were 59.5%, 48.7, 74.2%, and 62.5%, respectively. Bilateral pelvic fixation to the pelvis ($p = 0.001$) and patient age 50 years or less ($p < 0.0001$) were significant adverse factors for OAS. As a function of DFS, these were positive lymph nodes ($p = 0.02$), bilateral fixation to the pelvis ($p = 0.03$), and younger patient age ($p < 0.0001$), respectively. Patient age 50 years or less proved to be the only significantly unfavorable factor for PC ($p < 0.0001$). Larger size/volume ($p < 0.05$), positive lymph nodes ($p = 0.03$), bilateral pelvic disease ($p = 0.02$), and younger patient age ($p = 0.004$) were significantly adverse factors for DMFS. Using multivariate analysis, patient age 50 years or less, disease with bilateral fixation, and calculated volume more than 100 ml proved to be significantly adverse factors for OAS and DFS. In the analysis of PC, only patient age 50 years or less was a significantly adverse factor ($p = 0.0014$, relative risk [RR] = 14.93). Bilateral fixation to the pelvis ($p = 0.0055$, RR = 4.032), positive lymph nodes ($p = 0.0494$, RR = 2.637), and large calculated volume (>100 ml; $p = 0.0057$, RR = 4.831) proved to be significantly adverse factors for DMFS. For patients with stage III disease, size/volume and lymph node status derived from MRI showed a significant correlation with the development of distant metastasis, but failed to predict locoregional control. In addition, size/volume analysis showed no apparent relationship with disease-free survival. For patients with stage III disease, MRI may provide beneficial information predicting distant metastasis, but not for local control.

Key Words: cervical cancer, radiation therapy, MRI, tumor volume, pelvic fixation

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Magnetic resonance imaging (MRI) offers promising benefits in the management of cervical carcinoma as a function of tumor size,[1–3] and extent to surrounding organs,[3] lymph node metastasis,[4] evaluation of treatment response,[5,6] and the treatment outcomes from radiotherapy.[7–9] From these reports, tumor size,[7,8] and/or lymph node metastasis[7,8] are significant predictive factors of clinical outcomes. In our previous report, classification of size/volume and lymph nodes using MRI was clearly representative for predicting the outcome of patients with stage II disease.[10]

Radiotherapy has played an essential role in the treatment of cervical cancer. Several randomized control trials have shown the significant prolongation of both overall and disease-free survival in groups treated by concurrent chemoradiotherapy compared to those with radiation alone.[11–16] However, these data were chiefly based on those with stage I-II disease, and thus we cannot correctly evaluate the exact benefit from concurrent chemoradiation among patients with more advanced disease.

To improve results of patients with stage III disease, we should define the predictive factors in clinical outcome. We therefore performed a multiinstitutional retrospective analysis of patients with stage III disease treated with radiation alone. Using this analysis, we tried to establish whether objective parameter derived from MRI could predict both local and distant control.

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Our great interest is that disease fixation to the pelvis, which is thought to be a subjective staging criteria factor on Federation of Gynecology and Obstetrics (FIGO), is really meaningful compared to objective size/volume analysis using MRI.

MATERIALS AND METHODS

Patient Selection

This analysis included previously untreated patients with stage III cervical carcinoma who were treated with radiation alone for definitive intent from three institutes: the Aichi Cancer Center, the University of the Ryukyus School of Medicine, and the University of Mie School of Medicine. At the Aichi Cancer Center, chemoradiotherapy has been adopted for patients with stage III disease since 1997, and radiation alone has been the standard treatment policy before 1997. Forty-four patients at the University of Mie School of Medicine and 111 patients at the University of the Ryukyus School of Medicine were registered during the investigation period. Almost half of patients from both institutes received chemoradiotherapy, so they were excluded from this analysis. Finally, 80 patients with stage III disease were entered from the three institutes from 1989 to 1999. The histopathologic diagnosis of all patients was squamous cell carcinoma. Patients with other histopathologic diagnoses were excluded from the present analysis.

Patient age (*t* test; $p > 0.05$) and substage (chi-square test; $p > 0.05$) distribution were not significantly different among the three institutes. Pretreatment workup included history, gynecologic pelvic examination, chest radiograph study, abdominopelvic computed tomography (CT), peripheral blood count, and blood chemistry profiles. Staging workup using the FIGO staging system was determined with the agreement of both a gynecologist and radiation oncologist in each institute. MRI was performed for all patients before the start of radiotherapy. The patient characteristics of each institute are summarized in Table 1.

MRI Imaging Protocol

Immediately before the start of radiotherapy, MRI was performed on all patients. At two institutes (the Aichi Cancer Center and the University of Mie School of Medicine), MRI examinations were obtained on a 1.5-T superconductive scanner (Signa, General Electric Medical Systems, Milwaukee, WI, U.S.A.). At the University of the Ryukyu School of Medicine, 16 patients were imaged with a 0.5-T and 23 patients with a 1.5-T superconductive scanner. The details of the imaging protocol in these institutes were published in another report.[7,10]

Acquired images were judged by at least two radiation oncologists in each institute without knowledge of the clinical findings or treatment outcomes. The images were evaluated according to tumor size/volume and lymph node swelling.

TABLE 1. Patient characteristics

Factors	Total	Aichi Cancer Center	University of the Ryukyus	University of Mie
Patient number	80	30	39	11
Patient age				
Median	70	67.5	68	75.0
Range	30–87	47–84	30–87	61–83
FIGO stage				
IIIA	6	5	1	0
IIIB	74	25	38	11
Fixation to the pelvis (on physical examination)				
Unilateral	50	18	26	6
Bilateral	16	6	6	4
Unknown	14	6	7	1
Hydronephrosis				
Yes	18	11	3	4
No	55	15	33	7
unknown	7	4	3	0
SCC				
median	6.4	7.5	4.9	6.9
range	0.4–169	0.4–169	0.5–153	0.5–47.7

FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma.

Pelvic fixation to the pelvis was excluded from evaluation using MRI. It was defined by only physical examination.

Maximal tumor diameter was measured three-dimensionally based on T2-weighted images: anteroposterior (D_{ap}), lateral (D_l), and craniocaudal (D_{cc}). Tumor size was also calculated as the maximal diameter (D_{max}) among three computed diameters. The MR-derived tumor volume was calculated by the equation ($V = D_{ap} \times D_l \times D_{cc} \times \pi/6$) as an ellipsoid approximation.

Lymph nodes greater than 10 mm in minimum diameter were interpreted as positive nodes.[17]

Radiotherapy

All except two patients received both external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT), whereas the two remaining patients received EBRT alone. The treatment details of both EBRT and ICBT in each institute are summarized in Table 2. EBRT was given using 6-MV to 18-MV photon beams with a daily dose of 1.8 Gy to 2.0 Gy, five times a week. A total dose of 45.6 Gy to 50.4 Gy was delivered to the whole pelvic region. At the Aichi Cancer Center, EBRT was prescribed with a unique technique, namely, "two axial arc therapy using a multileaf collimator."[18] In this manner, the radiation doses to the bladder and rectum were reduced. In other hospitals, EBRT was delivered through anteroposterior parallel opposite portals, after which a center shield was inserted at the initiation of ICBT.

Twenty-seven patients received a radiation boost to the parametrium (bilateral 6, ipsilateral 21), 6 to the pelvic lymph node (bilateral 3, ipsilateral 3), and 6 to central tumor, respectively. The median radiation boost dose was 11.1 Gy, ranging from 2 Gy to 24 Gy. Three patients also received paraaortic nodal irradiation of 46 Gy with prophylactic intent.

Seventy-eight patients were treated with ICBT during the treatment sessions. Twenty-three patients at the Aichi Cancer Center received 2 insertions of a radium^{226} source. Four patients in the Aichi Cancer Center and five at the University of Mie School of Medicine received middle-dose-rate (1–1.5 Gy/h) ICBT using a cesium^{137} source via a remote afterloading system (RALS). Only one patient, from the Aichi Cancer Center, was treated with a combination of both radium^{226} and cesium^{137}. Six patients at the University of Mie School of Medicine and all at the University of the Ryukyus School of Medicine were treated by high-dose-rate RALS-ICBT using an iridium^{192} source.

Follow-up

Patients were followed up by radiation oncologists and gynecologic oncologists at 1-month to 2-month intervals for the first 2 years, and at 3-month to 4-month intervals there-

TABLE 2. Radiotherapy treatment

Factors	Total	Aichi Cancer Center	University of the Ryukyus	University of Mle
External beam radiotherapy				
Beam energy		6 MV	18 MV	10 MV
whole pelvis + parametrial boost dose (Gy)				
Median	50.4	59.3	50	50.4
Range	38–70.2	43.7–69.6	38–60	50.4–70.2
Whole pelvis (Gy)				
Median	40	—	40	30.6
Range	30–40	—	30–40	30.6
Radiation Boost				
Parametrium	27	17	8	2
Pelvic node	6	2	4	0
Local	6	6	0	0
Intracavitary brachytherapy				
Source		LDR	HDR	MDR
Fraction				
Median	3	2	3	4
Range	1–7	1–7	2–4	4–5
Total dose at point A (Gy)				
Median	20	26.0	18.0	25
Range	12–32	17–30	12–24	20–32

HDR, high dose rate; LDR, low dose-rate; MDR, medium dose rate.

after. Local failure was defined as tumor recurrence after complete remission by clinical and/or cytologic examination or persistence/progression after initial treatment. Follow-up examinations included physical and pelvic examinations, abdominopelvic CT, Pap smears, blood counts, and chemistry profiles. Chest radiographs were obtained every year in principle. The schedule for follow-up MRI of the pelvis varied slightly at each institute.

The last follow-up was performed on February 5, 2002. At that time, 41 patients were alive without disease and 10 patients were alive with disease. Only one patient was alive without accurate information on tumor recurrence 21.4 months after the initial treatment. Twenty-three patients died of disease 5.2 to 51.3 months after the initial treatment (median 20.2 months). Five patients died of intercurrent disease without any evidence of recurrent disease. The follow-up period for the 52 survivors ranged from 6.5 to 108.6 months (median 52.3 months).

Statistical Analysis

Overall survival (OAS), disease-free survival (DFS), pelvic control (PC), and distant metastasis–free survival (DMFS) rates were calculated from the beginning of radiotherapy according to the Kaplan-Meier method.[19] DFS was defined with all deaths and recurrences as the event. PC was defined with only local and/or pelvic failure as the events. Vaginal recurrence was defined as local failure. Death and/or recurrence without pelvic failure were not counted as the events in this category. DMFS accounted for all distant metastases as events. Extrapelvic lymph node metastasis was defined as distant metastasis. No deaths and pelvic recurrences without distant metastases were estimated as events.

For univariate and multivariate analysis, patient age, overall treatment time (OTT), serum concentration of SCC-antigen, tumor size, and volume were divided in two groups at several points. Disease substage (IIIA vs. IIIB) was also used in the present analysis. Proportions and means were compared by the chi-square test and the Student t test, respectively. The log-rank test[20] was used to compare survival curves. Cox's proportional-hazards model[21] was used to estimate the relative risk after adjusting for prognostic factors. The final model considered only those variables that were statistically significant at the 10% level in stepwise regression.

RESULTS

Assessment by MRI Examination

Tumor size was recorded on MRI findings. The median (range) diameters of D_{ap}, D_l, D_{cc}, and D_{max} were 38.5 mm (10–105 mm), 46.5 mm (21–86 mm), 50.0 mm (10–100 mm), and 52.0 mm (21–105 mm), respectively. The median tumor volume calculated by MRI was 44.3 ml (range 1.87–472.6 ml). The D_{ap} and D_l of the Aichi Cancer Center were significantly larger than those of the University of the Ryukyus (t test; $p < 0.05$). Linear regression analysis showed a statistically significant correlation within each pair of diameters and the calculated volume ($p < 0.0001$). Therefore, we did not use the two parameters of size and volume in the following multivariate analysis.

Twenty-seven patients were diagnosed with positive lymph node swelling. The status of lymph node swelling is shown on Table 3. The frequency of lymph node swelling was significantly higher in patients with D_{cc} greater than or equal to 60 mm ($p = 0.019$) compared to patients with $D_{cc} <$ 60 mm. The size/volume did not significantly differ within the groups divided by pelvic fixation, patient age, tumor marker, hydronephrosis, and OTT.

Treatment Outcomes and Failure Patterns

For all 80 patients, the 5-year OAS, DFS, PC, and DMFS rates were 59.5% (95% CI = 47.3–71.7%), 48.7% (95% CI = 36.5–60.9%), 74.2% (95% CI % = 63.4–85.0%), and 62.5% (95% CI = 50.0–75.0%), respectively. There were considerable differences regarding the radiation treatment among the three institutes. However, the results acquired from the three institutes were not significantly different ($p > 0.05$). Thus, we thought that the radiation treatment of each institute was equally efficacious, and did not use it in the following analysis.

At last follow-up, local recurrence had developed in 18 patients, of which 3 were accompanied by pelvic nodal failures. Pelvic nodal recurrence developed in 4 patients.

TABLE 3. Clinical findings assessed by magnetic resonance imaging

Factors	Median	Range
Tumor diameter (cm)		
Anteroposterior (D_{ap})	3.9	1.0–10.5
Lateral (D_l)	4.7	2.1–8.6
Craniocaudal (D_{cc})	5.0	1.0–10.0
Maximum diameter (D_{max})	5.2	2.1–10.5
Volume (cm^3)	44.3	1.87–472.6
Pelvic node status		**Number**
Negative		52
Solitary		11
Multiple		11
Unknown		6
Unilateral		14
Bilateral		13
Unknown		1

Volume was calculated as following formula = $D_{ap} \times D_l \times D_{cc} \times \pi/6$.