prognostic factor, even for N0M0 patients. In our study, histological grade was determined by biopsy specimens before treatment, but 96 patients (31.9%) were diagnosed with grade X. A reason for this result may be that it is difficult to perform accurate pathological subtyping with only a biopsy specimen. Because 31.9% of patients had an unknown histological grade, the prognostic impact of this histological grade is not clear. Because only 104 patients in Stage I and Stage II were divided into four categories of prognostic group, the power of the study may be insufficient to show the statistical significance. Therefore, additional study is needed to evaluate the role of prognostic group incorporation of new prognostic factors.

We recognize that our study has several limitations. First, only squamous cell carcinomas were included in this study and all patients in this study were treated with standard CRT in Japan (60 Gy and margin setting) (9, 20–22). In contrast, incidence of adeno-carcinoma has been dra-matically increasing in Western countries for which a lower dose of CRT followed by surgery is commonly used, Therefore, the results of this study might be different if similar analysis were performed in Western countries. Second, this is a single-institution retrospective study with the relatively small number of patients in comparison with the data-driven approach using worldwide data for staging in the 7th edition (3). Thus, small number of cases in each staging categories may be insufficient to show the statistical significance. Third, PET scan is not used in all patients in this study to decide positive or negative lymph node metastasis in general, although PET scans are being used more frequently in recent clinical practice. Therefore, further study is needed to validate our results in other large cohorts being evaluated with PET scans.

In conclusion, our study has identified several shortcomings for prognostic factors in the 7th TNM staging system for esophageal cancer patients undergoing CRT. According to our analysis, the T stage is the most meaningful prognostic factor in clinical practice for esophageal squamous cell carcinoma.

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Clinical Investigation: Thoracic Cancer

Recursive Partitioning Analysis for New Classification of Patients With Esophageal Cancer Treated by Chemoradiotherapy

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Summary

The objective of this study was to develop and validate a new staging system that incorporates lymph node size for esophageal cancer patients undergoing chemoradiotherapy. The new staging classification, which was based on the T stage and lymph node size, led to good separation of survival curves in both the developmental and validation datasets. The new staging system provided good prognostic power and discriminated effectively for esophageal cancer patients undergoing chemoradiotherapy.

Background: The 7th edition of the American Joint Committee on Cancer staging system does not include lymph node size in the guidelines for staging patients with esophageal cancer. The objectives of this study were to determine the prognostic impact of the maximum metastatic lymph node diameter (ND) on survival and to develop and validate a new staging system for patients with esophageal squamous cell cancer who were treated with definitive chemoradiotherapy (CRT).

Methods: Information on 402 patients with esophageal cancer undergoing CRT at two institutions was reviewed. Univariate and multivariate analyses of data from one institution were used to assess the impact of clinical factors on survival, and recursive partitioning analysis was performed to develop the new staging classification. To assess its clinical utility, the new classification was validated using data from the second institution.

Results: By multivariate analysis, gender, T, N, and ND stages were independently and significantly associated with survival ($p < 0.05$). The resulting new staging classification was based on the T and ND. The four new stages led to good separation of survival curves in both the developmental and validation datasets ($p < 0.05$).

Conclusions: Our results showed that lymph node size is a strong independent prognostic factor and that the new staging system, which incorporated lymph node size, provided good prognostic power, and discriminated effectively for patients with esophageal cancer undergoing CRT.

Keywords: Esophageal cancer, Chemoradiotherapy, TNM, Recursive partitioning analysis, Prognostic factor

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Introduction

Staging systems for cancer have evolved over time and continue to change as knowledge of cancer increases. Based on the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of distant metastasis (M), the TNM staging system is one of the most widely used staging systems. The tumor stage is the most important prognostic factor for any type of cancer, and planning for optimal treatment is mainly decided according to the tumor stage (1).

The American Joint Committee on Cancer (AJCC) TNM staging system for esophageal cancer was revised in the 2009 7th edition. A major modification in the 7th edition was the subdivision of N according to the number of involved lymph nodes. The modification was based on retrospective analysis of pathologic data from patients treated only by primary surgical resection (2, 3), although the current standard treatment for esophageal cancer incorporates neoadjuvant chemotherapy or chemoradiotherapy (CRT). We therefore evaluated the prognostic impact of the 7th edition staging system on esophageal cancer patients undergoing CRT (4). The results indicated that the 7th edition TNM classification had several limitations in determining the prognosis of patients undergoing CRT. For example, the 7th TNM staging system poorly distinguishes the prognoses of patients with Stage III and Stage IV disease undergoing CRT with regard to nondistant organ metastasis (4). Additional detailed classification that more accurately predicts prognosis after treatment may be necessary for clinical decision-making.

Pathological lymph node size has been reported to be a meaningful prognostic factor for survival in patients with esophageal cancer who undergo surgery (5, 6). We hypothesize that the size of nodal disease as an additional prognostic criterion for overall survival in esophageal cancer patients may have an impact on clinical outcome after CRT. However, to the best of our knowledge, this has not been evaluated in esophageal cancer patients undergoing definitive CRT. Although lymph node size is already integrated into the N staging system of head-and-neck carcinoma, the only criterion determining N stage in esophageal cancer is the number of infiltrated nodes.

The objectives of the present study were to investigate the prognostic impact of the largest diameter of all the identified metastatic lymph nodes (ND) and to develop and validate a new staging system on patients with esophageal squamous cell cancer who were treated with definitive CRT.

Methods and Materials

Patient population

This was a retrospective cohort study of esophageal cancer patients treated with definitive CRT at two institutions. Criteria for inclusion were the following: (*1*) carcinoma of thoracic esophagus; (*2*) histological diagnosis of primary esophageal squamous cell carcinoma; (*3*) no distant organ metastasis; (*4*) total radiation dose ≥50 Gy; (*5*) concomitant chemotherapy consisting of 5-fluorouracil and platinum; (*6*) no previous thoracic radiotherapy (RT); (*7*) no previous thoracic surgery; and (*8*) no salvage surgery. Patients who received chemotherapy followed by CRT were also excluded from this analysis. The developmental database

Table 1 Patient and tumor characteristics

Characteristic	Generation dataset $n = 261$	(%)	Validation dataset $n = 141$	(%)	p
Age (y)					<0.001
Median	65		67		
Range	39–82		44–87		
Gender					0.26
Male	224	(86)	115	(82)	
Female	37	(14)	26	(18)	
PS					0.27
0	75	(29)	48	(34)	
1	186	(71)	93	(66)	
Cancer site					0.37
Ut	50	(19)	25	(18)	
Mt	149	(57)	90	(64)	
Lt	62	(24)	26	(18)	
T stage (7th)					0.041
1	80	(31)	30	(21)	
2	17	(6)	19	(14)	
3	105	(40)	62	(44)	
4	59	(23)	30	(21)	
N stage (7th)					0.021
0	102	(39)	36	(26)	
1	91	(35)	69	(49)	
2	60	(23)	33	(23)	
3	8	(3)	3	(2)	
M stage (7th)					0.97
0	204	(78)	110	(78)	
1	57	(22)	31	(22)	
Histological grade (7th)					0.001
1	43	(17)	15	(11)	
2	112	(43)	43	(31)	
3	24	(9)	9	(6)	
X	82	(31)	74	(52)	
Stage (7th)					0.093
I	59	(23)	23	(16)	
II	55	(21)	22	(16)	
III	90	(34)	65	(46)	
IV	57	(22)	31	(22)	
Maximum lymph node diameter (cm)					0.008
Median	1.7		1.6		
Range	0.5–7		0.5–7		
Total radiation dose (Gy)					0.93
Median	60		60		
Range	50–64		50–60		
Chemotherapy regimen					<0.001
5-FU + CDDP	247	(95)	115	(82)	
5-FU + CDGP	14	(5)	26	(18)	

Abbreviations: 5-FU = 5-fluorouracil; CDDP = cisplatin; CDGP = nedaplatin; Lt = lower thoracic portion; Mt = mid-thoracic portion; PS = Eastern Cooperative Oncology Group performance status; Ut = upper thoracic portion.

consisted of 261 esophageal cancer patients treated at the Aichi Cancer Center Hospital between March 2003 and October 2009. The external validation database consisted of 141 esophageal cancer patients treated at Kansai Medical University between February 2006 and April 2010.

Pretreatment staging

Pretreatment staging evaluations included physical examination, laboratory tests, esophagogastroduodenoscopy, barium esophagography, contrast-enhanced computed tomography (CT) from the neck to upper abdomen, and positron emission tomography (PET). Pretreatment staging was based on the 6th edition of the AJCC Cancer Staging Manual and was determined during a meeting of thoracic surgeons, radiologists, gastroenterologists, and medical oncologists. Treatment strategy was also determined at the meeting.

RT treatment planning and treatment

RT was delivered using a linear accelerator (Clinac 21EX and Clinac 2100C at Aichi Cancer Center; Clinac 21EX at Kansai Medical University; Varian Medical Systems, Palo Alto, CA) with a 6- to 15-MV photon beam. In general, patients received 2 Gy per fraction, for a total of 60 Gy. A conventional beam arrangement that consisted of opposed anterior and posterior fields up to 36–40 Gy, and off-cord oblique fields was used. Spinal cords never received more than 45 Gy. Doses were prescribed according to Reports 50 and 62 of the International Commission on Radiation Units and Measurements (7, 8). Before treatment, all patients underwent three-dimensional treatment planning, which included tissue inhomogeneity correction. Treatment planning was based on CT scans of patients in the treatment position using 3- to 5-mm thick sections and 3- to 5-mm intervals. The gross tumor volume of the primary site (GTV-P) and the gross volume of involved lymph nodes (GTV-N) were determined. The primary clinical target volume (CTV-P) included the GTV-P plus 20–30 mm craniocaudal margins, and the lymph node clinical target volume (CTV-N) included the GTV-N without additional margins (9). The planning target volume (PTV) included both CTVs plus lateral and anteroposterior 5–10 mm margins and 10–20 mm craniocaudal margins. In addition, 5–8 mm leaf margins were added to the PTV.

The chemotherapy regimens used with RT consisted of 5-fluorouracil and cisplatin or nedaplatin. The doses and schedules were determined and administered as previously reported (9–13). Most of the Stage IIA-IVB patients received consolidation chemotherapy consisting of 5-fluorouracil and platinum after their chemoradiotherapy.

Follow-up

History and physical examination, complete blood cell count, gastrointestinal endoscopy, chest X-ray, and CT scanning of the neck, chest, and abdomen were performed approximately every 2–3 months for the first year after initiation of treatment. Thereafter, patients were followed every 3–6 months until death or until lost to follow-up. There were no differences in pretreatment examinations and treatment strategy between the two institutions.

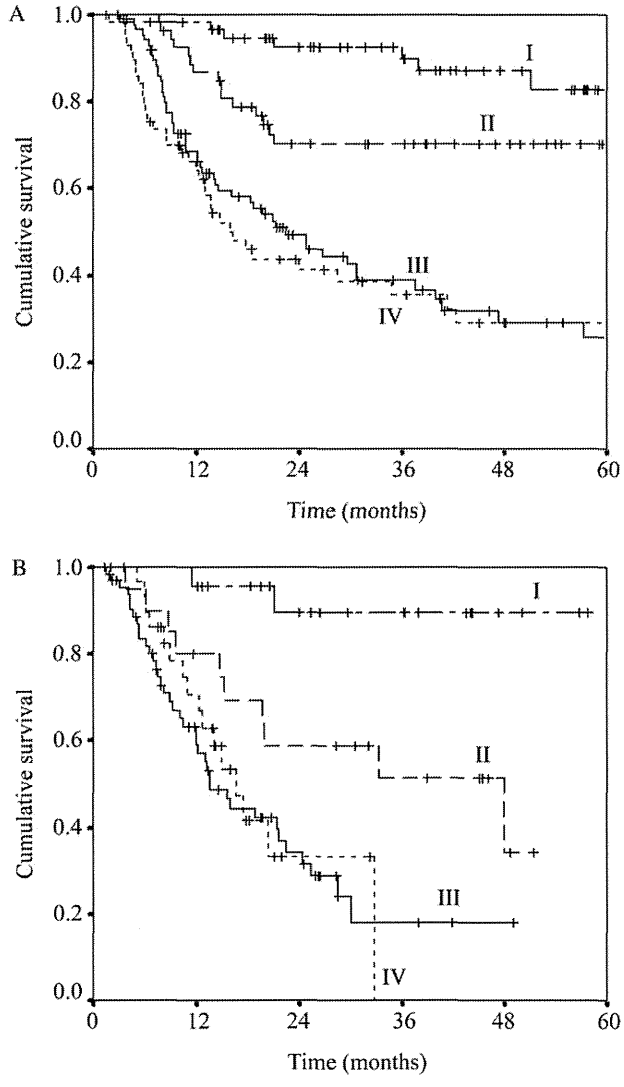

Fig. 1. Survival curves according to the TNM 7th classification of (A) the developmental dataset and (B) the validation dataset. The 3-year survival rates of disease Stages I, II, III, and IV according to the TNM 7th classification were 89.9%, 70.1%, 38.7%, and 35.5%, respectively, in the developmental dataset. The 3-year survival rates of disease Stages I, II, III, and IV according to the TNM 7th classification were 89.7%, 51.3%, 18.0%, and 0.0%, respectively, in the validation dataset.

Data collection

The following information was recorded from the medical record and radiological images of each patient: treatment initiation date, age, sex, Eastern Cooperative Oncology Group performance status, cancer site, histological grade, clinical stage according to the 7th AJCC edition, total radiation dose, final date assessing survival, and date of death. ND measurements and TNM staging according to the 7th AJCC edition, including number of lymph nodes, were independently redetermined by two radiologists at each institution (M.N. and T.K. at Aichi Cancer Center; M.N. and M.K. at Kansai Medical University). A lymph node was considered as positive for metastasis if the short axis was greater than 5 mm on CT (14) and there was visual correlation on PET scan. PET-positive lymph node

Table 2 Univariate and multivariate analysis in generation dataset

		Univariate analysis			Multivariate analysis		
	Patients (*n*)	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (y)							
<65	124	(reference)	–	–			
≥65	137	0.88	0.60–1.28	0.49			
Gender							
Male	224	(reference)	–	–	(reference)	–	–
Female	37	0.39	0.18–0.83	0.015	0.34	0.16–0.75	0.008
PS							
0	75	(reference)	–	–	(reference)	–	–
1	186	2.38	1.45–3.91	0.001	0.75	0.41–1.37	0.35
Cancer site							
Lt	50	(reference)	–	–			
Ut	62	1.23	0.68–2.23	0.50			
Mt	149	1.33	0.81–2.17	0.26			
T stage (7th)							
1	80	(reference)	–	–	(reference)	–	–
2	17	2.76	1.04–7.36	0.042	2.21	0.75–6.56	0.15
3	105	5.17	2.77–9.65	<0.001	4.36	2.04–9.32	<0.001
4	59	6.61	3.43–12.76	<0.001	6.45	2.65–15.72	<0.001
N stage (7th)							
0	102	(reference)	–	–	(reference)	–	–
1	91	3.18	1.91–5.31	<0.001	1.87	1.07–3.28	0.029
2	60	4.52	2.65–7.70	<0.001	1.77	0.94–3.33	0.078
3	8	7.49	3.00–18.72	<0.001	2.78	0.96–8.05	0.059
M stage (7th)							
0	204	(reference)	–	–	(reference)	–	–
1	57	2.34	1.56–3.51	<0.001	1.08	0.68–1.70	0.75
Histological grade (7th)							
1	43	(reference)	–	–	(reference)	–	–
2	112	2.39	1.25–4.57	0.009	1.78	0.90–3.50	0.095
3	24	2.25	0.98–5.20	0.057	1.53	0.65–3.62	0.34
X	82	2.17	1.10–4.30	0.026	1.72	0.86–3.47	0.13
ND							
0	97	(reference)	–	–	(reference)	–	–
0–2.8	132	3.36	2.03–5.54	<0.001	1.83	1.03–3.25	0.041
>2.8	32	7.85	4.27–14.42	<0.001	3.48	1.62–7.46	0.001

Abbreviations: CI = confidence interval; HR = hazard ratio; Lt = lower thoracic portion; Mt = mid-thoracic portion; ND = the largest diameter of all the identified metastatic lymph nodes; PS = Eastern Cooperative Oncology Group performance status; Ut = upper thoracic portion.

was also considered as positive, even if lymph nodes were less than 5 mm in the short-axis diameter on CT.

Statistical analysis

All patient characteristics were considered categorical variables, with the exception of age, tumor length, and ND, which were treated as continuous data. Specific comparisons between groups were made using chi-square and Mann-Whitney tests. Overall survival was calculated from treatment initiation date to the time of death from any cause or to time of last follow-up. Survival curves were constructed using the Kaplan-Meier method, and log–rank tests were used to determine the statistical significance of differences. To evaluate the impact of each stage group on overall survival, univariate and multivariate Cox proportional hazards modeling was applied using the developmental database. Therefore, the measure of association in this study was the hazard ratio (HR) plus the 95% confidence interval (CI). Recursive partitioning analysis (RPA) was performed to determine the optimal cutoff point of ND and to develop the new staging classification using the developmental database (15). To develop the new staging, variables entered into the RPA were those that had attained statistical significance in the multivariate analysis. Subgroups having similar survival outcomes were combined. The newly formed stages were evaluated using the validation database. Statistical analyses were performed using the SPSS statistical software package version 11 (SPSS Inc., Chicago, IL) and R version 2.12.0 (R Project for Statistical Computing, Vienna, Austria). A p value less than 0.05 was considered statistically significant.

Results

Patient characteristics

The characteristics of the study patients are summarized in Table 1. NDs ranged from 0.5 to 7.0 cm, with a median ND of

1.7 cm in the developmental dataset, and ranged from 0.5 to 7.0 cm, with a median ND of 1.6 cm in the validation dataset. There was a higher proportion of patients receiving nedaplatin combined with 5-fluorouracil in the validation dataset ($p < 0.001$). The values for age, tumor length, T stage, N stage, histological grade, ND, and chemotherapy regimen were all significantly different between the developmental and validation datasets ($p < 0.05$). The median follow-up period was 60 months (range, 20–97 months), with 109 of the 261 patients dead at the time of analysis in the developmental dataset. The median follow-up period was 36 months (range, 12–64 months), with 66 of the 141 patients dead at the time of analysis in validation dataset.

Univariate and multivariate analysis

Figure 1 shows the survival curves according to the TNM 7th classification of each dataset. The 3-year survival rates of disease Stages I, II, III, and IV according to the TNM 7th classification were 89.9%, 70.1%, 38.7%, and 35.5%, respectively, in the developmental cohort (Fig. 1A). Kaplan-Meier analysis of overall survival revealed significant differences between Stages I and II ($p = 0.025$), and between II and III ($p = 0.0001$). Survival of Stage III patients almost completely overlapped the survival of Stage IV patients ($p = 0.58$). The overlap in survival of Stages III and IV was similar in the validation cohort (Fig. 1B).

Table 2 shows the univariate and multivariate analyses for each prognostic factor, including ND. According to RPA, ND stages were best when classified as ND0 (the absence of lymph node metastases), ND1 (<2.8 cm), and ND2 (≥2.8 cm). By univariate analysis, gender, performance status, TNM stages, histological grade, and ND were significant predictors of survival. By multivariate analysis, gender, T, N, and ND stage were independently and significantly associated with survival (all $p < 0.05$).

Development of new staging using RPA

To develop the new staging, RPA was performed on the developmental dataset. RPA that included gender, T, N, and ND stage as variables showed that ND was the initial discriminator of survival (Fig. 2). The significant RPA-derived splits were only the T and ND stages. For these five groups derived by RPA, the 3-year survival rates of groups I, II, III, IV, and V were 90.0%, 60.2%, 76.4%, 39.7%, and 21.5%, respectively. By the log–rank test, there were no significant differences in survival between groups I and III ($p = 0.07$) or between II and III ($p = 0.38$). Because survival of group II patients overlapped the survival of group III patients, groups II and III were combined. The resulting new staging system is shown in Table 3. There were significant differences between each stage (all $p < 0.05$ by log–rank test) (Fig. 3A). The 3-year survival rates of the new Stages I, II, III, and IV were 90.0%, 67.4%, 39.7%, and 21.5%, respectively (Fig. 3A).

External validation dataset

A total of 141 patients treated at Kansai Medical University were evaluated as the external validation dataset. Four new stages, determined from the RPA of the developmental dataset, were created. As shown in Fig. 3B, this new staging system resulted in well separated survival curves (all $p < 0.05$ by log–rank test). The

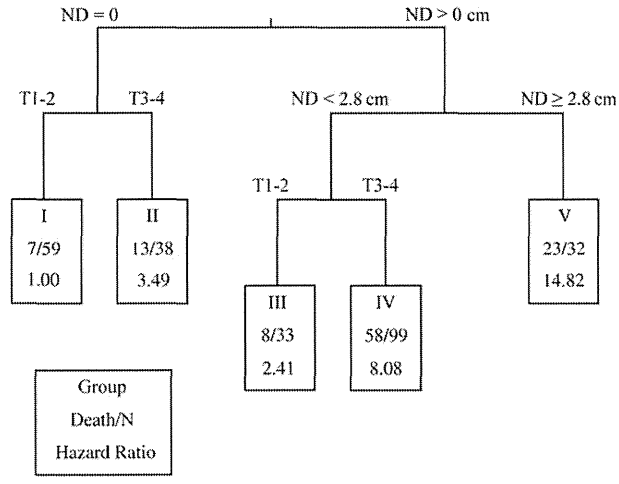

Fig. 2. Recursive partitioning analysis using gender, T, N, and ND stage as variables. In each terminal node, the upper row shows group number, the middle row shows the number of death and patients, and the low row shows the hazard ratio with reference to patients with Stage I.

3-year survival rates of the new Stages I, II, III, and IV were 90.2%, 53.2%, 22.6%, and 8.6%, respectively (Fig. 3B).

Discussion

Although neoadjuvant CRT followed by esophagectomy or definitive CRT have been standard therapies for resectable esophageal cancer (9, 10, 16–18), the 7th edition of the AJCC cancer staging system for esophageal cancer was based on pathologic data from patients treated by primary surgical resection alone (3). In the 7th edition, the new N factor, which was based on the number of positive regional lymph nodes and was redefined according to the locations of regional lymph nodes, is a major change from the 6th edition. Our previous report suggested that these staging criteria may be inappropriate for patients receiving CRT (4). Our results showed that the survival curve of Stage III patients almost overlapped the curve of Stage IV patients and that there were no

Table 3 New staging system

T classification	
T1	Tumor invasives lamina propria, muscularis mucosae, or submucosa
T2	Tumor invasives muscularis propria
T3	Tumor invasives adventitia
T4	Tumor invasives adjacent structures
N classification	
N0	No involved lymph nodes
N1	Metastasis in lymph node(s) less than 2.8 cm in greatest dimension
N2	Metastasis in a lymph node 2.8 cm or more in greatest dimension
New staging group	
I	T1–2N0
II	T1–2N1, T3–4N0
III	T3–4N1
IV	TanyN2

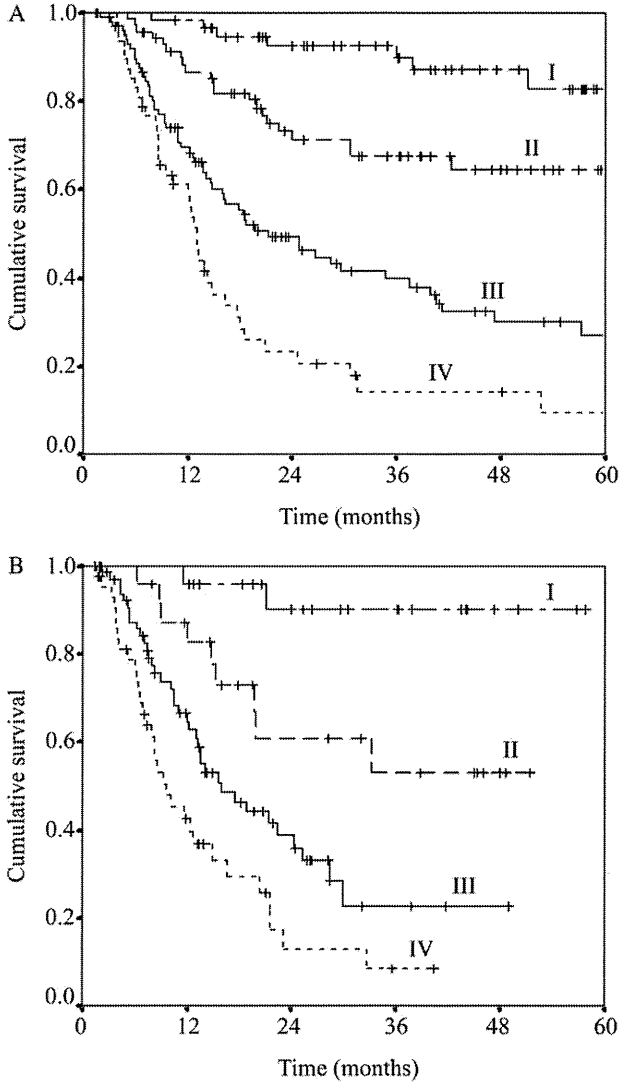

Fig. 3. Survival curves according to the new staging system of (A) the developmental dataset and (B) the validation dataset. The 3-year survival rates of the new Stage I, II, III, and IV were 90.0%, 67.4%, 39.7%, and 21.5%, respectively, in the developmental dataset. The 3-year survival rates of the new Stage I, II, III, and IV were 90.2%, 53.2%, 22.6%, and 8.6%, respectively, in the validation dataset.

significant prognostic differences between N1 and N3 diseases (4). Because the current staging system does not incorporate the size of involved lymph nodes, we performed two analyses: (*1*) the prognostic impact of ND was evaluated and (*2*) the new staging system was developed and validated for patients with esophageal squamous cell cancer who were treated with definitive CRT.

Our results showed that the size of lymph nodes, determined by ND, was the most significant factor for N assessments in patients with esophageal cancer undergoing definitive CRT. In previous studies, the number of lymph nodes, lymph node sizes, and metastatic to examined LN ratio were also significant prognostic factors for survival in esophageal cancer patients undergoing surgery alone (5, 6). Therefore, lymph node size may be a strong prognostic factor regardless of treatment modality.

RPA for patients in the developmental dataset referred with five terminal nodes. RPA indicated that the new N2 (ND $\geq$2.8 cm) was associated with the worst prognosis. By RPA, the 3-year survival rates of the patients staged with the new system were relatively similar in both the developmental and external validation cohorts. This new staging system resulted in good separation of the survival curves of both datasets. Thus, these results suggest ND is a more appropriate factor for incorporation in staging systems for patients with esophageal cancer undergoing definitive CRT than the current staging system. Incorporation of N staging, based on both the number of lymph nodes and ND, into the current staging system for esophageal cancer may improve clinical decision-making.

We recognize that our study has several limitations. First, only squamous cell carcinomas were evaluated, and all study patients were treated with the standard CRT for Japan (total radiation dose, 60 Gy) (9, 11). A second limitation is that this was a retrospective study using small number of patients. A third limitation is that several values in patient characteristics were significantly different between the developmental and validation datasets. Therefore, for validation, additional prospective, multicenter studies with large numbers of patients with adenocarcinoma or squamous cell carcinoma of the esophagus undergoing the current standard treatment, including neoadjuvant chemotherapy or CRT, are needed. Our results demonstrated that an ND of 2.8 cm is the most appropriate cutoff value, and more studies are needed to determine or validate the most appropriate cutoff value for ND.

In conclusion, our study demonstrated that lymph node size is a strong independent prognostic factor and that our new staging system, which incorporates lymph node size, as determined by ND, has good prognostic power and effectively discriminates patients with esophageal squamous cell cancer undergoing definitive CRT. We suggest that the revision of the current AJCC staging system for esophageal cancer should include N staging based on the size of involved lymph nodes.

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Clinical Investigation: Gynecologic Cancer

Insufficiency Fractures After Pelvic Radiation Therapy for Uterine Cervical Cancer: An Analysis of Subjects in a Prospective Multi-institutional Trial, and Cooperative Study of the Japan Radiation Oncology Group (JAROG) and Japanese Radiation Oncology Study Group (JROSG)

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Summary

We analyzed subjects of a prospective multi-institutional study to investigate pelvic insufficiency fractures (IF) after definitive pelvic radiation therapy for early-stage uterine cervical cancer. The 2-year overall cumulative incidence of both symptomatic and asymptomatic IF was 36.9%, and the cumulative incidence of symptomatic IF was 16.1%. Higher age (>70 years) and low body weight (<50 kg) were thought to be risk factors for pelvic IF.

Purpose: To investigate pelvic insufficiency fractures (IF) after definitive pelvic radiation therapy for early-stage uterine cervical cancer, by analyzing subjects of a prospective, multi-institutional study.

Materials and Methods: Between September 2004 and July 2007, 59 eligible patients were analyzed. The median age was 73 years (range, 37-84 years). The International Federation of Gynecologic Oncology and Obstetrics stages were Ib1 in 35, IIa in 12, and IIb in 12 patients. Patients were treated with the constant method, which consisted of whole-pelvic external-beam radiation therapy of 50 Gy/25 fractions and high-dose-rate intracavitary brachytherapy of 24 Gy/4 fractions without chemotherapy. After radiation therapy the patients were evaluated by both pelvic CT and pelvic MRI at 3, 6, 12, 18, and 24 months. Diagnosis of IF was made when the patients had both CT and MRI findings, neither recurrent tumor lesions nor traumatic histories. The CT findings of IF were defined as fracture lines or sclerotic linear changes in the bones, and MRI findings of IF were defined as signal intensity changes in the bones, both on T1- and T2-weighted images.

Results: The median follow-up was 24 months. The 2-year pelvic IF cumulative occurrence rate was 36.9% (21 patients). Using Common Terminology Criteria for Adverse Events version 3.0, grade 1, 2, and 3 IF were seen in 12 (21%), 6 (10%), and 3 patients (5%), respectively. Sixteen patients had multiple fractures, so IF were identified at 44 sites. The pelvic IF were frequently seen at the sacroileal joints (32 sites, 72%). Nine patients complained of pain. All patients' pains were palliated by rest or non-narcotic analgesic drugs. Higher age (>70 years) and low body weight (<50 kg) were thought to be risk factors for pelvic IF ($P=.007$ and $P=.013$, Cox hazard test).

Conclusions: Cervical cancer patients with higher age and low body weight may be at some risk for the development of pelvic IF after pelvic radiation therapy.

Introduction

Insufficiency fractures (IF) are a type of stress fracture, occurring after normal or physiologic stress on bone with decreased mineralization and elastic resistance (1). Insufficiency fractures of the pelvic bones are thought to be associated with postmenopausal or corticosteroid-induced osteoporosis (1, 2). Pelvic radiation therapy (RT) also can affect the development of pelvic IF, although the precise pathogenesis is as yet unclear (1, 2). Although some investigators (3-5) have reported that pelvic IF are an uncommon adverse event in irradiated patients with gynecologic cancer, others (6-10) have reported that radiation-induced pelvic IF were frequently observed in women after RT. It seems that the precise incidence of IF is unclear. The findings on conventional radiographs are usually subtle (2, 10) and may be misleading. The fractures usually show increased uptake on radionuclide bone scans. A pattern of increased uptake in the body of the sacrum and in one or both sacrum alae (1, 2, 11) is indicative of a fracture, but increased uptake may also be present in metastases and sacroiliac joint osteoarthritis (12). The importance of understanding a pelvic IF lies in the potential for its misdiagnosis as bony metastases. Computed tomography (CT) is capable of displaying fracture lines and/or sclerotic changes associated with IF (8, 9, 11), whereas magnetic resonance imaging (MRI) is highly sensitive for revealing the reactive bone marrow changes associated with IF (9, 13).

Not only for unresectable locally advanced stages, RT has played an important role in the treatment of early-stage cervical cancer. Originally, to determine the efficacy of definitive RT using high-dose-rate intracavitary brachytherapy (HDR-ICBT) with a low cumulative dose schedule in nonbulky early-stage cervical cancer patients, we conducted a prospective multi-institutional study (JAROG0401/JROSG04-2) (14). Two-year pelvic disease progression-free rate was the primary endpoint, and late complication including IF was one of the secondary endpoints in the study (14). At first, IF was evaluated by only symptomatic features. However, we noticed that some follow-up imaging features after RT had shown IF of pelvic bones in several asymptomatic patients. Therefore, we planned this additional study to assess pelvic IF by adding a minute imaging evaluation prospectively, without changing the schedule and methods of the follow-up CT and MRI in the protocol.

The purpose of this study was to investigate the incidence of radiation-induced pelvic IF using CT and MRI and to investigate the risk factors and radiation doses associated with IF, as well as the distribution of IF sites among patients with this complication. In our study, patients were treated with the constant RT method described in the protocol and followed with CT and MRI regularly. To our knowledge, this is the first multi-institutional prospective analysis on IF.

Methods and Materials

Patient eligibility criteria

The women enrolled in these analyses were a group of patients with cervical carcinoma who were treated with a protocol JAROG0401/JROSG04-2) (14). Eligible patients had histologically proven squamous cell carcinoma of the intact uterine cervix with International Federation of Gynecologic Oncology and Obstetrics (FIGO) stage Ib1/IIa/IIb disease and were aged 20-80 years. A complete physical examination, pelvic examination performed without anesthesia, and chest X-ray were required to determine the clinical stage. Patients were required to have cervical tumors <40 mm in diameter as assessed by T2-weighted MRI and negative pelvic and paraortic lymph nodes (<10 mm in shortest diameter) as

determined by CT. All patients were required to give their written informed consent.

Treatment

The treatment protocol has been described in detail previously (14). The treatment protocol consists of a combination of external-beam radiation therapy (EBRT) and HDR-ICBT. Interstitial brachytherapy and chemotherapy were not allowed. External-beam radiation therapy was delivered to a total dose of 50 Gy in 25 fractions over 5-6 weeks. The early part with 20 Gy was delivered to the whole pelvis. After that, 30 Gy was administered through the same whole-pelvic field with a midline block (MB) of 3- to 4-cm width. The MB was formed with multileaf collimators or custom cerrobend block. The first HDR-ICBT was performed within 10 days after the initial 20 Gy of EBRT. Treatment was to be completed within 56 days.

All patients were treated with a photon beam of 10 MV or greater. Both anteroposterior/posteroanterior (AP/PA) and a 4-field technique were allowed. In cases in which the 4-field technique was used, the portal arrangement was changed to the AP/PA technique after the insertion of the MB. Tissue heterogeneity correction was not used in the dose calculation. The upper border of the pelvic field was L4/5, and the lower border was a transverse line below the obturator foramen. The lateral borders of the AP/PA fields were 1-2 cm beyond the lateral margins of the bony pelvis. For the lateral fields, the anterior border was placed at a horizontal line drawn 1 cm anterior to the symphysis pubis anteriorly and a vertical line at the posterior border of the sacrum posteriorly. The upper and lower borders were the same as the AP/PA fields. The fields were shaped to shield normal tissues using a custom block or multileaf collimators. Prophylactic paraortic RT was not allowed.

High-dose-rate intracavitary brachytherapy using a tandem and 2 ovoids was performed once per week giving 24 Gy to point A in 4 fractions with ^{192}Ir afterloading machines.

Evaluation

After RT the patients were evaluated by both pelvic CT and pelvic MRI at 3, 6, 12, 18, and 24 months. Diagnosis of IF was made when the patients had positive findings on both CT and MRI, without recurrent tumor lesions or traumatic histories. Computed tomography findings of IF were defined as fracture lines or sclerotic linear changes in the bones, and MRI findings of IF were defined as signal intensity changes in the bones of >5 mm both on T1 and T2-weighted images (Fig. 1). All CT and MR images were evaluated together by 4 investigators. The cumulative occurrence rate of IF was calculated by the Kaplan-Meier method. Risk factors that could affect the incidence of IF (age, stage, body weight, simulation, beam technique, energy of X-ray, and location of facilities) were assessed by log-rank test and Cox hazard test. Statistical analyses were performed with SPSS 16.0 (SPSS, Chicago, IL).

The patients were also evaluated by CTCAE (Common Terminology Criteria for Adverse Events) version 3.0 every 3 months from 3-30 months. Clinical characteristics, including sites of IF and doses administered to IF lesions, were identified by a review of the medical records and imaging studies of the participating facilities, including isodose curves of pelvic RT.

The study was approved by the Protocol Review Committee of our study group and the local institutional review board of participating institutions.

Results

Patients

Between September 2004 and July 2007, 60 patients were enrolled from 13 institutions. One patient was considered ineligible, leaving 59 patients in the final patient cohort.

The median age was 73 years (range, 37-84 years). The eligible patients had squamous cell carcinoma of the uterine cervix, and the FIGO stages were Ib1 in 35, IIa in 12, and IIb in 12 patients. No patients had pelvic/paraortic lymphadenopathy. The median follow-up was 24 months.

Incidents and clinical characteristics of IF

A total of 21 patients were diagnosed with IF after RT. The 2-year overall cumulative incidence of both symptomatic and asymptomatic IF was 36.9% (Fig. 2). On CTCAE version 3.0, grade 1, 2, and 3 were seen in 12 (21.4%), 6 (10.2%), and 3 patients (5.3%), respectively.

On univariate analysis by log-rank test, age >70 years ($P=.004$) and body weight <50 kg ($P=.007$) were thought to be risk factors of pelvic IF. Multivariate analysis by Cox hazard test showed that age >70 years ($P=.007$) and body weight <50 kg ($P=.013$) were significant predisposing factors for developing IF (Table).

The cumulative incidence of symptomatic IF at 2 years was 16.1% (9 patients) in all patients (Fig. 2). Nine patients complained of pelvic or back pain. The pain was palliated by rest or non-narcotic analgesic drugs in all 9 cases, and no patients required surgical intervention. Sixteen patients had multiple fractures, so the pelvic IF was identified at 44 sites. The symptomatic patients had from 1-4 IF sites (mean 2.7 sites), and the asymptomatic patients had 1 or 2 IF sites (mean 1.7 sites). The pelvic IF was seen at the sacroileal (SI) joints (32 sites, 72%), pubis (9 sites, 20%), acetabula (2 sites, 4%), and lumbar spine (1 site, 2%) (Fig. 3).

The external-beam doses of all 44 IF sites were calculated from the isodose curves. It was estimated that the median dose was 49 Gy and the mean dose was 46 Gy (range, 23-50 Gy). The doses of 38 IF sites (86%) were estimated at >45 Gy.

Discussion

Insufficiency fractures occur most often in elderly women with postmenopausal osteoporosis (2). Other predisposing factors include rheumatoid arthritis, corticosteroid therapy, heparin use, diabetes mellitus, low body weight, current smoking, and RT (15). Fu et al (16) reported that the incidence of IF increased when the dose was above the threshold of 45 Gy. However, there have been no tolerance dose data for IF. In conventional pelvic RT, the irradiated dose of the pelvic bone is usually 45-50 Gy, and the development of IF after pelvic RT at this level has been considered a rare complication (3-5).

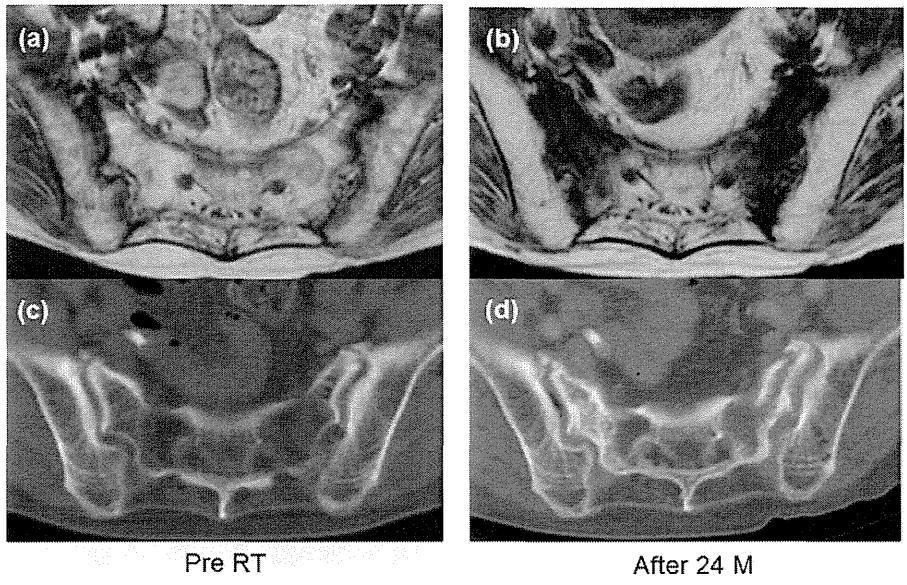

Fig. 1. Pelvic MRI shows low signal intensity in both sacroiliac joints (b) after radiotherapy (RT). Pelvic bone window CT shows (d) cortical fractures and sclerotic changes in the bilateral sacroiliac joints. M = month.

However, several recent studies (6-10) showed that the incidence of IF after pelvic RT might have been underestimated in gynecologic patients. Among these studies, the cumulative incidence of symptomatic IF at 2 years was 11.1%-14.9%, and that at 5 years was 8.2%-17.9%. In our series the cumulative incidence of IF was 36.9% at 2 years in all patients and 16.1% in symptomatic patients. The results of this study showed a relatively higher incidence of IF compared with previously reported data (2-10); however, the rate of occurrence of symptomatic IF was in accordance with other recent studies (6-10). In their prospective MRI study, Blomlie et al (13) reported that 89% of patients (16 of 18) had findings compatible with IF after pelvic RT. They showed that signal changes of MRI in pelvic bones were seen until 24 months after the end of RT, and 56% of patients (10 of 18) complained of pelvic pain. Abe et al (11) showed a 34% incidence of IF after pelvic RT using bone scintigraphy. We performed CT and MRI during the follow-up at least 2 times per year, so as to detect asymptomatic patients (12 of 21, 57.1%) with IF.

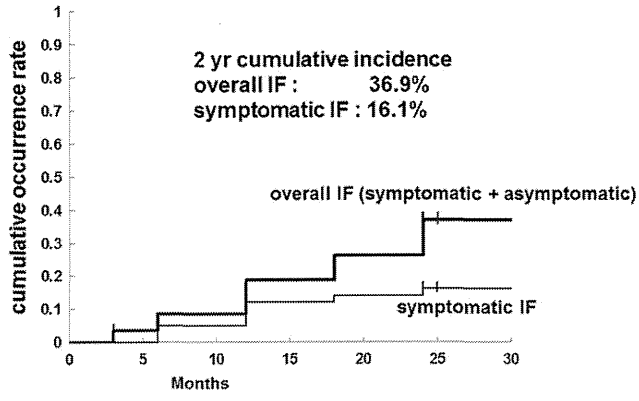

Fig. 2. Graph shows the overall incidence of both symptomatic and asymptomatic insufficiency fractures (IF) (thick line) and the incidence of symptomatic insufficiency fractures (thin line) after pelvic radiotherapy for cervical cancer.

The characteristics of irradiated patients can affect the incidence of IF. As revealed in our study, older patients receiving pelvic RT are more susceptible to the development of IF. In our study the incidence of IF at 2 years in patients aged >70 years was 52.8%, almost all the patients were elderly (the median age was 73 years), and all but 4 of the patients were postmenopausal. In the study by Ogino et al (6) all IF patients were postmenopausal, whereas in the study by Baxter et al (8) some of the patients were aged >65 years.

Our study showed that the SI joints are the most commonly involved site of pelvic IF, which agrees with the reports of several previous investigators (7, 9, 10). In our study most fractures were located at the SI joints; a solitary pubic bone fracture was seen in only 1 patient, and solitary acetabulum fracture was not seen. These findings indicated that initial mechanical failure of the sacrum causes other subsequent pelvic bone fracture (10, 13).

As has been reported by many investigators (2, 4, 6, 7, 13), our study showed that the symptoms of all patients were resolved after conservative management based on analgesics and rest. The extent of the lesions may correlate with the severity of symptoms. In the series reported by Blomlie et al (13), all patients without pain had smaller lesions (<1 cm^2) on MRI, and it was suggested that small fractures might not be painful. In our study symptomatic patients were more likely to have IF at multiple sites of pelvic bone (mean 2.7 sites) than asymptomatic patients (mean 1.7 sites).

The risk factors of osteoporosis are closely correlated with the development of IF (3, 6). Blomlie et al (13) showed that 95% of patients with IF reported in the literature were postmenopausal women. Ikushima et al (7) reported that the mean age of patients who developed IF was significantly higher than that of other patients (69 years vs 59 years, $P<.01$). Ogino et al (6) showed that low body weight (≤49 kg) and more than 3 deliveries were significant factors for the development of symptomatic IF. In our study, both low body weight (<50 kg) and older age (>70 years) were significant predisposing factors for IF in multivariate analysis. Many medical illnesses or medications, such as rheumatoid arthritis, hyperthyroidism, and corticosteroids, are also reported as risk factors for osteoporosis.

Table Risk factors associated with the development of IF

Variable	IF/n	*P*	
		Univariate	Multivariate
Age (y)		.004*	.007*
≤70	4/26		
>70	17/33		
Weight (kg)		.007*	.013*
<50	15/29		
≥50	6/30		
Stage		.347	.368
I	12/35		
II	9/24		
Simulation		.249	.271
X-ray	13/30		
CT	8/29		
Beam technique		.192	.211
AP/PA	15/35		
4-field	6/24		
Energy of X-ray		.928	.931
10 MV	14/40		
>10 MV	7/19		
Facilities		.932	.569
East	11/31		
West	10/28		

Abbreviations: AP/PA = anteroposterior/posteroanterior parallel opposing field; IF = insufficiency fracture.
* $P<.05$.

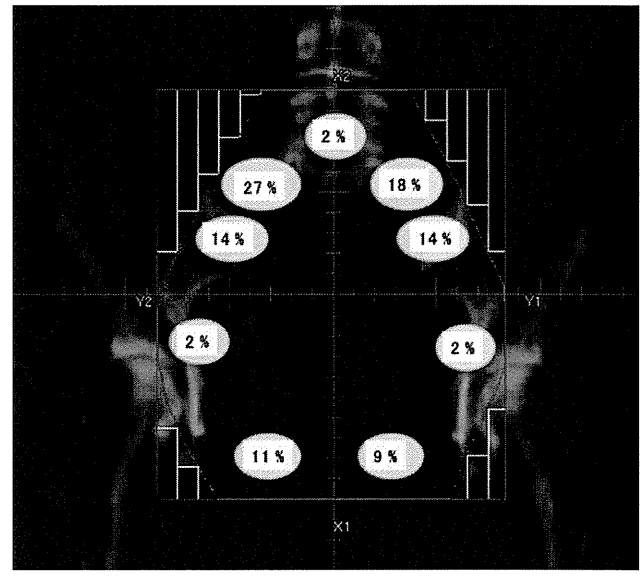

Fig. 3. Schematic shows the distribution of insufficiency fractures in our study population. Some patients had multiple fractures.

In our study, no patients had a history of either rheumatoid arthritis or hyperthyroidism.

It is well known that radiation toxicity is strongly correlated with irradiated volume and dose. In our study, both the 4-field box technique and the AP/PA parallel opposing technique were used. In the 4-field box technique, lateral portals could spare the irradiated volume of the small bowel and rectum and also spare the irradiated volume of the posterior portion of the sacrum and SI joints. Oh et al (9) reported that the incidence of IF was higher in patients receiving the AP/PA technique than in those receiving the 4-field box technique in univariate analysis. In our study there was no significant difference between the 2 techniques. However, in our study these techniques differed only until 20 Gy of EBRT, and the following 30 Gy of EBRT was administered through the same whole-pelvic field with MB.

Patients who received a higher irradiated dose to the pelvic bone had a greater risk of IF. In our study the external-beam doses of all 44 IF sites were estimated to have a median dose of 49 Gy, and the doses of 38 IF sites (86%) were estimated at >45 Gy. There might be a threshold dose for IF at approximately 45 Gy, as reported by Fu et al (16). Oh et al (9) reported that the risk factors of IF were receiving a higher dose (>50.4 Gy) and receiving curative RT. In our study all patients received 50 Gy by EBRT and received an additional dose of HDR-ICBT. Fu et al (16) calculated the contribution of the brachytherapy dose to the pelvic bone and estimated it to be approximately 10% of the central brachytherapy dose. It was uncertain whether this small additional dose of HDR-ICBT to the pelvic bones was one of the causes of the higher occurrence of IF in our study.

Concurrent chemoradiation therapy is used frequently in gynecologic cancer for increasing tumor control, but it is well known that it also increases radiation toxicity. Thus many investigators have thought that combination therapy with radiation and chemotherapy might increase the risk of IF, but there have been few studies to evaluate this (17). Jenkins et al (17) reported that combined treatment with radiation and chemotherapy might predispose to pelvic fracture in patients with cervical cancer.

Oh et al (9) suggested 2 approaches to reduce the risk of IF. The first approach is to improve the osseous environment by treatment of osteoporosis, and the second approach is to reduce radiation toxicity (9). Sambrook et al (18) reported that bisphosphonate has been used as an effective agent for treatment of osteoporosis, and Guise et al (19) reported that it has also been shown to be effective to reduce cancer-induced bone loss. Further study is required to determine whether it can reduce the risk of IF in patients with high-risk factors such as older age and lower body weight.

The irradiated volume and dose to the sacrum and SI joints might correlate with the risk of IF. Ogino et al (6) suggested that a multibeam arrangement by CT planning could shield the posterior portion of the sacrum and SI joints without inadequate coverage of the target volume. Intensity modulated radiation therapy (IMRT) can reduce the irradiated dose and volume of normal tissue (20). It may be difficult to achieve significant sparing to reduce the risk of IF because of its proximity to the target volume; however, bone-sparing IMRT may reduce the radiation dose to the pelvic bones and result in a decrease in the occurrence of IF.

There were some limitations to our study. First, we could not evaluate the presence and severity of osteoporosis in patients before treatment. This might have led to under- or overestimation of the true prevalence of pelvic IF.

Second, we did not obtain a short-time-inversion-recovery (STIR) sequence on MRI. Blomlie et al (13) reported that STIR imaging may be the best sequence for visualizing insufficiency fractures, but we did not use this technique because STIR imaging does not provide good contrast between gynecologic organs and the surrounding tissues.

Third, there is no histologic proof that a pelvic IF is indeed just that and not a pathologic fracture within a metastatic or other bone

lesion. However, many investigators (10-13) have emphasized that an appropriate reading of CT, MRI, and/or bone scan is able to definitively diagnose IF. And some investigators (10) have reported that biopsy of a lesion is not recommended because of the high probability of fracture and low diagnostic efficiency.

In conclusion, the development of IF is not a rare complication of standard pelvic RT for cervical cancer, especially in elderly women with low body weight. If patients complain of pelvic pain after pelvic RT for gynecologic malignancies, pelvic IF must be considered in the differential diagnosis. The symptoms of most patients are resolved after conservative management based on analgesics and rest. Knowledge of the IF is useful to rule out bone metastases and thus avoid inappropriate treatment. We plan to conduct a further prospective study in such patients to evaluate whether treatment of osteoporosis using bisphosphonate or sparing bones by using IMRT can decrease the risk of development of IF.

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Alternating chemoradiotherapy in patients with nasopharyngeal cancer: prognostic factors and proposal for individualization of therapy

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The purpose of this study is to assess the efficacy of alternating chemoradiation in patients with nasopharyngeal cancer. From 1990–2006, 100 patients with nasopharyngeal cancer were treated with alternating chemoradiation at the Aichi Cancer Center. Of these, 4, 2, 23, 34, 13 and 23 patients were staged as I, IIA, IIB, III, IVA and IVB, respectively. The median radiation doses for primary tumors and metastatic lymph nodes were 66.6 Gy (range, 50.4–80.2 Gy) and 66 Gy (range, 40.4–82.2 Gy), respectively. A total of 82 patients received chemotherapy with both cisplatin and 5-fluorouracil (5-FU), while 14 patients received nedaplatin (CDGP) and 5-FU. With a median follow-up of 65.9 months, the 5-year rates of overall survival (OAS) and progression-free survival (PFS) were 78.1% and 68.3%, respectively. On multivariate analysis (MVA), elderly age, N3, and WHO type I histology proved to be significantly unfavorable prognostic factors of OAS. As for PFS, there were T4, N3, and WHO type I histology in MVA. Acute toxicities of hematologic and mucositis/dermatitis ≥ Grade 3 were relatively high (32%); however, they were well-managed. Late toxicities of ≥ Grade 3 were three (3%) mandibular osteomyelitis and one (1%) lethal mucosal bleeding. Results for alternating chemoradiation for nasopharyngeal carcinoma are promising. In order to improve outcomes, usage of intensity-modulated radiation therapy and application of active anticancer agents are hopeful treatments, especially for groups with poor prognosis factors with WHO type I histopathology, T4 and/or N3 disease.

Keywords: nasopharyngeal carcinoma; alternating chemoradiation; WHO type I histopathology

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a common disease among Southern Chinese, Southeast Asian, Northern African and Inuit populations. In Japan, the USA and Western European countries it is relatively rare. Because of anatomical characteristics, surgical treatment is very difficult. In addition, the majority of NPC patients revealed undifferentiated carcinoma, which is relatively sensitive to radiation therapy. Therefore, radiotherapy is widely accepted as the first choice of therapy for NPC. In recent years, by randomized-control trials, chemoradiotherapy has shown significant survival benefits over radiotherapy alone, improving both local and distant control [1–4]. In addition, meta-analysis of eight randomized trials showed significant benefits for OAS and event-free survival [5]. The pooled hazard ratio of death was 0.82 (95% confidence interval, 0.71–0.94; $P = 0.006$), corresponding to an absolute survival benefit of 6% at 5 y from the addition of chemotherapy. Thus, the standard treatment for locally advanced NPC is now believed to be concurrent chemoradiotherapy. However, several key factors need further clarification. Firstly, the chemotherapy used in the Intergroup 0099 study (IGS) consisted of three courses each of concurrent administration of cisplatin (CDDP) and adjuvant chemotherapy with both CDDP and 5-fluorouracil (5-FU). However, about two thirds (63%) of patients could receive concurrent chemotherapy, and about half (55%) could receive the full course of adjuvant chemotherapy. Secondly, a higher incidence of adverse events ≥ Grade 3 was observed in the chemoradiation group than in the radiation alone group (59% vs 34%). Finally, chemoradiation reduced distant metastasis; however, it did not reach sufficient levels. Of the 18 patients with recurrence in the

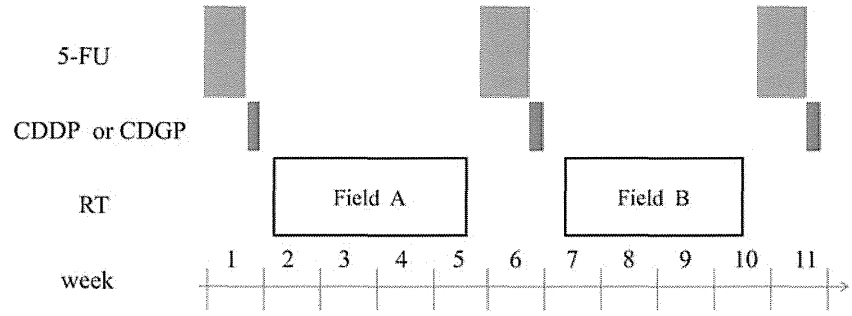

Fig. 1. Study design of alternating chemoradiotherapy. 5-FU = 5-fluorouracil 800 mg/m^2 on Days 1–5 continuous infusion, CDDP = cisplatin 50 mg/m^2 Day 6–7, CDGP = nedapatin 130 mg/m^2 on Day 6, RT = radiotherapy, Field A = large field including from the skull base to supraclavicular fossa, Field B = boost field including the nasopharynx and metastatic lymph nodes.

chemoradiation arm, 10 (56%) developed distant metastasis (DM) in the IGS. A considerable incidence of DM still developed in the IGS due to insufficient dose intensities of chemotherapy, instead of increasing adverse events.

In the Aichi Cancer Center, we conducted alternating chemoradiotherapy for advanced NPC patients from 1987 and reported promising results with sufficiently better compliance (94%), of which the 5-year OAS and PFS rates were 75% and 63%, respectively [6]. In the present study, we analysed the efficacy of alternating chemoradiotherapy for NPC with relatively longer follow-up and sought to refine our treatment strategy according to data regarding failure patterns.

MATERIALS AND METHODS

Patient characteristics

Between 1990 and 2006, a total of 100 consecutive patients with newly diagnosed histology-proven nasopharyngeal carcinoma underwent definitive chemoradiotherapy (CRT) in the Aichi Cancer Center. All patients underwent fiber-optic nasopharyngoscopy and magnetic resonance imaging (MRI) to assess the extent of primary and cervical lymph nodes. Evaluation of distant metastasis was done by chest X-ray, computed tomography (CT), liver ultrasonography, and bone scintigraphy. After 2002, positron emission tomography (PET) or PET-CT was also used to evaluate the extent of the disease. In addition, laboratory data, electrocardiograms, and 24-h creatinine clearance were evaluated to assess general condition. For this analysis, all patients were restaged according to the 6th edition of the American Joint Committee on Cancer (AJCC) staging system [6].

Treatment schedule

Chemotherapy

The treatment scheme is shown in Fig. 1. Details of the treatment regimen have been reported in another article [7]. Chemotherapy regimens were a combination of CDDP and 5-FU (FP) or nedaplatin (CDGP) and 5-FU (FN) regimens. In the FP regimen, 5-FU was administered continuously at a dose of 800 mg/m^2 on Days 1–5 and CDDP at a dose of 50 mg/m^2 on Days 6–7. In the FN regimen, 5-FU was administered continuously at a dose of 800 mg/m^2 on Days 1–5 and CDGP at a dose of 130 mg/m^2 on Day 6. Chemotherapy was performed in principal three times at 4-week intervals. However, when a WBC count <3000/mm^2 or a platelet count <100 000/mm^2 was obtained at the scheduled date of drug administration, chemotherapy was postponed and radiation therapy was alternately prescribed. When hematological data obtained two weeks after radiotherapy did not meet the inclusion criteria (WBC count >3000/mm^2 and platelet count >100 000/mm^2), the next cycle of chemotherapy was withdrawn. When the WBC count decreased to <1000/mm^2 or the platelet count decreased to <25 000/mm^2 after chemotherapy, doses of both 5-FU and CDDP were decreased by 25% at the next cycle. In addition, the dose of CDDP only was decreased by 25% when serum creatinine levels >1.5 mg/dl were noted.

Radiotherapy

Using a 6–10 MV photon beam by linear accelerator, external beam radiotherapy commenced 2–3 d after the completion of previous chemotherapy. At simulation and daily treatment, the head, neck and shoulder were immobilized in a hyperextended position using a thermoplastic mask. Radiotherapy was performed with a daily fraction of 1.8–2.0 Gy. The initial radiation field covered the nasopharynx and upper and middle cervical regions using bilateral opposing portals and lower cervical, and supraclavicular region using anterior single field irradiation at a dose of 36–40 Gy. Then, a shrinking field of 26–30 Gy was boosted to the nasopharynx and involved lymph nodes using the dynamic conformal rotational technique. In the shrinking field, we kept enough margins of primary tumors and involved lymph nodes from the edge of field. Those margins were mainly decided dependent on proximity to

critical structures such as the brain-stem, spinal cord, optic pathway and temporal lobes. During the second period of chemotherapy, radiotherapy was temporarily interrupted to spare the increasingly acute toxicity of 5-FU. Additional boosts of up to 10 Gy with stereotactic multiple arc treatment were also permitted, if residual tumors existed at primary sites.

Follow-up and statistical consideration

Toxicities of CRT were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [8]. During the treatment period, complete blood counts and biochemical examinations were performed at least once a week. After completion of CRT, the treatment response was assessed by fiberoptic nasopharyngoscopy, MRI and/or PET/CT. The frequency of follow-up was every month for the first year, once every two months between the second and third post-treatment year, and once every three months after the third post-treatment year. Fiberoptic nasopharyngoscopy was performed at every visit, and post-treatment MRI scans were obtained every three months for the first year and then every six months thereafter. The survival period was calculated from the start of treatment to death or the last follow-up examination, and progression-free survival was defined as the period from the start of treatment to the progression of tumors or death by any cause. Overall survival and progression-free survival curves were calculated by the Kaplan-Meier method [9]. The log-rank test was used to compare survival curves. A Cox-proportional hazard model was used for multivariate analysis. Differences in the ratios between the two groups were assessed by the chi-square test.

RESULTS

Patient characteristics

Between June 1990 and March 2005, 100 patients with NPC received definitive CRT in the Aichi Cancer Center. Table 1 shows patient characteristics in this cohort. We analysed all patients who were treated with CRT. The median age was 55 years old (range, 28–80). Performance status was distributed as 2 of 0, 93 of 1, 3 of 2, and 2 of 3, respectively. Of these, 8 patients (8%) had histopathology with keratinizing squamous cell carcinoma (WHO type I), and 70 patients (70%) had Stage III–IVB disease. During this period the number of patients with NPC who were treated with radiotherapy alone was 13. The common reasons for radiotherapy alone were advanced age or poor general condition.

Table 1. Patient characteristics

Characteristics			*n*
Age, years: median (range)		55 (28–80)	
Gender:			
	Male		72
	Female		28
Performance status			
		0	2
		1	93
		2	3
		3	2
Histology			
		type I	8
		non type I	90
		others	2
T stage			
		1	37
		2a	15
		2b	15
		3	15
		4	18
N stage			
		0	11
		1	31
		2	34
		3a	9
		3b	15
Stage			
		I	4
		IIA	2
		IIB	24
		III	34
		IVA	12
		IVB	24

Treatment contents

The median dose to the primary site was 66.6 Gy (range, 50.4–80.2 Gy), and the median dose to involved lymph nodes was 66 Gy (range, 40.4–82.2 Gy), respectively. The median period of the whole course of alternating CRT was

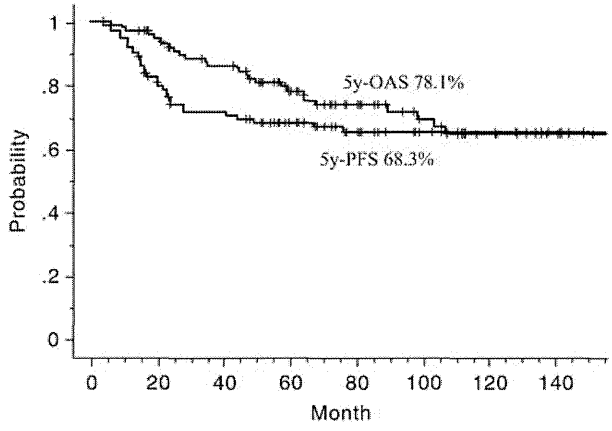

Fig. 2. Overall survival (OAS) and progression-free survival (PFS) curves.

85 days (range, 47–147 days), and the median period of overall treatment time of radiation therapy (OTT) was 69 days (range, 42–110 days).

Treatment outcomes

The 5-year rates of OAS and PFS were 78.1% and 68.3%, respectively (Fig. 2). The 5-year rates of OAS of the group divided by stage were 100, 100, 86.1, 77.6, 91.7 and 60.3% for Stage I, IIA, IIB, III, IVA and IVB, respectively. The 5-year rates of OAS and PFS of 96 patients who received alternating CRT were 78.2% and 68%, respectively. As for initial response after completion of CRT, complete remission (CR) rates of primary and nodal lesions were 86% and 83%, respectively. At a median follow-up of 65.9 months (range, 3.9–22.9 months), 62 were alive without disease, 11 were alive with disease, 18 died from the disease, 2 died from other diseases (both esophagus carcinoma) and 7 died from unknown reasons.

The 5-year rates of loco-regional progression-free survival (LRPFS) and distant metastasis-free survival (DMFS) were 77.9% and 87.8%, respectively.

A total of 32 patients (32%) developed treatment failure at one or more sites. Disease progression developed in 19 for primary, 9 for regional and 11 for distant sites at the last follow-up. Among 11 patients with distant failure, the most frequent site was the lung in 8, followed by bone in 4 and the liver in 2.

Of 21 patients who developed locoregional recurrence, 13 were treated with additional chemoradiation. Of the remainder, 2 patients were re-treated with radiotherapy alone, and 4 with only chemotherapy. One patient received neck dissection for regional failure, and another did not receive any treatment because of the patient's refusal for treatment.

Out of 11 patients who developed distant metastasis, 9 were treated by chemotherapy, and 2 patients received palliative radiotherapy only.

Univariate analysis

Univariate analysis (UVA) results are listed in Table 2.

Elderly age, male, WHO type I histology, and N3 were revealed as significant unfavorable prognostic factors of OAS. The 5-year rate of OAS of the group with WHO type I histology was significantly lower than that with non-type I histology (33.3% vs 81.6%, $P<0.0001$, Fig. 3). The group with N3 lesions had significantly worse 5-year OAS (60.3%) than that with N0–2 (84%; $P=0.0017$). The 5-year rates of OAS of patients who received reduced dose and planned dose chemotherapy were 76.6% and 78.6%, respectively ($P=0.75$).

As for PFS, significantly unfavorable factors were revealed as WHO type I histology, T4 and N3.

The 5-year PFS rate of the group with N3 was significantly lower than that with N0–2 (41.5% vs 76.5%, $P=0.001$). The 5-year PFS rate of the group with T4 was significantly lower than that with T1–3 (54.5% vs 71.4%, $P=0.014$). The 5-year rates of PFS of patients who received reduced dose and planned dose chemotherapy were 69.7% and 66.7%, respectively ($P=0.59$).

The 5-year rate of LRPFS of the group with WHO type I histology was significantly lower than that with non-type I histology (21.4 % vs 84.5 %, $P<0.0001$).

The 5-year rate of DMFS of patients with N3 was significantly lower than that with N0–2 (62.8% vs 95.1%, $P<0.0001$). The 5-year LRPFS of patients with T4 was significantly lower than that with T1–3 (63.3% vs 81.1%, $P=0.027$).

Multivariate analysis

Multivariate analysis (MVA) results are listed in Table 3. On MVA, significantly unfavorable prognostic factors of OAS were elderly age, WHO type I histology and N3, respectively. As for PFS, they were WHO type I histology, T4 and N3, respectively.

Treatment compliance

Regarding the contents of chemotherapy, 82 patients received FP, while 14 received FN. Four patients had other chemotherapy regimens, as described below. One patient with Stage I (cT1N0M0) received two courses of CDDP/5-FU followed by definitive radiotherapy. One patient received six courses of weekly docetaxel (TXT) because of elderly age and poor medical condition. One patient received chemotherapy with both CDGP and TXT because 5-FU was inappropriate due to a past history of myocardial infarction. One patient received concurrent administration with decreased doses of CDGP and 5-FU due to elderly age. Chemotherapy compliance is shown in Table 4. In 96 patients who received alternating CRT, over 90% of patients received three courses of chemotherapy and 70% of patients received the planned dose of three courses. In

Table 2. Univariate analyses for overall survival and progression-free survival

Factors	No.	5-year OAS (%)	*P*-value	5-year PFS (%)	*P*-value
Gender					
Female	28	88.7	0.017	77.9	0.15
Male	72	73.8		64.4	
Age (years)					
<51	48	93.4	0.0006	73.6	0.26
≥51	52	64.2		63.4	
PS					
0, 1	95	79.1	0.148	69.9	0.1
2, 3	5	60		30	
Histology					
WHO non type I	90	81.6	$P<0.0001$	72.1	$P<0.0001$
type I	8	33.3		14.3	
T stage					
T1–3	82	78.2	0.79	71.4	0.014
≥T4	18	77.4		54.5	
N stage					
N0–2	76	84	0.001	76.5	0.001
N3	24	60.3		41.5	
Total treatment duration (day)					
<85	48	69	0.0615	62.3	0.135
≥85	52	85.6		73.8	
OTT (day)					
<69	49	78.2	0.884	72.2	0.36
≥69	51	78.2		64.8	
Dose for primary site (Gy)					
<66	30	76.7	0.712	70	0.7
≥66	70	78.7		67.5	
Dose for metastatic LN (Gy)					
<66	35	77.5	0.683	71.8	0.78
≥66	54	74.8		65.1	

OAS = overall survival, PFS = progression-free survival, PS = performance status, WHO = World Health Organization, OTT = overall treatment time of radiotherapy, LN = lymph node.

detail, 29 patients received reduced dose chemotherapy while 67 patients received the planned dose of three courses. The most common reason for dose reductions was renal dysfunction (47%), followed by severe mucositis (20%). The median total dose of CDDP was 300 mg/m^2 (range, 150–340 mg/m^2), CDGP was 375 mg/m^2 (range, 80–400 mg/m^2), and for 5-FU was 12 000 mg/m^2 (range, 3050–12 000 mg/m^2). In the cohort of patients who received reduced dose chemotherapy, the median total doses of CDDP, CDGP and 5FU were 250 mg/m^2, 330 mg/m^2 and 9400mg/m^2, respectively. Unplanned interruption of RT was experienced in 14 patients (14%), and 2 out of 14 patients required a break in RT over seven days. Severe mucositis (36%) was the most common reason for interruption of RT, followed by infection of the hyperalimentation catheter (29%).

Treatment toxicity

Acute toxicities observed during treatment are listed in Table 5. The most common toxicity was leukopenia. Grade

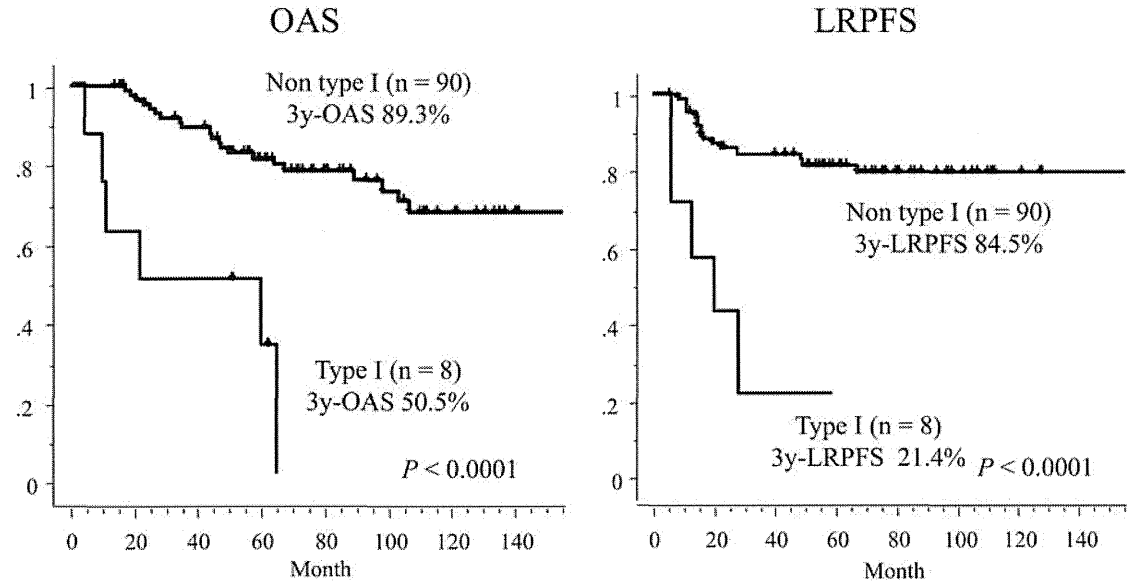

Fig. 3. Overall survival (OAS) and locoregional progression-free survival (LRPFS) curves of groups divided by WHO histopathological types.

Table 3. Multivariate analyses for overall survival and progression-free survival

		OAS		PFS	
Factors	**No.**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Gender					
Female	28		0.109		0.5
Male	72	2.76 (0.104–1.257)		1.36 (0.291–1.836)	
Age (years)					
<51	48		0.0018		0.198
≥51	52	4.92 (0.074–0.551)		1.62 (0.294–1.290)	
Histology					
WHO non type I	90		0.0034		0.0004
type I	8	4.62 (0.077–0.603)		5.747 (0.067–0.454)	
T stage					
T1–3	82		0.555		0.023
T4	18	1.36 (0.264–2.047)		2.5 (0.181–0.881)	
N stage					
N0–2	76		0.0076		0.0025
N3	24	3.03 (0.147–0.745)		3.012 (0.163–0.680)	
OTT (day)					
<69	49	1.10 (0.395–2.065)	0.8092		0.605
≥69	51			1.215 (0.393–1.724)	

HR = hazard ratio, CI = confidence intervals, OAS = overall survival, PFS = progression-free survival, WHO = World Health Organization, OTT = overall treatment time of radiotherapy.