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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

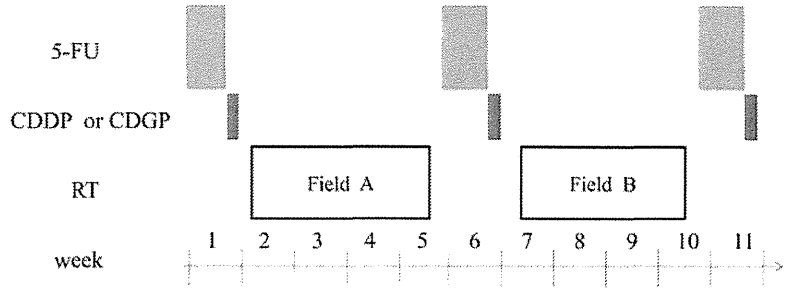

Fig. 1. Study design of alternating chemoradiotherapy. 5-FU = 5-fluorouracil 800 mg/m^2 on Days 1–5 continuous infusion, CDDP = cisplatin 50 mg/m^2 Day 6–7, CDGP = nedapatin 130 mg/m^2 on Day 6, RT = radiotherapy, Field A = large field including from the skull base to supraclavicular fossa, Field B =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

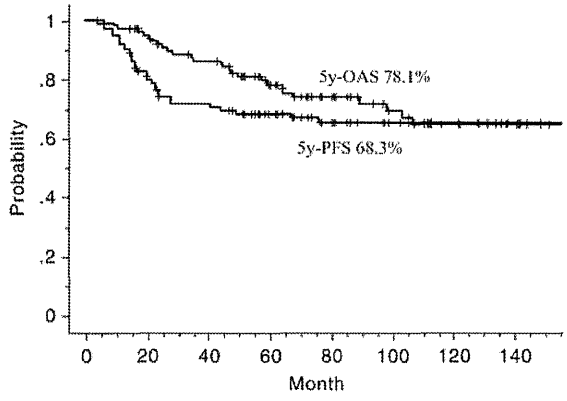

Fig. 2. Overall survival (OAS) and progression-free survival (PFS) curves.

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

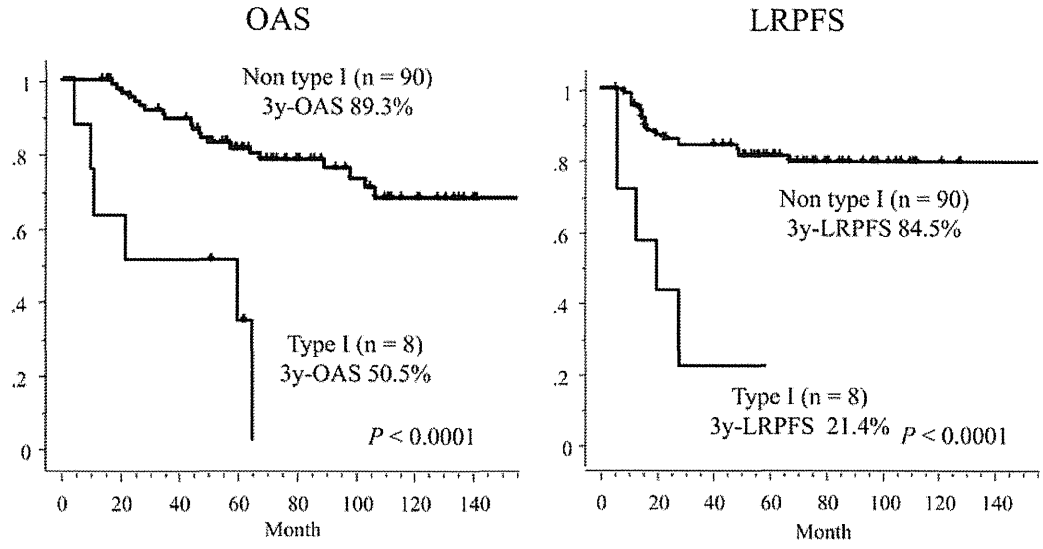

Fig. 3. Overall survival (OAS) and locoregional progression-free survival (LRPFS) curves of groups divided by WHO histopathological types.

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.

3 or higher leukopenia, neutropenia, thrombocytopenia and anemia occurred in 37, 22, 11 and 18 patients, respectively. Grade 3 or higher mucositis and dermatitis developed in 20 and 18 patients, respectively.

Late toxicities are listed in Table 6. Three Grade 3 osteomyelitis of the mandible occurred in this series. One patient died because of late toxicity due to lethal mucosal bleeding. The patient diagnosed as cT3N1M0 with histology of Type I received 80 Gy to the primary site including additional SRT boosts of 10 Gy due to an insufficient response at the planned 70 Gy. The patient developed active mucosal bleeding in the nasopharynx, and died five years later. We experienced no Grade 3 or higher late toxicity of brain necrosis, visual disturbance or swallowing disturbance.

DISCUSSION

A randomized control trial showed survival advantages of concurrent chemoradiotherapy over radiation alone, thus it is believed to be the standard treatment for locally advanced NPC. In the IGS, Stage III–IVB patients with NPC were randomized to CRT or RT, and the combined CRT group was treated with radiation and concurrent triweekly CDDP followed by three adjuvant cycles of FP [1]. The 3-year rate of OAS of the RT-only group was significantly lower than that of the CRT group (46% vs 76%; $P < 0.001$), and the same results were noted for the 3-year rate of PFS (24% vs 69%; $P < 0.001$). However, some problems with the results from the IGS were identified. Firstly, results of the RT arm in the IGS seem to be unacceptably bad because the reported 3-year rates of OAS for the same stages were over 70%. One of the reasons for this discrepancy is that the rate of WHO type I histology in the IGS series (24%) is larger than that of endemic regions, which is believed to have adversely impacted on clinical results. Secondly, the compliance of chemotherapy was insufficient in the IGS. The completion rates of planned chemotherapy of concurrent and adjuvant series were reported as 63% and 55%, respectively. In order to confirm this result, the IGS should be extrapolated in endemic regions [4]. In Hong Kong, the NPC-9901 trial on patients with T1-4N2-3M0 disease was designed to confirm the therapeutic ratio achieved by the IGS regimen. Regarding the compliance of chemotherapy, 65% of patients completed all six cycles, and 79% had five cycles. The CRT arm achieved significantly higher failure-free survival (72% vs 62% at 3 years, $P = 0.027$), mostly as a result of improvements in locoregional control. However, DMFS did not improve significantly (76% vs 73%, $P = 0.47$) and OAS was identical (78% vs 78%, $P = 0.97$). In other RCTs reported by Lin and Chen, the CRT arm significantly improved PFS and OAS [2, 3].

There is also evidence by meta-analysis dealing with eight randomized trials of 1753 patients regarding locally advanced NPC. In this analysis, the pooled hazard ratio of death for adding chemotherapy was 0.82 (95% confidence interval, 0.71–0.94; $P = 0.006$), corresponding to an absolute survival benefit of 6% at 5 years (56% vs 62%). A

Table 4. Compliance of chemotherapy

	n	median (range)
Total cycles given		
1	2	
2	7	
≥3	87	
Total dose given		
Cisplatin (mg/m^2)		300 (150–340)
Nedaplatin (mg/m^2)		375 (80–400)
5-fluorouracil (mg/m^2)		12 000 (3050–12 000)

Table 5. Acute, severe and life-threatening toxicities due to chemoradiotherapy

Toxicity	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5	unknown	≥ Gr 3
Leukopenia	4	12	43	32	5	0	4	37
Granulocytopenia	18	27	28	17	5	0	5	22
Anemia	6	33	39	14	4	0	4	18
Thrombocytopenia	28	37	10	8	3	0	4	11
Liver dysfunction	71	20	5	1	0	0	1	1
Renal dysfunction	71	28	0	0	0	0	1	0
Vomiting	33	14	50	3	0	0	0	3
Mucositis	0	13	67	19	1	0	0	20
Dermatitis	0	37	45	17	1	0	0	18
Salivary gland changes	1	13	86	0	0	0	0	0

Table 6. Late, severe and life-threatening toxicities due to chemoradiotherapy

Toxicity	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5	≥ Gr 3
Swallowing dysfunction	95	4	1	0	0	0	0
Visual dysfunction	99	0	1	0	0	0	0
Hearing impairment	81	5	14	0	0	0	0
Osteomyelitis	96	0	1	3	0	0	3
Brain necrosis	99	1	0	0	0	0	0
Bleeding	99	1	0	0	0	1	1

significant interaction was observed between the timing of chemotherapy and overall survival ($P = 0.005$), with the highest benefit resulting from concomitant chemotherapy [5]. However, increasing acute toxicities caused by administration of chemotherapy were also reported in this analysis. In the IGS, acute toxicities of ≥ Grade 3 were reported as 50% and 76% for RT and CRT arms, respectively. Similarly, in the NPC-9901 trial, toxicities of ≥ Grade 3 were observed as 53% and 84% for RT and CRT arms, respectively ($P < 0.01$). The 3-year actuarial rate of late toxicity was slightly higher in the CRT arm than in that of the RT arm, although it was not significant (28% vs 13%, $P = 0.24$).

In our institute, we adopted alternating CRT for NPC from 1987. In a previous report, 32 patients with NPC received alternating CRT, and the 5-year rates of OAS and PFS were 75% and 63%, respectively. A Phase II study of alternating chemoradiotherapy for patients with NPC was performed in four medical institutions including our institution from 1997 and reported promising results with high compliance (91%), of which the 2-year OAS and PFS rates were 94% and 83%, respectively [10]. In the present study with longer follow-up and a larger cohort, the 5-year rates of OAS and PFS were 78.1% and 68.3%, respectively. We think these data are comparable with previous series. In addition, we believe that acute and late complication rates were sufficiently low according to longer follow-up with 65.9 months.

We believe alternating chemoradiotherapy has several advantages in CRT for NPC. Because the radiation field has to be large, severe mucositis and dermatitis sometimes develops and leads to a treatment break. In addition, late complications, such as disturbances in swallowing or hearing sometimes become significant problems. Alternating chemoradiotherapy has the potential benefit in reducing acute toxicities. As for reported data of the NPC-9901 trial, acute mucositis and skin reactions over Grade 3 were observed in 62% and 20% patients in the CRT arm, respectively. In the present study, acute mucositis or dermatitis of ≥ Grade 3 developed in 20% and 18%, respectively. By alternating chemotherapy and radiotherapy, we could also use intensive multi-agent chemotherapy regimens such as FP or FN without increasing acute and late complications. Although our data is a retrospective analysis in a single institute, the 5-year rate of OAS in the present study (78.1%) was more promising than that of the IGS trial (67%). Regarding the compliance of chemotherapy, over 90% patients in the present study could receive three courses of chemotherapy and 70% of our cohort had completed planned full doses. As a result the total dose of chemotherapy in patients who received a reduced dose was still about 80% of the planned dose. Our data is thought to be more encouraging than that of the IGS, in which only 55% patients completed the planned chemotherapy. Failure patterns in CRT for NPC patients are thought to be both loco-regional, but also in distant sites. In the present study, DMFS at 5-years was 87.8%, which was higher than that of the reported series. The 3-year DMFS rate of the NPC-9901 study was reported as 76%. We believe that it was caused by the advantages of intensive chemotherapy in the present study. An unexpected RT break was needed in 14 patients (14%), of which only 2 patients needed RT breaks longer than one week.

The argument against alternating CRT is that planned RT interruptions may lead to sacrifices in treatment efficacy. In many studies, it is well known that prolongation of overall treatment time negatively influences clinical outcomes. *In vitro*, accelerated repopulation occurred 28 days after the start of RT; thus, prolongation of treatment time led to the development of radiation resistance. In the present study, OTT was not significantly related to clinical outcome. One of the reasons is that the high compliance of the present study would have helped avoid essential prolongation of OTT in our cohort.

In the present series, WHO type I histopathology was a significantly unfavorable factor of both OAS and PFS. The incidence of WHO type I histology in Western countries is very different from East Asian countries. In the IGS series conducted in North America, the rate of WHO type I histology was 22%, which was higher than the rates in studies

conducted in endemic regions. WHO type I histopathology, keratinizing squamous cell carcinoma, was reported to be much less related to EBV infection than non-keratinizing carcinoma. It was also reported to be less sensitive to RT [11]. However, there are not so many reports regarding clinical results. One of the reasons is that the proportion of type I histopathology is very low in endemic regions. In Japan, the proportion of type I histopathology is about 20%, which was similar to North America. Kawashima *et al.* reported a Japanese multi-institutional survey of 333 NPC patients, in which the proportion of type I histopathology was 19% [12]. In that series, type I histopathology proved to be a significantly worse prognostic factor of OAS and PFS on both UVA and MVA. In the present study, the population of type I histopathology was 8%; however, these eight patients had remarkably poor prognosis. Six of the eight patients developed treatment failure. In our series, WHO type I histopathology was a significantly worse factor of both OAS (3-year rates; 50.5% vs 89.3%; $P < 0.0001$) and LRPFS (3-year rates; 21.4% vs 84.5%, $P < 0.0001$). The majority of failure patterns of these patients were in loco-regional sites. In order to improve treatment outcomes of these patients, dose escalation without increasing adverse events is believed to be promising. In recent years, intensity-modulated radiation therapy (IMRT) is widely used for head and neck cancer because of its dose conformity ability for PTV, reducing doses to normal tissue. RTOG 0225, a multi-institutional Phase II trial was conducted to test the feasibility of IMRT with or without chemotherapy for NPC. A 90% LRPF rate was reported as well as an acceptably low incidence of Grade 3 adverse events without xerostomia of Grade 4 [13]. In our institution, we started IMRT for NPC patients using Helical Tomotherapy until June 2006, and we have reported our preliminary clinical results [14]. In the future, dose escalation for patients with type I histopathology using IMRT will be helpful for improving clinical results.

The 5-year rates of PFS and LRPFS of patients with T4 were significantly inferior to those with T1–3, even though there was no significant difference in the 5-year rates of DMFS between these two groups. Because of the proximity of tumors to critical structures such as the brain-stem, spinal cord, optic pathway and temporal lobes, the radiation fields and dose coverages for primary tumors are often compromised. Preliminary results of radiation dose escalation for patients with T3–T4 NPC show good local control (2-year rate of locoregional control; 95.7%) and survival (2-year rate of OAS; 92.1%) [15]. For these patients, dose escalation using IMRT is also promising improved clinical results.

The 5-year rates of OAS and DMFS of patients with N3 were significantly inferior to those with N0–2 in the present series. On the other hand, N3 showed no apparent correlation with worsening LRPF. From this result, patients with N3 are expected to have a higher incidence of distant metastasis. Thus, a more effective regimen of chemotherapy should be considered to overcome limitations. In fact, TAX 324, a randomized Phase III trial, has shown the distinct survival advantages of multi-agent intensive chemotherapy including docetaxel and FP over PF for locally advanced head and neck cancer [16].

We believe that the present results for alternating chemoradiotherapy are promising compared to previously reported series of concurrent chemoradiotherapy. However, several subgroups with some risk factors proved to have insufficient outcomes. In order to refine clinical results without increasing adverse events, there is room for modification especially in patients with high-risk factors. Dose escalation using IMRT for type I histopathology and/or T4 disease and more intensive modifications of chemotherapy for N3 disease should be considered in future.

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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.

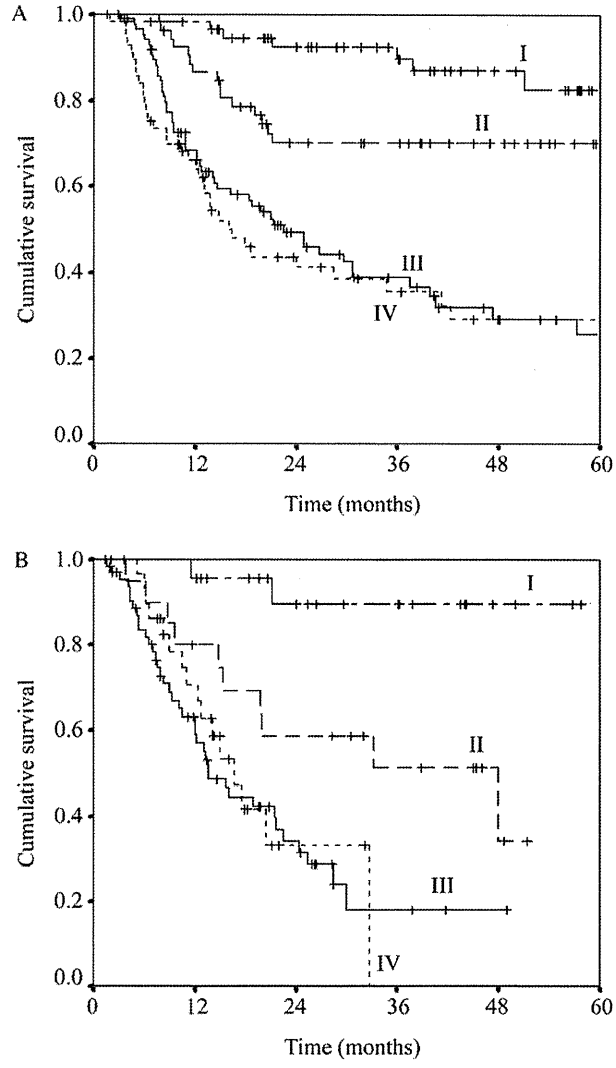

Fig. 1. Survival curves according to the TNM 7th classification of (A) the developmental dataset and (B) the validation dataset. The 3-year survival rates of disease Stages I, II, III, and IV according to the TNM 7th classification were 89.9%, 70.1%, 38.7%, and 35.5%, respectively, in the developmental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

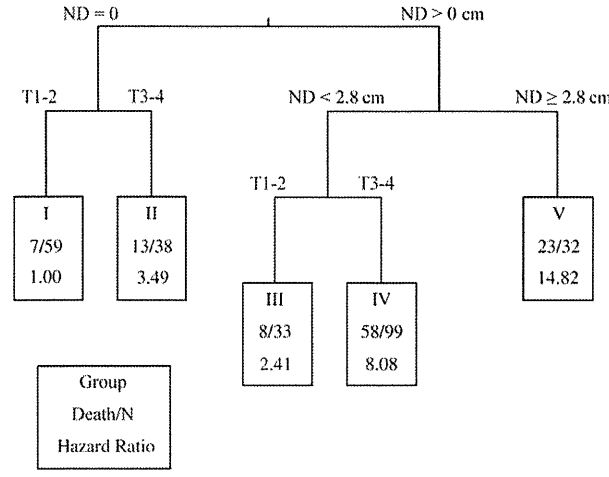

Fig. 2. Recursive partitioning analysis using gender, T, N, and ND stage as variables. In each terminal node, the upper row shows group number, the middle row shows the number of death and patients, and the low row shows the hazard ratio with reference to patients with Stage I.

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

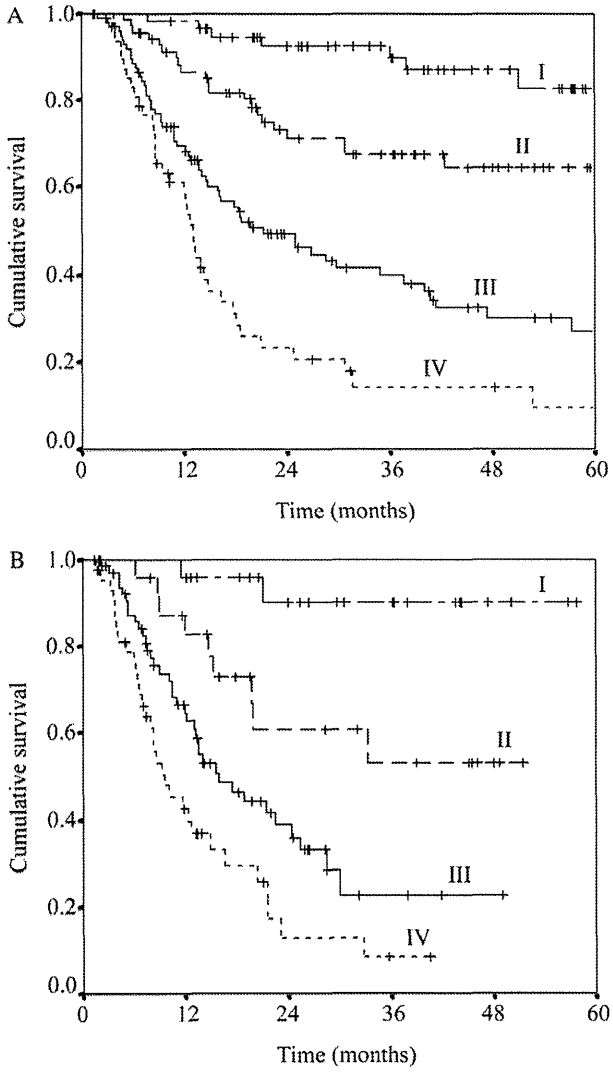

Fig. 3. Survival curves according to the new staging system of (A) the developmental dataset and (B) the validation dataset. The 3-year survival rates of the new Stage I, II, III, and IV were 90.0%, 67.4%, 39.7%, and 21.5%, respectively, in the developmental dataset. The 3-year survival rates of the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

A case of cervical multicentric Castleman disease treated with intensity-modulated radiation therapy using helical tomotherapy

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Abstract Castleman disease (CD) is a rare lymphoproliferative disorder. Two clinical entities are described: a unicentric form with disease confined to a single lymph node region and a multicentric form characterized by generalized lymphadenopathy and systemic symptoms. Although surgery is regarded as standard therapy for the unicentric form, no consensus has been reached concerning the standard treatment for multicentric CD. We report here a case of cervical multicentric CD treated with intensity-modulated radiation therapy (IMRT), using helical tomotherapy to minimize xerostomia in comparison with conventional radiotherapy. A 29-year-old woman complained of neck swelling. Computed tomography showed lymphadenopathy in both sides of the neck. The patient was diagnosed with the plasma cell subtype of CD on biopsy. After initial treatment with prednisone, IMRT was planned to avoid normal structures, for example the parotid gland. The cervical lymphadenopathy shrank gradually during IMRT with 44 Gy in 22 fractions. Four years and 3 months after IMRT, regrowth of cervical lymph nodes has not been detected. The parotid function improved dramatically on quantitative salivary scintigraphy between 3 and 12 months after IMRT. Radiotherapy could be an option for multicentric CD, and IMRT is an effective means of minimizing xerostomia in head and neck lesions.

Keywords Castleman disease · Multicentric · Plasma cell · Intensity modulated radiation therapy · Xerostoma

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Introduction

Castleman disease was first described in 1954 by Castleman et al. [1] and it is still poorly understood because of its rareness. This lymphoproliferative disorder has been histopathologically categorized into two main subtypes and one mixed variant as follows: a hyaline vascular subtype (HV), plasma cell subtype (PC), and mixed variant (MV) [2]. The HV subtype is the most common histological variant of Castleman disease, accounting for 90% of cases. The HV subtype is characterized by small, hyalinized follicles surrounded by circumferentially arranged layers of small lymphocytes interconnected by a prominent vascular stroma. The PC subtype appears as germinal centers with dense plasma cell infiltration in the less vascular interfollicular stroma. The MV subtype is pathologically a mixture of the two other subtypes. Two

clinical entities have also been described: a unicentric form with disease confined to a single lymph node region and a multicentric form characterized by generalized lymphadenopathy, and systemic symptoms such as fever, night sweats, weight loss, splenomegaly, anemia, and hypoalbuminemia [3]. This classification correlates with histopathological variants. The HV subtype is mostly unicentric and the PC and MV subtypes seem to be mostly multicentric [4]. Surgery is regarded as the standard therapy for the unicentric form, with several retrospective series reporting excellent response [5]. Radiotherapy (RT) has also been described as a definitive treatment for both unicentric and multicentric Castleman disease with variable response [5].

A reduction in the ability to produce saliva (i.e., xerostomia) is a common toxicity associated with RT of head-and-neck cancers [6]. In particular, reduced stimulated salivary flow, which is often permanent, negatively affects patient quality of life. Modern RT techniques, in particular intensity-modulated radiation therapy (IMRT), enable highly conformal dose distributions that can selectively spare critical organs at risk, for example the parotid salivary glands. Helical tomotherapy (HT) is a novel IMRT treatment modality. HT is a form of 3D conformal radiation therapy in which treatment beams are spatially and temporally modulated to maximize the dose delivered to the tumor while minimizing the dose delivered to normal structures [7]. In addition, detectors within the tomotherapy system provide megavoltage computed tomographic (MVCT) images of the patient, which can be obtained immediately before treatment for setup, registration, and repositioning. This paper describes a case history of multicentric Castleman disease at cervical sites treated with HT to minimize xerostomia.

Case report

A 29-year-old woman presented to the department of otorhinolaryngology with a complaint of neck swelling. She had no systemic symptoms, for example fever or anemia. Physical examination revealed multiple palpable tumors in the cervical lesions. Computed tomography (CT) of the neck showed a lymphadenopathy in the cervical lesions. CT of the neck to the pelvic site showed no abnormality other than hemangioma of the spleen. There were no laboratory abnormalities. An infection test including HIV turned out to be negative. An incisional biopsy of the cervical enlarged lymph node was performed to obtain material for histological examination. Histopathology from the specimen revealed germinal centers with dense plasma cell infiltration (Fig. 1a) and germinal centers penetrating vessels (Fig. 1b), as seen in the PC subtype of Castleman disease. Because the tumor was regarded as unresectable, prednisone was proposed at a dose of 20 mg/day to reduce the size of the tumor, to relieve the patient's discomfort due to cervical lymphadenopathy. Although the tumor decreased to some extent after a while, it became enlarged again on cessation of prednisone treatment. Because her symptom was only discomfort due to cervical lymphadenopathy, we believed local therapy such as RT might be effective, at least for a palliative purposes. IMRT with HT was planned to minimize xerostomia compared with conventional RT. Magnetic resonance imaging (MRI) of the neck before IMRT showed a lymphadenopathy in both sides of the neck (Fig. 2a, b). The enlarged cervical nodes were levels Ib, II, III, IV, and V. Gross tumor volume (GTV) was defined as a lymph node with a more than 10 mm short axis on MRI. Clinical target volume (CTV) included the GTV with an expansion of 10 mm.

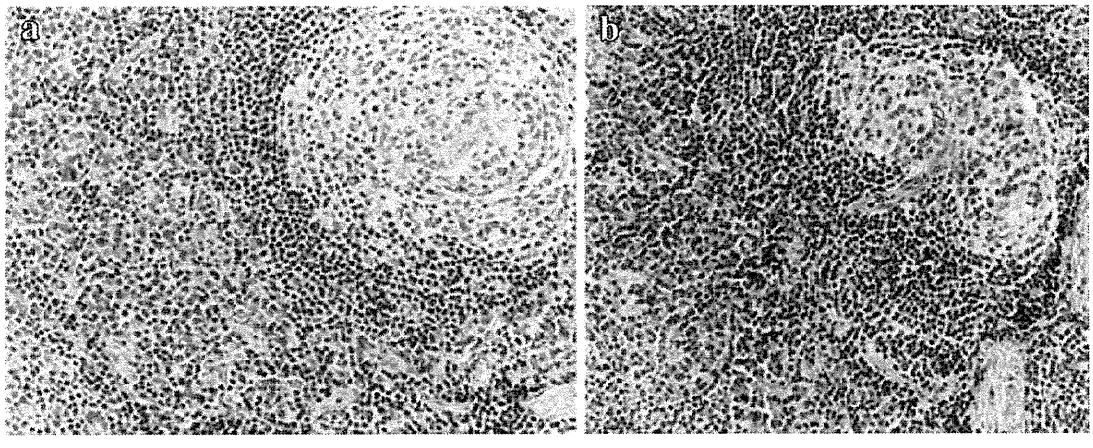

Fig. 1 Histopathology of the specimen revealed germinal centers with dense plasma cell infiltration (**a**) and germinal centers penetrating vessels (**b**) as seen in the plasma cell subtype of Castleman disease (H&E staining)