with or without chemotherapy, at the National Cancer Center Hospital. All tumors were cytologically or histologically confirmed NSCLC. Patients' disease was staged by the tumor-node-metastasis (TNM) staging system (UICC, version 6, 2002). The diagnostic workup included a bone scan, brain scan by computed tomography (CT) or magnetic resonance imaging, CT scan of the chest, and CT or ultrasound imaging of the abdomen. The criteria for inclusion in this study were irradiation with a dose of 60 Gy or more as a part of the initial treatment and a clinical response better than stable disease. After excluding patients with metastatic disease, whose primary tumor was located in the apex of the lung (superior sulcus), and whose post-treatment evaluation was inadequate, the remaining 127 patients served as the subjects of the analysis.

Details of treatment

Radiotherapy

Gross tumor volume (GTV) was defined as the demonstrable extent of the primary tumor and the metastatic lymph nodes, GTVp and GTVn, respectively. GTVn was defined as abnormally enlarged regional lymph nodes measuring over 1.0 cm along their short axis. Clinical target volume (CTV) consisted of the adjacent mediastinum and ipsilateral hilum (CTV of the subclinical nodal region, CTVs) as well as CTVp and CTVn which were assumed to be equal to GTVp and GTVn, respectively. A planning target volume (PTV) margin of 1–1.5 cm was drawn around each CTV.

External-beam radiotherapy with a 6, 10, or 15 MV photon beam was delivered using a linear accelerator. A majority of the patients were treated with anteroposterior opposing fields encompassing CTV to a dose of 40 Gy/20 fractions (2 Gy per fraction, 5 days per week), followed by an off-cord boost to the GTV by oblique opposing fields, to a total dose of 60–68 Gy/30–34 fractions. No attempt was made to encompass the supraclavicular areas in most patients; the supraclavicular areas were treated only electively. Initially, treatment planning was performed by using an X-ray simulator for the anteroposterior fields and a CT-port for the oblique opposing fields, but after the end of 1999, most treatment planning, especially to define the off-cord boost, was performed using a CT-based planning system (FOCUS, Computed Medical Systems).

The dose to the spinal cord was limited to 45–50 Gy. The size of the treatment fields was adjusted so that it did not exceed half of the hemithorax before introducing CT-based planning system, or so that the volume of normal lung tissue receiving a dose over 20 Gy would be less than 40%.

Chemotherapy

Systemic chemotherapy was used in 87 patients (68.5%), and the majority of the patients received platinum-based chemotherapy sequentially or concurrently with the radiation therapy. One of the representative regimens was 2–3 cycles of cisplatin 80 mg/sqm on day 1 and vinorelbine 25 mg/sqm on days 1 and 8 (or vindesine 3 mg/sqm on days 1, 8, and 15) in 21–28 days. The second most common regimen was cisplatin 80 mg/sqm on day 1, vindesine 3 mg/sqm on days 1 and 8, and mitomycin C 8 mg/sqm on day 1, in 21–28 days. The other regimens are summarized in Table 1.

Evaluation

Patients were followed at 4- to 6-week intervals for 6 months after treatment and at 3- to 6-month intervals thereafter. Chest X-ray and laboratory workups were performed at each post-treatment visit. Unless there were changes in the chest X-ray or in symptoms, a CT scan was performed about 2–3 months after the treatment for the assessment of the treatment response, and every 6–12 months thereafter. Follow-up information was obtained from the medical charts and death certificates.

Table 1
Baseline patient characteristics.

Characteristics	Patients	(%)
Median age (yr)	65 (36–83)	
Gender		
Male	106	83
Female	21	17
Performance status (WHO)		
0	12	9
1	109	86
2	6	5
Stage		
I (A/B)	5(1/4)	4
II (A/B)	12(3/9)	9
III (A/B)	110(59/51)	87
Histology		
Adenocarcinoma	64	50
Squamous cell carcinoma	39	31
Large cell carcinoma	4	3
NSCLC (not otherwise specified)	20	16
Chemotherapy (concurrent/sequential)	87(63/24)	69
Chemotherapy regimens		
Cisplatin + vindesine or vinorelbine	48	55
Carboplatin + paclitaxel	12	14
MVP (cisplatin + vindesine + mitomycin)	12	14
Nedaplatin or nedaplatin + paclitaxel	11	13
Others	4	5

When evaluating overall survival, an event was defined as death from any cause. When evaluating progression-free survival, an event was defined as documented tumor progression (loco-regional or distant) or death from any cause. Local or loco-regional failure was judged to have occurred if there was radiographic evidence of progressive disease. Absence of progression of residual disease for more than 6 months following treatment was considered evidence of loco-regional control. A recurrence in supraclavicular nodes was considered regional failure, not an elective nodal failure, because the supraclavicular regions are not routinely included within the radiation fields in our practice. Treatment failure was not always confirmed histologically. Elective nodal failure (ENF) was defined as recurrence in CTVs without evidence of local failure, as the first event or even after distant metastasis.

The adequacy of field borders was assessed in terms of CTVs coverage and PTV margin in patients with loco-regional failure. The failure patterns were analyzed to distinguish in-field recurrence from out-of-field recurrence; "in-field" included CTVs as well as CTVp and CTVn.

The Kaplan–Meier method was used from the start of the treatment to calculate the overall survival and progression-free survival of all the 127 patients.

Results

A total of 127 patients, median age 65 years (range, 36–83), met the criteria for evaluation in this study. The majority of patients had stage IIIA ($n = 59$) or IIIB ($n = 51$) disease. Other baseline characteristics of the patients and details of their treatment are summarized in Table 1.

At a median follow-up time of 50.5 months (range, 14.2–83.0) of the surviving patients, 95 had experienced treatment failure. Median survival time was 23.5 months (range, 4.2–109.7), and median time to progression was 9.0 months (range, 2.2–109.7). The 2-year cumulative survival rate and 2-year progression-free survival rate were 51.4% and 27.6%, respectively. The survival

curves are shown in Fig. 1. Patients with early progressions were excluded because of the criteria for inclusion in this study: a clinical response better than stable disease.

Eighty-seven (69%) patients received chemotherapy concomitantly or sequentially with the radiotherapy. The overall survival time of the patients who received chemotherapy was 21.7 months (range, 7.6–33.9), as opposed to 19.1 months (range, 6.8–32.7) among those who did not receive chemotherapy, and the difference was not statistically significant ($p = 0.10$). There were no statistically significant differences in disease-free survival nor loco-regional control according to whether the patients had received chemotherapy. Concurrent use of chemoradiotherapy did not affect survival among the 87 patients who received chemotherapy (data not shown).

There were 53 patients with a first loco-regional failure, alone ($n = 41$) or with distant metastasis ($n = 12$), and the majority of the failures were in-field ($n = 38$, 72%). Nine (21%) patients had out-of-field recurrences in the form of supraclavicular node metastasis ($n = 5$) or pleural metastasis ($n = 4$), with or without local recurrence. There were no isolated ENFs (Table 2).

Four patients (7%) experienced nodal failure in CTVs simultaneously with local or distant failure. Three of them had received a prophylactic dose of 40 Gy to the CTVs, and the other had inadequate margin of the CTVs field. Other characteristics of these patients are shown in Table 3. There were no "marginal only" failures among in-field failures; all the failures at the field borders were associated with out-of-field failures.

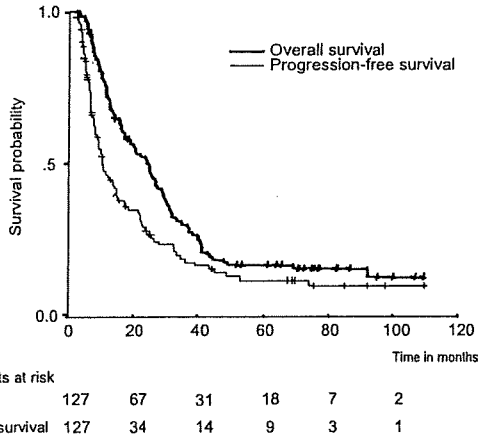

Fig. 1. Overall and progression-free survival curves of all the 127 patients. Patients with early progressions were excluded because of the criteria for inclusion in this study: a clinical response better than stable disease.

Table 2
Details of all the first failures.

Types of event	Patients	%
Loco-regional alone	41	43%
In-field		
CTVpn	30	
CTVpn + CTVs[a]	2	
In-field + out-of-field		
CTVpn + pleural effusion	2	
CTVpn + supraclavicular nodes	2	
Out-of-field		
Supraclavicular nodes	3	
Pleural effusion[b]	2	
Loco-regional + distant	12	13%
In-field + out-of-field		
CTVpn + CTVs	2	
Distant alone	42	44%
All events	95	

[a] One also had concurrent failure in the contralateral hilum.
[b] One also had concurrent supraclavicular recurrence.

Conventional X-ray simulation was performed in 8 (6%) patients, while 70 (55%) had CT-based simulation and remaining 49 (39%) had both (initially with X-ray simulation, followed by CT-based simulation for off-cord boost). A majority ($n = 122$, 96%) of the patients were treated with anteroposterior opposing fields as elective nodal irradiation, followed by oblique opposing fields to the total dose.

ENI was incomplete ($n = 12$) or not performed ($n = 6$) in 18 of the 53 patients with loco-regional failure because of diminished pulmonary function or deteriorated performance status. All the incomplete ENIs were due to insufficient CTVs coverage. In 12 of the 18 patients, the failure was in the tumor volume, in 3 patients it was in the pleura, and in 2 patients it was in the supraclavicular nodes. Only 1 patient had recurrence in both the tumor volume and the uninvolved nodal area.

Discussion

In this series of NSCLC cases treated with conventional fields and doses, the loco-regional failures after radiotherapy mainly occurred in the tumor volumes, and there were no isolated ENFs.

There are several possible reasons for these results. First, micrometastasis in the CTVs may have been controlled by prophylactic delivery of 40 Gy to the region, and depending on the location of the primary tumor, the sites of occult metastasis may often have received additional unintentional radiation doses. Kepka et al. reported an isolated ENF rate of 9% in 185 patients treated with the ENI using 3-dimensional conformal radiotherapy (3D-CRT). Their analysis showed that the ENF occurred more frequently in the regions that received under 40 Gy than in the regions that received higher doses (69% vs. 31%, respectively, $p = 0.04$) [7]. However, despite the same ENF rate of 9% in 1705 patients in the four trials conducted by the Radiation Therapy Oncology Group (RTOG), a retrospective evaluation of in-field progression revealed that neither in-field progression nor survival was affected by the adequacy of ENI [8]. Field adequacy did not have any negative impact on regional control in our series either (Tables 3).

Second, the amount of micrometastasis in unenlarged mediastinal regional nodes may have been small enough to be controlled by chemotherapy, which has been shown to have activity that reduces the incidence of distant micrometastasis in advanced NSCLC. However, the degree of systemic and local efficacy of chemotherapy did not reach statistical significance in our series, probably because of the small number of patients and their heterogeneity (data not shown).

Third, since the failure sites in the majority of patients were distant, they would have died of their disease before the ENF became apparent. As a result, the loco-regional failure rates may have been lower than their true values because we did not investigate regional sites once a patient developed distant metastasis.

The therapeutic significance of treating subclinical nodal regions during and after surgery for NSCLC has been questioned. Some studies have established the presence of considerable microscopic nodal disease in clinically uninvolved lymph nodes [9,10], but the role of mediastinal lymphadenectomy remains controversial and has been limited to the precise staging of the disease [11–13]. A study by Izbicki et al. which compared systemic mediastinal lymphadenectomy with mediastinal lymph node sampling showed that radical systemic mediastinal lymphadenectomy had no effect on the disease-free or overall survival of patients with limited nodal involvement [13,14]. The role of adjuvant radiotherapy after complete resection also remains unclear [15–17]. A systemic

Table 3
Patients with CTVs failure.

	Patient #1	Patient #2	Patient #3	Patient #4
Age (yr)/Sex	45/Female	74/Female	61/Male	78/Male
Reason for inoperability	Unresectable	Unresectable	Decreased pulmonary function	Unresectable, age
Stage	IIIA	IIIA	IIB	IIIB
Primary location	Left lower lobe	Right upper lobe	Right lower lobe	Left upper lobe
Histology	Adenocarcinoma	Adenocarcinoma	Squamous cell carcinoma	Adenocarcinoma
Chemotherapy	Yes	Yes	No	No
Response	Partial response	Partial response	Partial response	Partial response
Site of first failure	Distant and loco-regional	Distant and loco-regional	Loco-regional	Loco-regional
Field border adequacy	Yes	Yes	No	Yes
Dose to CTVs failure	40	40	0	40
Death	No	No	Yes	No

review and meta-analysis [18] showed that postoperative radiotherapy was detrimental to patients with early NSCLC, although there may have been some efficacy in patients with N2 tumors. These arguments also raise questions about the clear benefit of ENI in regard to survival.

In-field loco-regional failure was a major site of failure in the current study: all the recurrences in the CTVs were associated with failure in the gross tumor volume. Thus, more intensive treatment strategies are needed to enhance loco-regional control without sacrificing safety. One possible strategy is to reduce the ENI field in regard to the patients' risk factors while escalating the total dose. Such an attempt has already been made in regard to surgery: Asamura et al. retrospectively reviewed the prevalence of lymph node metastasis with respect to the location of the primary tumor or other characteristics to decide on the optimal lobe-specific extent of systematic lymph node dissection for NSCLC [19,20]. By using such predictors, including the location of the primary tumor, histology, or nodal stage [21–24], it is possible to identify the nodal areas at risk and to optimize the extent of ENI in radiation therapy as well. On the other hand, more precise diagnosis by novel technology, such as positron emission tomography [25], may enable the omission of ENI and avoid unnecessary irradiation to areas at low risk for subclinical disease.

In terms of the technical feasibility of dose escalation, Grills et al. found that intensity-modulated radiation therapy without ENI for NSCLC increased the deliverable mean target dose in node-positive patients by 25–30% over 3D-CRT and by 130–140% over traditional ENI [26].

Because omitting ENI is likely to leave microscopic disease untreated, there is concern that it may result in increased failure in these areas. However, the preliminary results of dose escalation trials have shown that isolated ENF outside the irradiated volume occurred in fewer than 6% of the cases and that omission of ENI did not seem to sacrifice outcome [2–5,27]. There is insufficient evidence to support the use of ENI for any patient with localized NSCLC (Stages I–III), irrespective of whether chemotherapy is administered [28]. There has been only one randomized trial that compared high-dose thoracic radiotherapy without ENI and standard dose radiotherapy with ENI, and it showed a survival benefit of high-dose thoracic radiotherapy without ENI [29]. One possible explanation for this finding is that incidental doses to elective nodal areas may contribute to the eradication of the subclinical disease. The pattern of ENF according to nodal regions was described by Rosenzweig et al., who implemented the use of involved-field radiation therapy with dose escalation in 524 patients [6]. Since the majority of the 42 ENFs that were observed occurred in the areas that received less than 45 Gy, the incidental doses to elective nodal areas may have been substantial despite the attempt not to treat these regions in their study. In addition, Zhao et al. reported that involved-field radiation therapy with a dose escalated to 70 Gy delivered a considerable dose to CTVs, and when the primary tumor was large or centrally located, the percentages of CTVs in the lower paratracheal region, subcarinal region and ipsilateral hilar region receiving over 40 Gy were 33%, 39%, and 98%, respectively [30].

Because of the retrospective nature of our study, no conclusions about the value of ENI for NSCLC can be drawn. However, the finding that in-field loco-regional failure, as well as distant metastasis, was a major type of failure with the standard field and dose of thoracic radiotherapy confirmed the need for more intensive treatment.

Further investigation to verify the true significance of ENI or to identify best candidates for ENI is necessary before it is abandoned in the context of dose escalation.

Conclusion

The loco-regional failures after radiotherapy in this series of NSCLC cases treated with conventional fields and doses mainly occurred in the tumor volumes, and there were no isolated ENFs. The results confirmed the need for more intense treatment to improve local control.

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Gender Difference in Treatment Outcomes in Patients with Stage III Non-small Cell Lung Cancer Receiving Concurrent Chemoradiotherapy

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Objective: To identify any gender differences in the outcomes of concurrent platinum-based chemotherapy and thoracic radiotherapy for unresectable stage III non-small cell lung cancer (NSCLC).
Methods: A comparative retrospective review of the clinical characteristics and treatment outcomes between female and male NSCLC patients receiving chemoradiotherapy.
Results: Of a total of 204 patients, 44 (22%) were females and 160 (78%) were males. There was no difference in age, body weight loss, performance status or disease stage between the sexes, whereas never-smokers and adenocarcinoma were more common in female patients (55% vs. 3%, $P < 0.001$, and 73% vs. 55%, $P = 0.034$, respectively). Full cycles of chemotherapy and radiotherapy at a total dose of 60 Gy were administered to ~70% and >80% of the patients, respectively, of both sexes. Grade 3–4 neutropenia was observed in 64% of the female patients and 63% of the male patients. Severe esophagitis was encountered in <10% of the patients, irrespective of the sex. The response rate was higher in the female than in the male patients (93% vs. 79%, $P = 0.028$), but the median progression-free survival did not differ between the sexes. The median survival time in the female and male patients was 22.3 and 24.3 months, respectively ($P = 0.64$).
Conclusions: This study failed to show any gender differences in the survival or toxicity among patients treated by concurrent chemoradiotherapy. These results contrast with the better survival in female patients undergoing surgery for localized disease or chemotherapy for metastatic disease.

Key words: gender – female – non-small cell lung cancer – chemotherapy – radiotherapy

INTRODUCTION

Lung cancer in women differs from that in men with respect to its incidence, association with smoking, and histological distribution (1). Several epidemiological studies have shown that female smokers have a 1.5- to 3-fold higher risk of developing lung cancer than male smokers, suggesting that women may have an increased susceptibility to the carcinogens in tobacco. Never-smokers with lung cancer are more likely to be female than male, and in East Asian countries, as high as 70% of the women diagnosed with lung cancer have never smoked in their lives. Women are more likely to develop adenocarcinoma than squamous cell carcinoma, the latter being more common in men. This difference cannot be explained fully by differences in the smoking patterns, and potentially suggests basic differences in the etiology of lung cancer between the sexes (1).

Prospective cohort studies and a large population-based study have consistently shown that female gender is a favorable prognostic factor in patients with non-small cell lung cancer (NSCLC). These studies, however, included patients

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with all stages of cancer, and the therapies administered are not specified (2–4). The existence of a gender difference in survival remains controversial among patients with locally advanced NSCLC receiving radiation-based treatment. Some studies have shown better survival in females than in males (5–7), whereas others have shown no difference in survival between the sexes (8,9). Many patients in these studies, however, received radiotherapy alone, which is no longer the standard treatment for locally advanced disease. Furthermore, all but one of these studies included patients with stage I–II disease who were considered unsuitable for surgical treatment because of poor general condition. One study that addressed gender differences in unresectable stage III NSCLC patients treated by chemoradiotherapy showed a median survival time in women of 19.7 months and in men of 21.7 months ($P = 0.26$) (10). The objectives of this study were to compare the outcomes of concurrent chemoradiotherapy between female and male patients with stage III NSCLC.

PATIENTS AND METHODS

Study Population

Patients with unresectable stage III NSCLC who underwent concurrent platinum-based chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1994 and 2005 were eligible for this study. A total of 204 patients were identified. Patients treated by sequential chemotherapy and thoracic radiotherapy were excluded from this study, because we consider that the standard of care for unresectable stage III NSCLC without effusion is concurrent chemoradiotherapy, and sequential treatment is only given to patients in poor general condition or those with tumors too large for radiotherapy initially, which are expected to shrink sufficiently for radiotherapy after chemotherapy. All patients underwent a systematic pre-treatment evaluation and standardized staging procedures, which included physical examination, chest X-rays, computed tomographic (CT) scans of the chest and abdomen, CT or magnetic resonance imaging of the brain, and bone scintigraphy. Chemotherapy consisted of cisplatin combined with either vinorelbine ($n = 125$), vindesine with or without mitomycin ($n = 46$), or other drugs ($n = 6$) repeated every 4 weeks, carboplatin and docetaxel ($n = 10$) administered weekly, and nedaplatin and paclitaxel administered every 4 weeks ($n = 17$).

A retrospective review of the medical charts of the patients was conducted to determine the gender, age, smoking history, body weight loss, performance status, clinical stage, histology, success of treatment delivery, incidence/severity of hematological toxicity and esophagitis, tumor responses, and survival parameters. The histological classification of the tumor was based on the criteria of the World Health Organization (11). Toxicity was graded according to the Common Terminology Criteria for Adverse Events v3.0. Objective tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (12).

Statistical Methods

The demographic, clinical and histopathologic characteristics were compared between the genders. The χ^2 and Mann–Whitney tests were used to evaluate the differences in the categorical and continuous variables, respectively. Overall survival was measured from the start of chemotherapy to death from any cause. For progression-free survival (PFS), both the first evidence of disease progression and death from any cause were counted as an event. A patient who did not develop any event at the last follow-up was censored at that time. Survival curves were calculated according to the Kaplan–Meier method. Cox's proportional hazard models were used to adjust for potential confounding factors such as tumor stage and performance status (13). The significance of P value was set to be <0.05. All of the above-mentioned analyses were performed using the Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Patient Demographics

Of the 204 patients, 44 (22%) were females and 160 (78%) were males (Table 1). There were no differences in age, body weight loss or performance status between the sexes, whereas never-smokers were more common among female patients (55% vs. 3%, $P < 0.001$). Adenocarcinoma accounted for the main histological type in both sexes, but was more common in female patients (73% vs. 55%, $P = 0.034$). No difference in the distribution of the clinical stage was noted between the sexes.

Treatment Delivery

The delivery of chemoradiotherapy was good in both sexes. Three to four cycles of chemotherapy were administered in 68% of the female patients and 69% of the male patients. A total radiation dose of 60 Gy was given to 89% of the female patients and 86% of the male patients.

Toxicities

Grade 3–4 neutropenia was observed in 64% of the female patients and 63% of the male patients (Table 2). The frequency of febrile neutropenia was also the same between the sexes. Severe esophagitis was encountered in <10% of the patients, irrespective of the sex.

Treatment after Recurrence

The use of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) was evaluated in

43 of the 44 female patients and 153 of the 160 male patients. Gefitinib was given to 7 female and 25 male patients, and erlotinib to 1 female and 1 male patient. Thus, in all, EGFR-TKIs were given to 8 (18.2%) female and 26 (16.3%) male patients.

Table 1. Patient characteristics.

Characteristics	Female ($n = 44$)		Male ($n = 160$)		P value
	N	%	N	%	
Age					
Median (range)	57 (29–74)		58 (35–78)		0.28
Smoking history					
Never	24	55	5	3	<0.001
Former	5	11	77	48	
Current	15	34	78	49	
Body weight loss					
≤4.9%	36	82	126	79	0.66
≥5.0%	8	18	34	21	
Performance status					
0	12	27	51	32	0.62
1	32	73	107	67	
2	0		2	1	
Histology					
Adenocarcinoma	32	73	88	55	0.034
Non-adenocarcinoma	12	27	72	45	
Stage					
IIIA	17	39	69	43	0.53
IIIB	27	61	91	57	
Period					
1994–99	17	39	47	29	0.24
2000–05	27	61	113	71	

Table 2. Grade 3–4 toxicity

Toxicity	Grade	Female ($n = 44$)		Male ($n = 160$)		P value
		N	%	N	%	
Leukopenia	3	23	52	79	49	0.44
	4	9	21	33	21	
Neutropenia	3	13	30	49	31	0.19
	4	15	34	51	32	
Thrombocytopenia	3	1	2	5	3	0.97
	4	0		1	1	
Febrile neutropenia	3	9	21	37	23	0.59
	4	1	2	1	1	
Esophagitis	3	2	5	14	9	0.79

Response and Survival

There were 3 patients showing complete response (CR), 38 showing partial response (PR) and 2 showing stable disease (SD) among the 43 female patients evaluable for response, and 10 patients showing CR, 116 showing PR, 24 showing SD and 7 showing progressive disease among the 157 male patients evaluable for response. The response rate was higher in the female than in the male patients (93% vs. 79%, $P = 0.028$). Disease progression was noted in 36 of the 44 (82%) female patients and 131 of the 160 (82%) male patients. The median PFS did not differ significantly between the sexes: 9.2 months in the females and 9.7 months in the males ($P = 0.67$, Fig. 1). The median survival time in the female and male patients was 22.3 and 24.3 months, respectively ($P = 0.64$, Fig. 2). Survival analyses in subgroups showed the

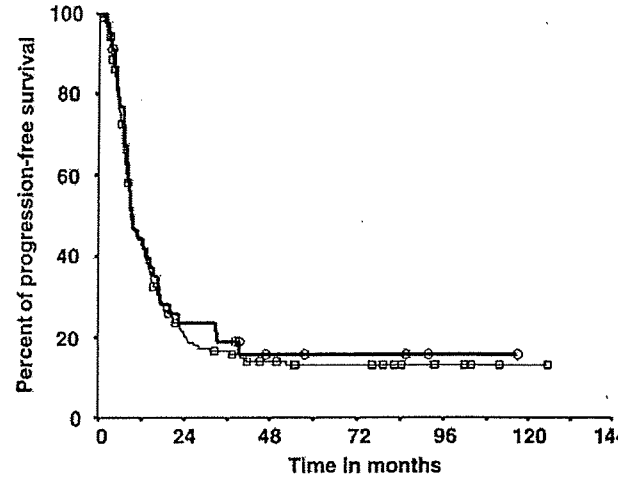

Figure 1. Progression-free survival by sex. Thick line, females; thin line, males.

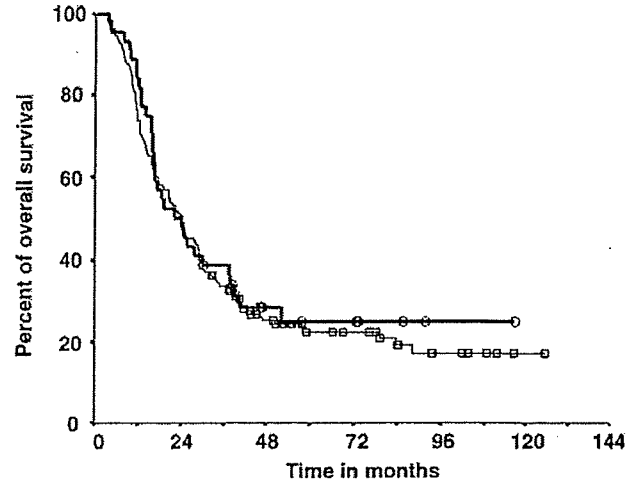

Figure 2. Overall survival by sex. Thick line, females; thin line, males.

Table 3. Factors associated with overall survival

Variables	Hazard ratio (95% confidence interval)	
	Univariate analyses	Multivariate analyses
Age	1.01 (0.99–1.03)	—
Sex		
Female	1	1
Male	1.10 (0.74–1.62)	1.16 (0.71–1.90)
Smoking habit		
No	1	1
Yes	1.00 (0.63–1.59)	0.75 (0.41–1.36)
Body weight loss		
≤4.9%	1	—
≥5.0%	1.19 (0.81–1.75)	—
Performance status		
0	1	1
1–2	1.59 (1.11–2.28)	1.44 (0.97–2.15)
Histology		
Adenocarcinoma	1	1
Non-adenocarcinoma	0.76 (0.53–1.10)	0.74 (0.51–1.08)
Stage		
IIIA	1	1
IIIB	0.96 (0.70–1.32)	0.79 (0.56–1.11)
Period		
1994–99	1	1
2000–05	0.62 (0.45–0.86)	0.65 (0.45–0.92)

absence of any gender differences either among patients with adenocarcinoma or among those with non-adenocarcinoma. Similarly, no gender differences were observed either among smokers or among never-smokers. Univariate Cox's proportional hazard analyses showed that the performance status and treatment period were significantly associated with the survival (Table 3). After adjustment for the smoking history and histological type, the gender had no impact on the overall survival (Table 3).

DISCUSSION

Although prospective cohort studies and a population-based study have reported better survival in women than in men with NSCLC, these results may be biased by potential confounding factors, because these studies included highly heterogeneous patients in terms of the stage, therapy, co-morbidities and other prognostic factors (2–4). Thus, whether there is any significant difference in survival between male and female patients receiving radiation-based treatment remained controversial, and this study failed to show any significant gender difference in the survival in NSCLC patients receiving concurrent chemoradiotherapy.

Several previous studies have suggested a better prognosis in female than in male NSCLC patients treated by surgery (2,14–18), whereas our results were inconsistent with this suggestion. This may be attributable to the difference in the distribution of the disease stage (pathological stages I, II and III) between these studies and our study, including pathological stages I, II and III. The magnitude of the gender difference in survival has been suggested to vary with the disease stage. Some studies have shown a diminishing gender difference as the disease stage advanced from stages I to III, with disappearance of the gender difference among patients with stage III disease (14,15), whereas others have shown relatively constant gender difference through all the disease stages (2,16,17). A study on the gender difference in the survival in surgically resected NSCLC patients showed a better overall survival in women than men, but no significant difference in the cancer-specific survival between the two sexes (18). These results suggest that the gender difference in survival in NSCLC patients undergoing curative surgery, especially patients with early-stage disease, can be explained by the mortality related to diseases other than lung cancer.

Among local or locally advanced NSCLC patients receiving radiotherapy-based treatment, the gender difference in survival has been controversial (5–9), but potential confounding factors in these studies prevent an accurate interpretation of the results. In these studies, as high as 30% of the patients had medically inoperable stage I–II disease and 3–22% of the patients had a performance status of 2. In addition, 36–100% of patients were treated by thoracic radiation alone, whereas the others also received some form of chemotherapy as part of the treatment. Neither the current study nor another previous study showed any gender difference in the survival (10). The patients in both of these studies were limited to stage III NSCLC patients with a performance status of 0–1 who were treated by concurrent chemoradiotherapy.

Several studies have been conducted on the gender differences in survival among patients with stage IIIB–IV disease treated by systemic chemotherapy (19–24). Of these, many showed a better survival in female patients than in male patients (19–22), but the causes of this gender difference in survival remain unknown. Our previous study also showed a better survival in female patients, which was explained partly by the large number of female patients (56% vs. 44%) receiving gefitinib, and the 4-fold longer duration of gefitinib treatment (144 vs. 35 days) in these patients (25). In contrast, only 18% of the female patients and 16% of the male patients received EGFR-TKIs in this study. Thus, treatment with EGFR-TKIs had little influence on the patient survival in this study.

Clear difference in the frequency of adenocarcinoma and smoking history between female and male patients has been reported repeatedly, and this study also showed that adenocarcinoma and never-smokers were more common among the female patients. Thus, it would be reasonable to think that differences in the tumor cell characteristics between the

female and male patients may be responsible for the difference in survival between the two sexes. However, survival analyses conducted separately in subgroups among patients with adenocarcinoma and those with non-adenocarcinoma, or among smokers and non-smokers have failed to reveal any gender differences in the survival among any subgroups. In addition, a multivariate analysis showed no difference in survival between the sexes after adjustment for the tumor histology and smoking history.

The threshold for drug toxicity may also differ between women and men. In general, chemotherapy-related toxicity is reported to be slightly more severe in women, and to the best of our knowledge, there are no reports on the gender difference in radiation-related toxicity. This study showed no difference in the severity of esophagitis or hematological toxicity between the two sexes. We did not examine pulmonary toxicity in this study, because our previous large retrospective study showed no difference in the incidence or grade of pulmonary toxicity between the sexes (26).

Among several limitations of this study, the most important is the small sample size that made it difficult to draw definitive conclusions. Indeed, small difference in survival between the sexes, if any, could not be detected in this small number of patients. It is difficult, however, to expand the study population without an increase in its heterogeneity. A population-based study with >20 000 patients, for example, included patients with all stages of lung cancer, and the therapies administered were not specified. Furthermore, the quality of data on diagnosis and treatment was not uniform (4). Thus, the results of that study may be biased, despite of the huge number of patients. We cannot overlook this problem especially when analyzing stage III NSCLC patients treated with radiation-based treatment, because the quality control of radiotherapy has not been fully developed in Japan, and therefore, indication, methods and outcomes of thoracic radiotherapy may vary among hospitals.

In conclusion, this study failed to reveal any significant differences in the treatment outcomes, including survival and treatment toxicity, between female and male patients with stage III NSCLC receiving concurrent chemoradiotherapy. These results are in sharp contrast to the reported better survival in female patients with localized disease treated by surgery or those with metastatic disease treated by systemic chemotherapy.

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Conflict of interest statement

None declared.

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CLINICAL INVESTIGATION **Cervix**

PROSPECTIVE STUDY OF ALTERNATING CHEMORADIOTHERAPY CONSISTING OF EXTENDED-FIELD DYNAMIC CONFORMATIONAL RADIOTHERAPY AND SYSTEMIC CHEMOTHERAPY USING 5-FU AND NEDAPLATIN FOR PATIENTS IN HIGH-RISK GROUP WITH CERVICAL CARCINOMA

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Purpose: To assess the efficacy of alternating chemoradiotherapy combined with extended-field conformal radiotherapy for patients with high-risk cervical cancer.

Methods and Materials: Patients with previously untreated cervical cancer, with Stage III/IVA disease, or Stage IB/II with high-risk factor (primary tumor diameter ≥50 mm or positive lymph node) were entered into this study. Three cycles of chemotherapy with 3,500 mg/m^2 of 5-fluorouracil (5-FU) and nedaplatin (NDP) were accompanied with pelvic irradiation of 45.6–51.3 Gy in 24–27 fractions over 6 weeks. Prophylactic (36 Gy/20 fractions) or definitive (45–56 Gy) irradiation for para-aortic region was followed by pelvic irradiation.

Results: Between 1998 and 2004, 40 patients were recruited for this protocol study. Eighteen patients from Phase I setting were registered. Twenty-two patients were treated with NDP of 140 mg/m^2 (the recommended dose) in the Phase II segment. Twenty-five patients had T3 disease, and 25 patients had nodal disease including para-aortic involvement ($n = 5$). Overall/progression-free survival rates at 5 years were 78.8 and 66.5%, respectively. The median follow-up time was 61.8 months (25.5–106.7). Hematologic and gastrointestinal Grade 3 or more toxicities were relatively high rate (27.5–45%); however, they were well manageable. Two for bladder toxicity of Grade 3 were noted. Comparing the data from historical control group evaluated by magnetic resonance imaging, alternating chemoradiotherapy revealed a significant favorable factor for survival and disease recurrence in multivariate analysis ($p < 0.05$).

Conclusion: Acquired results from our unique protocol for cervical cancer with high-risk factor were thought to be promising, considering that the majority of our cohort consisted of high-risk population.

Extended field, Alternating chemoradiotherapy, Nedaplatin, Cervical cancer, Conformational radiotherapy.

INTRODUCTION

Standard treatment for patients with advanced-staged cervical carcinoma is now believed to be concurrent chemoradiotherapy. Chemoradiotherapy improves overall survival (OAS) and progression-free survival (PFS), whether or not platinum was used. Absolute benefit was reported as 10% advantage of OAS and 13% of PFS (1). Chemoradiation showed a significant benefit for local recurrence and a suggestion of a benefit for distant recurrence, although this trend was more markedly noted among patients with Stage I-II disease compared with those of Stage III -IVA (2–5). Contents of chemotherapy regimen was varied much, although weekly administration of cisplatin was now widely used because Gynecologic Oncology Group (GOG) 120 could not showed an apparent advantage of addition of 5-fluorouracil (5-FU) compared with single use of cisplatin (2, 6).

Nedaplatin (NDP) is an active agent for cervical carcinoma (7), shown to have treatment effects equivalent to those of the widely used cisplatin but with less renal and gastrointestinal toxicity (8). Its dose-limiting toxicities (DLT) are thrombocytopenia and myelosuppression, and its recommended dose (RD) in Japan is 100 mg/m^2. However, we have reported the possibility of dose escalation of NDP when used in combination with 5-FU before the administration of NDP. In our previous report, the RD of NDP was 150 mg/m^2 (9). Theoretically, the antitumor effect of concurrent administration is

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identical, but the increasing acute toxicity is an important problem. Thus the intensity of both radiotherapy and chemotherapy would be compromised in this setting. Alternating chemoradiotherapy (ALCRT) is a method for resolving this problem; avoiding the concurrent usage of these two modalities may reduce the acute toxicity, allowing the full dose of chemotherapy to be maintained. We have also reported excellent outcomes of ALCRT in nasopharyngeal cancer (10). As with nasopharyngeal cancer, patients with cervical cancer with advanced stage had hazard of metastatic disease progression, so intensity of chemotherapy is thought to be an important issue for patient management.

To investigate the efficacy and feasibility of ALCRT for high-risk cervical carcinoma, we performed a Phase I/II study at our institution.

METHODS AND MATERIALS

Eligibility criteria

Previously untreated patients with histologically diagnosed as squamous cell carcinoma of uterine cervix were entered into this study. Eligible patient was defined as having a high risk factor (Stage I-II; tumor size ≥50 mm or positive pelvic node OR all Stage III-IV disease); good performance status (PS), adequate organ function; age 20–75; and informed consent. Importance of prognostic indicator of magnetic resonance imaging (MRI) has been reported multi-institutional study (11, 12), and we take account for patient selection for this protocol. Patients with lymph node metastasis limited to para-aortic region who were diagnosed by imaging are also included this study.

Before enrollment, each patient underwent complete physical, laboratory, and stage assessments. The laboratory examinations consisted of complete blood count, serum chemistry, 24-h creatinine clearance, and electrocardiography. The staging workup included chest radiography, computed tomography (CT) of the whole abdomen, and pelvic MRI. Lymph nodes measuring 10 mm or more along the long axis on CT or MRI scan was defined as metastatic nodes. Patients were required to have a white blood cell count ≥3,000/μL, platelet count ≥100,000/μL, hemoglobin level ≥10.0 g/dL, normal hepatic (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level <2.5 times the upper normal limit) and renal function (24-h creatinine clearance level ≥60 mL/min), and normal electrocardiogram. Written informed consent was obtained from all patients. The protocol was approved by the institutional review board.

Response and toxicity evaluations

To evaluate responses and toxicity, all patients underwent complete blood count and serum chemistry analysis one to two times per week. The response evaluation was judged 2 months later from last day of whole treatment. Response evaluation was done with physical examination with smear cytology, pelvic MRI scan, and whole-abdominal CT scan.

Magnetic resonance imaging was repeated every 3–4 months for the first 2 years and twice per year thereafter. A CT scan of the whole abdomen was repeated every 6 months. Toxicity was assessed and graded using the National Cancer Institute Common Toxicity Criteria, version 3.0. The grading of late urinary and gastrointestinal toxicities due to radiotherapy was in accordance with the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer toxicity criteria (13). The DLT were defined as Grade 4 hematologic toxicities or any nonhematologic Grade 3 or higher toxicities, except diarrhea, nausea, and vomiting. The chemotherapy dose and schedule modifications for toxicity are shown in Table 1.

Phase I component

The primary end point of the Phase I part of the study was to determine the maximum tolerated dose (MTD) and the RD of NDP for the Phase II segment, when combined with 120-h infusion of 3,500 mg/m^2 5-FU and definitive radiotherapy on an alternating schedule, for patients with cervical cancer with high-risk factors.

Dose escalation scheme

The starting dose of NDP was 100 mg/m^2, as suggested by a previous study (9). Additional increases of 20 mg/m^2 up to the MTD were permitted. According to our previous report, the dose of NDP did not exceed 150 mg/m^2 (9). At least 3 patients were treated at each dose level. The end point to close the study was a DLT if observed in 2 of 3 patients or in 3 of 6 patients at the same dose levels.

Table 1. Chemotherapy and radiotherapy dose and schedule modifications for toxicity

Toxicity	Modifications
Chemotherapy	
Grade 4 leukopenia, granulocytopenia	25% reduction of both nedaplatin and 5-FU
Grade ≥3 thrombocytopenia	25% reduction of both nedaplatin
Grade 2 renal dysfunction	
Grade ≥3 diarrehea	25% reduction of 5-FU
Grade 2 liver dysfunction	
Grade ≥3 liver or renal reaction	Withheld additional chemotherapy
Nonhematologic Grade >3: toxicity, except for nausea/vomiting	Chemotherapy postponed until recovery
Radiotheraphy	
Grade 4 leukopenia, granulocytopenia	Postponed until recovery to Grade 2
Grade 4 thrombocytopenia	Postponed until recovery to Grade 2
Grade 3 leukopenia, granulocytopenia, and infection or Grade 2 fever	Postponed until recovery of infection and fever
Schedule modification	
Chemotherapy was started with a white blood cell count ≥2, 500 μ^{-1}, platelet count ≥100, 000 μ^{-1}, hemoglobin level ≥8.0 g dl^{-1}, total bilirubin ≤2.0 mg/dL serum creatinine ≤1.2 mg/dL, and esophagitis Grade ≤3. If these data did not fulfill the criteria, radiotherapy was continued until these data recovered . As soon as these data improved, the next cycle of chemotherapy should be started, resting radiotherapy between courses of chemotherapy.	

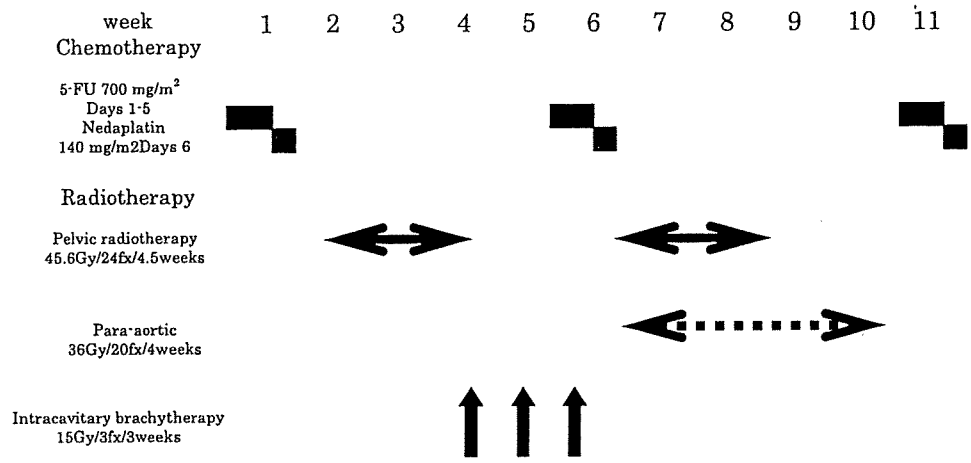

Fig. 1. Treatment scheme of the Phase I/II study of alternating chemoradiotherapy with nedaplatin and 5-FU in patients with advanced cervical carcinoma.

The previous doses before the MTD were considered the RD for the Phase II study.

Phase II component

The primary end point of the Phase II segment of the study was PFS of alternating chemoradiotherapy at the RD. The secondary end points were the OAS and the feasibility of this protocol. The same patient eligibility requirements, treatment schedules, dose and schedule modifications, and response and toxicity criteria as in the Phase I part of the study applied.

Treatment schedule and modifications

Chemotherapy. The treatment scheme is shown in Fig. 1. Prophylactic antiemetics therapy, using a 5-hydroxytryptamine type III receptor blocker and dexamethasone was given to all patients. The details of the administration of chemotherapy have been reported (9, 14). The dose of NDP was elevated to find MTD. MTD was decided to dose limiting toxicities as to Grade 4 of hematologic toxicities and Grade 3 of nonhematologic toxicities excluding diarrhea and nausea/vomiting. After deciding RD, patients were treated with RD of NDP.

Radiotherapy. Radiation therapy using a megavoltage photon beam (6–10 MV) by linear accelerator (CLINAC; Varian Medical Systems) was started 1–2 days after the end of systemic chemotherapy. The gross tumor volume (GTV) was defined as the total volume of the primary tumor evaluated by MRI scan (GTV primary) and the involved lymph nodes (GTV node) assessed by either MRI or abdominopelvic CT scan. A patient with lower vaginal involvement was arranged the adequate inferior margin of radiation field for tumor extent using iodine powder or metallic ring at planning setup. The clinical target volume (CTV) for involved lymph node (CTV node) was defined as the GTV node with 1cm margin in every direction. CTV pelvis was defined as entire uterus and regional pelvic lymph node according to the guidelines of Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer consensus. CTV pan was defined as para-aortic lymph node region located up to upper border of the 12th thoracic spine. In general, CTV pan was included both inferior vena cava and abdominal aorta with 1-cm margin for every direction. The planning treatment volume (PTV) for involved lymph node (PTV node) was defined as the CTV node with a 0.5–1 cm margin. The PTV pelvis and PTV pan was defined as the CTV plus a 0.5–1 cm margin in all directions. Radiotherapy was given with daily 1.9 Gy fractions to 45.6 Gy in 24 fractions for PTV pelvis by biaxial dynamic conformal radiation therapy (11, 12, 15). If patients had a positive pelvic lymph node, they received 51.3 Gy of 27 fractions to PTV pelvis followed by an additional boost dose for PTV node up to a total dose of 57.3 Gy. Patients with positive pelvic lymph node or diagnosed as Stage III or more stage received a prophylactic para-aortic lymph node irradiation of 36 Gy with 20 fractions was planned by dynamic conformal radiotherapy (15). Patients with positive lymph node on para-aortic region receive an additional boost to PTV node up to 54 Gy. Radiotherapy was interrupted during the administration of the second and third cycles of chemotherapy. Intracavitary brachytherapy (ICBT) was accompanied with external beam radiotherapy (EBRT). Both EBRT for PTV primary and ICBT should not be treated in same day. During treatment course, MRI of the pelvis was taken to evaluate response. If primary tumor was thought to shrink to a sufficiently small volume within the high-dose volume of ICBT, brachytherapy was started. All EBRT was planned by radiation treatment planning system FOCUS or XiO (CMS Inc.). Before March 2002, the source of intracavitary brachytherapy was radium, and then was replaced with iridium. High-dose-rate ICBT was delivered using microselectron. The radiation therapy dose and schedule modifications for toxicity are shown in Table 1.

Statistical considerations

The survival time was defined as the period from the start of treatment to death or the last follow-up evaluation, and the PFS was defined as the period from the start of treatment to progression of disease or death, for any reason. The statistical differences between the two groups were assessed with the chi-square test. The OAS and PFS curves were calculated using the Kaplan-Meier method (16). The log–rank test (17) was used to compare survival curves. Cox-proportional hazards model (18) was used for a multivariate analysis.

RESULTS

Characteristics of patients

Between September 1998 and December 2004, 40 patients at the Aichi Cancer Center Hospital, Japan, were enrolled in this Phase I/II study. The patient characteristics of each group are shown in Table 2.

In the Phase I segment, 18 women were enrolled. In the Phase II segment, 22 women were enrolled using RD of NDP.

Phase I study

Dose escalation and toxicity. The principal toxicities observed in the Phase I study are summarized in Table 3. At the first dose level (100 mg/m^2), none of the 3 patients had DLT. At the second dose level (120 mg/m^2), 1 case of Grade 4 thrombocytopenia developed among the 6 patients. This dose level was considered safe, and the dose was increased to the next level. At the third dose level (140 mg/m^2), one case each of Grade 3 liver dysfunction and diarrhea developed among 6 patients. In next dose level (150 mg/m^2), two cases of neutropenia in 3 patients developed, then the MTD was determined to be 150 mg/m^2 and an RD of 140 mg/m^2 was used in the Phase II part.

Completion of therapy. As shown in Table 2, 23 of 40 patients were able to receive three cycles of chemotherapy. Four patients reduced their doses of NDP during the second cycle of chemotherapy. Twenty-three (58%) patients received the third cycle of systemic chemotherapy, but the NDP dose had to be reduced in 4 of these patients. Two patients received only a single cycle of chemotherapy because of toxicities. The 5-FU dose was not reduced in any patients in the Phase II part of the study. Delay or inability to administer the third cycle of chemotherapy was chiefly from hematologic toxicities.

Table 2. Patient characteristics and treatment contents

Factors	Number
Age (y)	54 (34–74)
Performance status	
0	4
1	36
T stage	
1b	
2a	2
2b	10
3a	3
3b	22
N stage	
0	15
I	25
FIGO stage	
I	3
II	11
III	21
IV	5
Maximum tumor size (mm)	61 (35–100)
Radiation theraphy	
EBRT	
Pelvic region (Gy)	53.6 (41.8–64.6)
Paraaortic region	36 (14.4–54)
OTT(days)	51 (34–78)
ICBT	
Source	
Radium	24
Iridium	16
A point dose	23.1 (7.5–27.6)
Fraction	2 (1–4)
Chemotherapy	
Dose of NDP (mg/m^2)	
100–120	9
140	28
150	3
Cycle of chemotherapy	
1	2
2	15
3	23

Table 3. Results of Phase I component

NDP (mg/m^2)	100	120	140	150	Total
Leukopenia	0/3	0/6	0/6	2/3	2/18
Anemia	0/3	0/6	0/6	0/3	0/18
Thrombocytopenia	0/3	1/6	0/6	0/3	1/18
Liver	0/3	0/6	1/6	0/3	1/18
Renal	0/3	0/6	0/6	0/3	0/18
Diarrhea	0/3	0/6	1/6	0/3	1/18
Emesis	0/3	0/6	0/6	0/3	0/18
Vomiting	0/3	0/6	0/6	0/3	0/18
Fever	0/3	0/6	0/6	0/3	0/18
Stomatitis	0/3	0/6	0/6	0/3	0/18
Total	0/3	1/6	2/6	2/3	5/18

A median dose of 53.6 Gy (range, 41.8–64.6 Gy) was administered to pelvic lesion by EBRT. All patients received ICBT using low-dose-rate or high-dose-rate ICBT. The median dose of sum of point A dose of ICBT was 23.1 Gy ranged from 7.5 to 27.6 Gy. All patients could be treated with planned pelvic radiotherapy including ICBT. The median dose of para-aortic region was 36 Gy (range, 14.4–54 Gy). Para-aortic irradiation stopped in 2 patients at 14.4 Gy and 18 Gy because of acute gastrointestinal toxicity. Five patients received an additional radiotherapy to involved para-aortic lymph node with a dose of 46–54 Gy using cone down technique.

Treatment outcomes

Response and survival. The following 22 patients were treated with dose level of RD. Between 1998 and 2004, 65 patients were treated with this protocol, and 40 patients of 65 were evaluated for treatment efficiency. The reasons for exclusion of 25 patients were patient's age, previous treatment before chemoradiotherapy, and refusal of chemotherapy. Thus we evaluated these 40 patients including Phase I study regarding to treatment outcome and feasibility. At the median follow-up of 61.8 months (range, 8.6–106.7 months), 10 patients had died of the disease, 3 were alive with the disease, and 27 were alive without disease.

The OAS and PFS rates at 5 years were 78.8% (95%CI, 65.6–92.1%) and 66.5% (95%CI, 51.4–81.6%), respectively.

Four patients had residual tumor or disease progression at the primary site, and 5 patients had relapses at the pelvic region with or without local failures. Eight patients had distant metastasis during the follow-up period. The OAS and PFS rates were not significantly different between patients received three cycles of chemotherapy and those with one or two cycles ($p > 0.05$).

Table 4. Adverse event of acute adverse event in alternating chemoradiotheraphy with all 40 patients

	1	2	3	4	% of toxicities Grade 3
Leukopenia	4	10	25	1	65
Neutropenia	4	14	14	5	47.5
Anemia	4	21	7	7	35
Thrombocytopenia	12	8	10	8	45
Liver	13	10	3	0	7.5
Renal	10	1	0	0	0
Diarrhea	14	15	9	2	27.5
Emesis	4	19	17	0	42.5
Vomiting	15	25	0	0	0
Fever	0	13	1	0	2.5

Toxicity

The toxicities observed in 40 patients during treatment and follow-up are shown in Table 4. The most common toxicity was leukopenia. Grade 3 or higher leukopenia and granulocytopenia occurred in 26 and 19 patients, respectively. Grade 3 or higher thrombocytopenia and anemia occurred in 18 and 14 patients, respectively. Grade 3 or higher diarrhea occurred in 11 patients. Significant increase of neutropenia and diarrhea was noted in patients with three cycles of chemotherapy compared to those of one or two cycles ($p < 0.05$). There was no treatment-related death. We experienced two cases of Grade 3 of urinary bladder and six Grade 2 of the rectum regarding to late adverse event. No patients developed with Grade 3 or higher of late rectal toxicity. Late toxicity of the rectum and bladder showed no significant difference between patients with three cycles of chemotherapy and those with one to two cycles.

Comparison of historical control group

Between 1986 and 1998, we treated 43 patients with radiotherapy alone who were thought to be eligible for this protocol criteria using staging workup including MRI. During this period, systemic chemotherapy is not generally planned in our institutes; the majority of patients visited during this period were recruited in this cohort. In addition, MRI study was routinely performed to evaluate tumor volumetry in this period. This group (*historical control group*) was compared with the ALCRT group. Patient's characteristics of both groups were summarized in Table 5. Age and radiation dose of the historical control group proved to be significantly higher compared with those of ALCRT ($p < 0.05$). Stage distribution and tumor size did not show a significant difference between the two groups, although tumor size of ALCRT group had a slightly larger than that of the historical control group. ALCRT group showed a tendency for larger ratio of patients with positive lymph node compared with that of the historical control group ($p = 0.07$).

OAS and PFS showed a significant improvement in ALCRT group by univariate analysis. The 5-year OAS rate of ALCRT group is 78.8% (95%CI, 65.6–92.1%) and that of the historical control group is 48.8% (95%CI, 33.9–63.8%; $p = 0.02$, Fig. 2). The 5-year PFS rate of ALCRT group is 66.5% (95%CI, 51.4–81.6%) and that of historical control group is 37.2% (95%CI, 22.8–51.7%; $p = 0.006$, Fig. 3).

Table 5. Patient characteristics of both protocol group and historical control group

Factor	Protocol group	Historical control
Age (median: y)	54*	67
Size (median: mm)	61	55
Pelvic radiation (mean: Gy)	53.6**	59.2
Stage III-IV (%)	65	69.8
Lymph node–positive (%)	62.5***	42.9

* $p < 0.0001$.
** $p = 0.017$.
*** $p = 0.07$.

In multivariate analysis, ALCRT also showed a significant reduction both death and disease progression (Table 6). Hazard ratio of the ALCRT group was 0.639 (95%CI, 0.41–0.96; $p = 0.03$) in OAS and 0.534 (95%CI, 0.35–0.81; $p = 0.002$) in PFS. Late adverse event according to bladder and rectum showed no significant increase in ALCRT group compared with those of historical control group ($p < 0.05$).

DISCUSSION

To the best of our knowledge, this is the first report of successful outcome of chemoradiotherapy using extended-field radiotherapy. The OAS and PFS rates at 5 years were 78.8% (95%CI, 65.6–92.1%) and 66.5% (95%CI, 51.4–81.6%), respectively. Our results of OAS and PFS are thought to be quite comparable to the reported data of concurrent chemoradiotherapy (5, 6, 19) (Table 7). Our protocol has shown acceptable treatment compliance without increasing late toxicities with relatively long follow-up (median, 61.8 months). In addition, our cohort has a higher proportion of both advanced clinical stage and lymph node involvement including para-aortic region compared with reported data (1, 5, 6, 19).

We believe dynamic conformal radiotherapy have a benefit to reduce toxicities especially for chemoradiotherapy setting

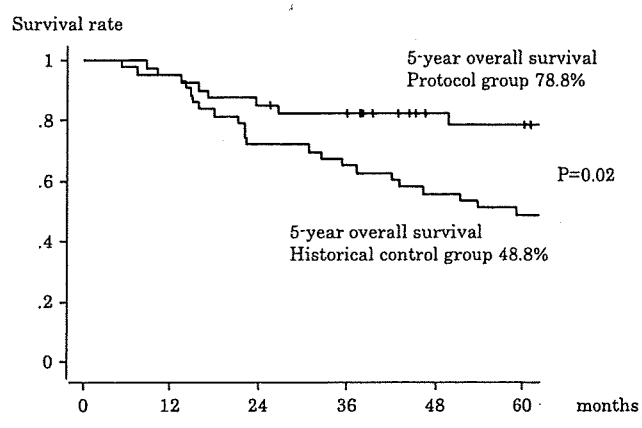

Fig. 2. Overall survival curves of groups of protocol treatment and historical control.

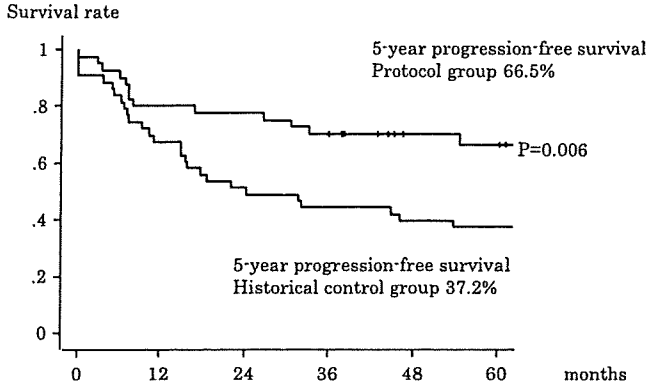

Fig. 3. Progression-free survival curves of groups of protocol treatment and historical control.

with large treatment volume such as extended-field radiotherapy (15, 20, 21). In many reports, researchers used a contiguous field technique for extended field treatment (22–26). This method had an advantage in a short treatment period and an accurate treatment volume. Sequential method such as ours is thought to have a deficit in longer treatment time and would have a potentially loss of disease control. Although patient number was small ($n = 5$), all patients with positive para-aortic disease are well controlled in our protocol. Thus we believe no apparent clinical disadvantage as to sequential radiotherapy for pelvic and para-aortic irradiation. There is another problem of sequential method as to field matching. Both pelvic and para-aortic field should be arranged carefully, because a gap between two fields had a potential risk of underdose or overdose. In this report, we did not experience both regional failure on gap area and late toxicity from excessive dose by overlapping. We also have reported acceptable outcome using sequential EBRT for para-aortic region in definitive and postoperative intent (15, 27). In these reports, para-aortic field was treated with four-field technique (27) or dynamic conformal radiotherapy (15) in sequential setting. In fact, many reports have failed to improve clinical results by simultaneous extended-field chemoradiotherapy (22–24). RTOG 0116 recruited patients with cervical carcinoma and high common iliac or para-aortic metastasis (22). Patients received extended contiguous field radiotherapy up to 54–59.4 Gy with concurrent administration of 40 mg/m^2 of weekly cisplatin. A total of 26 patients were entered, and

Table 6. Mulivariate analysis of several prognostic factor regarding to overall and progression-free survival

	Overall survival		Progression-free survival	
Factor (reference group)	Hazard ratio	p-value	Hazard ratio	p-value
Age (<62 y)	0.922	0.664	0.927	0.684
Stage (I–II)	1.10	0.600	1.073	0.673
Size (<60 mm)	1.10	0.597	1.409	0.049
Lymph node (no)	1.12	0.597	0.857	0.336
Modality (CRT)	0.639	0.031	0.534	0.0024

Table 7. Comparison clinical results of chemoradiotherapy with or without extended-field radiation

Author	Number	5-year survival	Toxicity (Grade 3 or more)
Varia	95	39 (3 y)	37.7
Grigsby	30	29 (4 y)	80
Maltefano	13	69	0
podczaski	33	31	6
Small	26	60 (18 months)	40
Present	40	78	5
chemoradiotherapy without extended field radiotherapy			
GOG85*	177	NS	4
GOG120			
Weekly CDDP	192	70	2.7
CDDP+5FU*	191	70	0.9
RTOG9001	193	73	13

Abbreviations: GOG = Gynecologic Oncology Group; CDDP = cisplatin; NS = not stated; * = same chemotherapy regimen; RTOG = radiation therapy oncology group.

developed 40% of late Grade 3/4 toxicity, including 8 patients requiring surgical intervention. Estimated OAS at 18 months was 60%. The majority of failure of these studies was based on low compliance from acute or late severe gastrointestinal toxicity. These reports also could not acquire comparable clinical results with standard chemoradiotherapy (22, 24). We reported promising clinical efficacy without increasing toxicity, so we believe sequential para-aortic irradiation should be taken into consideration in practice.

As for method of chemotherapy, cisplatin is now widely accepted as standard care for chemoradiotherapy for cervical cancer (2, 4, 6, 19). The GOG 120 study compared with definitive radiotherapy and hydroxyl-urea and concurrent chemoradiotherapy with cisplatin (6). In the GOG 120 study, two chemoradiotherapy arms were applied—such as weekly cisplatin and combination of 5FU and cisplatin (same arm of GOG 85). In recent report, there was no apparent benefit of addition of 5FU within both two arms, although dose of cisplatin varied much (100 mg/m^2 for the combined arm vs. 240 mg/m^2 for the weekly arm). In the RTOG 9001 study, 5-FU and cisplatin were used with concurrently in chemoradiotherapy arm. The sum of cisplatin of RTOG 9001 study was 225 mg/m^2. RTOG 9001 reported a subset analysis for Stage IB-II versus III-IV, statistical significance only for Stage IB-II subset was noted, leading some to suggest that chemoradiotherapy was not effective in more advanced disease stage (28). The update of RTOG 9001 demonstrated that, because the early stage of disease accrued to the protocol, a strong trend only was noted in the patients with more advanced disease (Stage III-IV) (5). Among three studies (GOG 85, GOG 120, RTOG 9001), the ratio of Stage III-IV disease ranged from 30% to 53.8%, and that of positive lymph node was 12.5–24%. In our cohort, the ratio of both advanced stage disease (III-IV: 65%) and positive lymph node was larger ratio (62.5%) compared with those reported study (4, 6, 19).

One of the reasons of our successful result regardless worse prognostic population of our ALCRT experience was sufficient dose intensity of systemic chemotherapy.

This method had an advantage of intensive drug administration because of minimizing acute toxicities, especially for mucosa and intestine; therefore, patients having potentially distant microscopic disease are thought to be better candidates for ALCRT. In previous report, major failure site of patient with Stage III disease in our institute was distant metastasis (12, 20), then we believe our treatment protocols are promising, especially for advanced disease and extended lymph node involvement with potentially hazards of para-aortic region. Using the ALCRT method, we could achieve high-dose administration (1.4 times higher than domestic standard dose of NDP) of a multidrug agent with successful compliance without increasing toxicity.

Finally, we have used NDP, the derivatives of cisplatin developed in Japan. This antitumor agent had a promising activity for cervical cancer (7, 8) and less toxicities of renal and gastrointestinal (29). We believe one of the reasons of our successful result of ALCRT was lower toxicity of NDP compared with cisplatin. In fact, our cohort showed no significant increase gastrointestinal toxicity and could archive a acceptable compliance of protocol compared with reported data using cisplatin (22). Again we should emphasize our reported effective outcomes of ALCRT with NDP for other malignancies (14, 30).

Our protocol seemed to have a promising advantage for patients with advanced disease or positive lymph node patients. However, this study has a definite limitation because of the retrospective comparison to historical matched control group. The several biases regarding patient selection and treatment content should be considered. In addition, our historical control group received radiotherapy alone, which was not present standard care.

But we believe that an acquired result of ALCRT was quite comparable, slightly better (78% vs. 70–73% in 5-year survival; Table 7) than those of standard chemoradiotherapy without para-aortic irradiation. Compared with their reported data, we should emphasize that our cohort had worse prognostic factors. To evaluate clinical efficacy of ALCRT, especially for more advanced disease or positive lymph node, properly randomized controlled trial comparing ALCRT with NDP with concurrent chemoradiotherapy using cisplatin should be tested in the future.

CONCLUSION

Using both dynamic conformational technique and ALCRT setting, extended-field radiation therapy could be successfully combined with intense multiagent chemotherapy. ALCRT is thought to significantly reduce both recurrence and mortality of patients with advanced cervical carcinoma, chiefly with Stage III or positive lymph nodes. We believed that our promising data of the Phase II study warranted advancing to Phase III study comparing ALCRT with NDP to standard concurrent chemoradiotherapy using cisplatin.

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特集 乳癌診療と教育：次世代への期待

放射線療法

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Radiation Therapy of Breast Cancer：Oguchi M[*1] and Shikama N[*2] ([*1]Department of Radiation Oncology, Cancer Institute Hospital, The Japanese Foundation for Cancer Research, [*2]Department of Radiation Oncology, St. Luke's International Hospital)

The main goal of adjuvant radiation therapy is to eradicate residual disease thus reducing local recurrence and improving survival rate. Radiation therapy is regularly employed after breast-conservation surgery. Shorter hypo-fractionation schemes achieve comparable results to standard fractionation schemes. A further radiation boost is commonly given to the tumor bed. The new strategies such as accelerated partial breast irradiation are under investigation for selected patients in breast-conservation setting. Postoperative chest wall and regional lymph node radiation therapy has traditionally been given to selected patients considered at high risk for local-regional failure following mastectomy. Radiation therapy can decrease local-regional recurrence in this group, even among those patients who receive adjuvant chemotherapy. Delaying radiation therapy for several months after surgery until the completion of adjuvant chemotherapy appears safe and may be preferable for patients at high risk of distant dissemination. The rate of second malignancies following adjuvant radiation therapy is very low.

Key words：Breast cancer, Radiation therapy
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はじめに

乳癌に対する放射線療法については，多数の論文から厳選されたエビデンスを総括した日本乳癌学会のガイドラインや放射線治療計画ガイドラインの他に，多数の教科書にて記載が充実している．このため標準治療として国内で最も確立されている放射線療法であると考えられてきた．厚生労働省がん研究助成金「井上班・手島班・光森班」による経年的臨床実態調査：patterns of care study（PCS）の結果では，各種ガイドラインの発行などにより着実な日常診療の改善が認められるものの，一部に問題があることが示された．

1．診療の最近の進歩

1）乳房温存療法における術後放射線療法は局所制御だけでなく生存に関して有益である

乳房温存手術後の乳房照射の有用性は，10の臨床試験に登録された7,311症例を分析したEarly Breast Cancer Trialists' Collaborative Group（EBCTCG）による2005年のメタアナリシスによって証明された[1]．温存手術後に放射線治療を加えることにより，局所再発は70％減少し，15年での死亡の絶対リスクが5.4％減少することが示された．放射線治療により乳房内再発を４件予防することにより１件の乳癌死を予防できると見積もられている．術後療法として内分泌化学療法だけでは局所制御効果は不十分であり，放射線療法により乳房内再発率の有意な減少がみられる[2]．乳房温存療法後の局所再発の危険因子は，切除断端陽性，若年患者（35歳あるいは40歳以下）があげられる．

2）乳房切除術後放射線療法（PMRT）は局所制御だけでなく生存に関して有益である

乳房切除術照射は局所再発減少と死亡絶対リスク減少の有用性があることが，メタアナリシスから示された．EBCTCGメタアナリシス（8,505例）の結果から，5年局所領域リンパ節再発率を23％から6％に減少させることが証明され，36のランダム化比較試験のメタアナリシス（13,199例）結果でも，局所領域リンパ節再発の相対危険率を70～80％減少させた[1, 4]．局所領域リンパ節再発の危険因子としては，4個以上の腋窩リンパ節転移陽性例，原発巣の大きい患者（5 cm以上），深部断端陽性例などである[5]．

3）局所（胸壁・領域リンパ節）再発に対する救済放射線療法

乳房切除術後の胸壁再発やリンパ節再発は，多様な病態を呈し，遠隔転移を伴うことがまれでない．乳房切除術により長期間に無病であった後の限局性胸壁再発は期待生命予後が長いので，再度の長期間無病状態を目指して積極的に救済治療することが推奨される[6]．

4）遠隔転移（骨・脳・肺・他）に対する緩和目的の放射線療法

メタアナリシスでは，骨転移の疼痛緩和に対する線量－効果関係は明らかでない[7]．骨融解性病変が高度で比較的長い予後が期待される場合は分割照射法が推奨される．1回照射と分割照射を比較した最近のメタアナリシスでは前者において同一部位への再照射率が高く，病的骨折が高くなる傾向があるものの，両者間に全寛解率や完全寛解率に差がみられない点では一致している[7, 8]．放射線治療と高用量ビスフォスフォネートを併用すると疼痛緩和だけではなく，画像的に骨硬化もみられる．ストロンチウム－89によるアイソトープ治療については日本でも多施設共同オープン試験が行われ，疼痛尺度と鎮痛剤使用量を組合せた有効率は46％であった．投与後8週ころに血液毒性がnadirとなるため，化学療法の継続または予定されている患者への適応には慎重を要する．

1～4個の脳転移を対象とした臨床試験が行われ，全脳照射に定位手術的照射を追加する意義が示された[9, 10]．JROSG99-1では定位手術的照射単独ではなく，全脳照射を併用する方が局所制御割合が高いことが示された[11]．

2．現在の研究の焦点は何か

1）放射線療法の適応に関する研究

（1）乳房温存術後乳房照射は全員に必要か？

局所再発のリスクが少なく放射線療法を省略できる群を同定する研究や，切除断端陰性（取りきれたこと）の保証をする研究が実施されている．腫瘍が小さいほど，手術の切除範囲が大きいほど，患者の年齢が高いほど，放射線療法は省略できる可能性があると考えられる．4つのランダム化比較試験において，放射線療法を省略できるデータは示されていない[12, 13]．エストロゲン受容体陽性の70歳例では，内分泌療法を行えば，放射線療法を省略できるかもしれないという意見もある．国内でも局所再発リスクが少なく放射線治療を省略し得る群を同定する臨床試験が実施されている．今後も，真に放射線療法を必要とする患者を同定する努力を続けるべきであろう．

（2）乳房切除術後照射：PMRTの適応は？

腋窩リンパ節転移1～3個の患者に関するDanish 82b+82c Trialの解析結果は，PMRTにより局所領域リンパ節再発の抑制効果と生存率の向上（15年生存率相対リスク17％改善）が示された[14]．この群の全患者にPMRTを行うべきか，幅広い合意はいまだ得られていない．摘出リンパ節中の転移リンパ節の割合（nodal ratio）が高いほど局所領域リンパ節再発率が高いことが報告され，局所領域リンパ節再発の高リスク患者を見出しPMRTが必要な患者を同定する研究が続けられている．

2）放射線照射法に関する研究

（1）加速乳房部分照射への期待