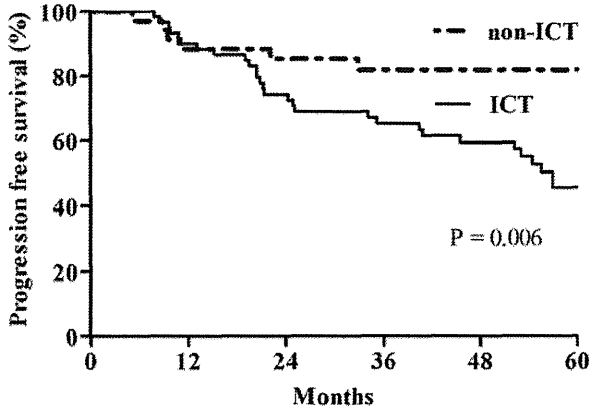

Fig. 4. Progression-free survival of groups using induction chemotherapy (ICT) and non-ICT. The difference between the two groups was statistically significant ($P = 0.006$).

Table 2. Second primary cancer

Site	Number
Esophagus	29
Stomach	11
Lung	5
Oropharynx	4
Colon	4
Larynx	2
Oral cavity	2
Prostate	2
Breast	1
Liver	1
Malignant lymphoma	1

Patterns of treatment failure

At the last follow-up in March 2012, 43 of 97 patients (44.3%) had developed treatment failure: 19 (19.6%) had developed local failure, 23 (23.7%) had developed lymph node failure, and 17 (17.5%) had developed distant failure. Of the 17 patients with distant failure, 11 patients had lung metastasis, four patients had bone metastasis and two patients had skin metastasis. Of the entire group of patients analyzed, 14 (14.4%) had recurrence at two or more sites. Of the 21 patients who received planned surgery, 11 patients (52.3%) developed recurrence. Nine (81.8%) of these patients developed recurrence at regional and/or distant sites.

Second primary cancer

Second primary cancer developed in 44 (45.3%) of the 97 patients (Table 2). The most common site was the esophagus (29 patients), followed by the stomach (11 patients), oropharynx (4 patients) and lung (5 patients). Both synchronous and metachronous double cancers were observed.

Among the 29 patients with esophageal cancer, eight patients were diagnosed before treatment with HPC and 21 patients were diagnosed simultaneously or after treatment for HPC. Of the 21 patients, 18 patients were manageable with curative intent. Seventeen of these patients had superficial esophageal cancer. Regarding the treatment of these 18 patients, six patients were treated with CRT and 12 patients underwent an endoscopic mucosal resection (EMR).

Univariate and multivariate analysis

Table 3 shows the results of the univariate analysis, and Table 4 shows the results of the multivariate analysis for OS, PFS and LC. On univariate analysis, the clinical stage (I–III vs IV), T-stage (T1–2 vs T3–4) and N-stage (N0–1 vs N2) were significant prognostic factors for OS (Table 3). The clinical stage, T-stage, N-stage, total duration of therapy, second primary cancer (yes vs no) and ICT (yes vs no) were significant prognostic factors for PFS. An advanced T-stage was the only significantly unfavorable factor for LC. Using multivariate analysis, only an advanced T-stage remained significant regarding prognostic factors of OS, PFS and LC. Although ICT was a significantly unfavorable factor for PFS in univariate analysis, it was not significant in multivariate analysis.

Treatment toxicities

Acute toxicities of Grade 3 to 4 were observed in 34 patients (35%) (Table 5). The most common hematologic toxicity of Grade 3 to 4 was thrombocytopenia (14.4%). Only one patient demonstrated skin reactions of Grade 3. Grade 3 dysphagia caused by acute mucositis occurred in 20 patients (20.6%).

Regarding late adverse events, pharyngeal edema of Grade 4 occurred in two patients and hypothyroidism of Grade 2 occurred in three patients. No treatment-related death was observed. Among the 20 patients who had Grade 3 dysphagia caused by acute mucositis, three patients remained permanently gastrostomy-dependent due to dysphagia. For these three patients, a gastrostomy was performed after completion of the initial treatment (range 9–14 months). One of these patients was still alive without recurrent disease at the last follow-up, and the other two patients had died due to double cancer.

DISCUSSION

We have reported the clinical results of definitive CRT for HPC at our institution. Table 6 shows the results of the treatment outcomes of HPC reported in past studies. Some

Table 3. Univariate analyses for correlation of prognostic factors according to overall survival, progression-free survival and local control

Factor		n	5-Year OS	P value	HR (95% CI)	5-Year PFS	*P* value	HR (95% CI)	5-Year LC	*P* value	HR (95% CI)
Age (years)	<65	47	68.1	0.149	1.000 (Referent)	60.1	0.613	1.000 (Referent)	83.8	0.120	1.000 (Referent)
	≧65	50	60.7		1.629 (0.760–3.492)	54.9		1.382 (0.883–1.913)	67.0		1.999 (0.837–4.775)
Subsite	PS	72	65.9	0.506	1.000 (Referent)	59.2	0.184	1.000 (Referent)	83.0	0.231	1.000 (Referent)
	Others	25	61.8		0.957 (0.386–2.375)	48.9		1.525 (0.828–2.843)	67.1		2.460 (0.874–6.929)
Stage	I–III	46	76.9	0.007*	1.000 (Referent)	72.3	0.004*	1.000 (Referent)	84.5	0.071	1.000 (Referent)
	IV	51	54.1		2.133 (0.996–4.565)	41.1		2.190 (1.198–4.006)	68.6		2.394 (1.010–5.674)
T	T1–2	54	76.3	0.003*	1.000 (Referent)	65.2	0.017*	1.000 (Referent)	88.1	0.001*	1.000 (Referent)
	T3–4	43	50.4		2.539 (1.161–5.554)	47.1		2.303 (1.221–4.341)	63.1		4.563 (1.870–5.140)
N	N0–1	49	75.7	0.005*	1.000 (Referent)	71.9	0.003*	1.000 (Referent)	84.1	0.074	1.000 (Referent)
	N2	48	54.0		2.876 (1.394–5.934)	42.9		2.463 (1.347–4.505)	68.7		2.252 (0.951–5.325)
RT dose (Gy)	<66.6	43	67.6	0.531	1.000 (Referent)	55.2	0.885	1.041 (0.561–1.934)	82.0	0.392	1.000 (Referent)
	≧66.6	54	62.9		1.394 (0.608–2.797)	61.0		1.000 (Referent)	74.3		1.563 (0.659–3.706)
Total duration of therapy (days)	<85	47	69.4	0.368	1.000 (Referent)	76.8	0.001*	1.000 (Referent)	85.9	0.118	1.000 (Referent)
	≧85	50	60.7		1.388 (0.650–2.936)	40.5		2.228 (1.22–4.071)	68.5		2.067 (0.873–4.895)
Second primary cancer	No	53	56.3	0.204	1.506 (0.800–2.835)	45.6	0.037*	0.558 (0.304–1.023)	73.3	0.368	1.499 (0.620–3.618)
	Yes	44	74.2		1.000 (Referent)	71.8		1.000 (Referent)	85.3		1.000 (Referent)
ICT	No	36	69.7	0.359	1.000 (Referent)	81.9	0.006*	1.000 (Referent)	87.6	0.118	1.000 (Referent)
	Yes	61	62.1		1.371 (0.634–2.963)	45.4		2.397 (1.285–4.473)	71.4		2.235 (0.923–5.416)

HR = hazard ratio, CI = confidence interval, RT = radiotherapy, PS = pyriform fossa, ICT = induction chemotherapy, OS = overall survival, PFS = progression-free survival, LC = local control.
*significant.

Table 4. Multivariate analyses for correlation of prognostic factors according to overall survival, progression-free survival and local control

	OS		PFS		LC	
Factor	**HR (95% C.I.)**	***P* value**	**HR (95% C.I.)**	***P* value**	**HR (95% C.I.)**	***P* value**
Stage	0.836 (0.088–6.128)	0.736	0.586 (0.074–4.620)	0.586	0.958 (0.109–8.467)	0.969
T	3.137 (1.580–6.225)	0.001*	1.822 (1.976–3.402)	0.044*	4.419 (1.562–12.503)	0.005*
N	2.491 (0.316–19.634)	0.386	2.854 (0.376–21.666)	0.310	1.934 (0.242–15.428)	0.534
Total duration of therapy (days)	NA	NA	1.538 (0.502–4.717)	0.451	NA	NA
Second primary cancer	NA	NA	0.618 (0.321–1.190)	0.151	NA	NA
ICT	NA	NA	1.631 (0.486–5.684)	0.442	2.573 (0.741–8.932)	0.137

ICT = induction chemotherapy, OS = overall survival, PFS = progression-free survival, LC = local control, HR = hazard ratio, C.I. = confidence interval, NA = not available
*significant

Table 5. Incidence of moderate to severe toxicity

	Number of patients by toxicity grade	
Factor	**Grade 3**	**Grade 4**
Acute toxicity		
Neutropenia	6	6
Thrombocytopenia	8	4
Anemia	6	0
Mucositis	20	0
Liver function	1	0
Renal function	0	0
Late toxicity		
Pharyngeal dysphagia	3	0
Laryngeal stenosis	0	2
Osteonecrosis of jaw	0	0

studies have also reported the efficacy of ICT for HPC [4, 7]. ICT was usually performed for resectable advanced disease because definitive radiotherapy was selected based on assessment of the tumor response after chemotherapy, and serious complications caused by salvage surgery could be avoided [3]. However, in various clinical studies, the LC and OS rates of the ICT groups were not superior to those of the CCRT groups [1]. Our study was a retrospective analysis using limited cases, and a selection bias could have affected the results. In our study as well, the results of the ICT group were slightly inferior to those of the non-ICT groups; the 5-year OS rates, 5-year PFS rates and 5-year LC rates of the ICT group vs non-ICT groups were 62.1% vs 69.7%, 45.4% vs 81.9% and 71.4% vs 87.6%, respectively.

Some studies have reported outcomes including other sites of head and neck cancer [1, 8, 9], including a postoperative series and a radiotherapy alone series [4, 10–12]. However, few reports regarding definitive CRT for HPC have been published [13, 14]. Lefebvre *et al.* [4] reported the results of a randomized Phase III study comparing an ICT arm with immediate surgery, with or without a postoperative radiotherapy arm, for patients with Stage II–IV HPC. One hundred and ninety-four patients were enrolled in this trial, and the 3/5-year OS rates were 57/30% for the ICT group and 43/35% for the postoperative radiotherapy arm, with 3/5-year disease-free survival (DFS) rates of 43/25% and 32/27%, respectively [4]. Tai *et al.* [14] published the treatment outcomes of ICT followed by CCRT in 42 patients with Stage III–IV HPC at a single institution. The 3-year OS, DFS and LC rates were 35.3%, 33.1% and 54.8%, respectively, with a median follow-up time of 42.9 months [14]. Our reported series included 73 patients with Stage III–IV disease (75%) with relatively longer follow-up, and the acquired results seem to be favorable compared to past studies. With multivariate analysis, the T-stage was the only significant prognostic factor for OS, PFS and LC. We believe our practical results are quite meaningful because of sufficient organ preservation and disease control.

Historically, dysphagia has been reported as significant late toxicity after CRT for patients with HPC. Fukuda *et al.* [9] reported that in low-dose weekly docetaxel-based

Table 6. Results of the treatment outcome for hypopharyngeal cancer

Authors, year	Primary	No. of patients	Treatment	No. of stage III–IV (%)	Chemotherapy	OS (%) (years)	PFS or DFS (%) (years)
Vandenbrouck (1987) [12]	HPC	152	RT alone	130 (85.5)	none	65 (3)	25 (3)
						40 (5)	NA
Lefebvre (1996) [4]	HPC	100	ICT + RT	93 (93)	CDDP + 5-FU	57 (3)	43 (3)
						30 (5)	25 (5)
Altundag (2004) [7]	HPC/LC	5/40	ICT + RT or ICT + CCRT	45 (100)	CDDP + 5-FU	78 (1)	50 (2)
Tai (2008) [14]	HPC	42	CCRT or ICT + CCRT	42 (100)	CDDP + 5-FU + MTX	35 (3)	33 (3)
Lambert (2009) [8]	HPC/LC	27/55	CCRT	82 (100)	CDDP + 5-FU	63 (3)	73 (3)
Fukada (2009) [9]	HPC	34	CCRT or ICT + CCRT	34 (100)	Docetaxel + CDDP + 5-FU	56 (3)	32 (3)
Present	HPC	97	CCRT or	73 (75)	CDDP + 5-FU (or NDP)	76 (3)	60 (3)
			ICT + CCRT (or RT alone)			68 (5)	57 (5)

HPC = hypopharyngeal cancer, LC = laryngeal cancer, RT = radiotherapy, ICT = induction chemotherapy, CCRT = concurrent chemoradiotherapy, CDDP = cisplatin, 5-FU = 5-fluorouracil, MTX = methotrexate, NDP = nedaplatin, OS = overall survival, PFS = progression-free survival, DFS = disease-free survival, LC = local control, NA = not assessed.

chemoradiotherapy for locally advanced oropharyngeal cancer or HPC patients, Grade 3 dysphagia occurred as late toxicity in two patients (3%), and percutaneous endoscopy gastrostomy (PEG) was required in one patient with Grade 3 dysphagia. Lambert *et al.* [8] reported that in concurrent platinum-based chemoradiotherapy for advanced laryngeal cancer and HPC patients, five patients (6%) were still dependent on PEG for adequate intake for a mean duration of 43 months after radiotherapy. In the present study, three patients (3%) were gastrostomy-dependent at the last follow-up because of Grade 3 dysphagia as late toxicity. However, this incidence was relatively low compared to the reported series. Mekhail *et al.* [15] reported that 91 out of 158 patients treated with definitive CRT or RT required feeding tube placement at some time during treatment, and the predictor of a need for feeding tube placement was a hypopharyngeal primary site, female gender, a T4 primary tumor, or treatment with CRT. Furthermore, they reported that PEG patients had more dysphagia than NG tube patients at three months (59% vs 30%, respectively; $P = 0.015$) and at six months (30% vs 8%, respectively; $P = 0.029$), and the median tube duration was 28 weeks for PEG patients compared with eight weeks for NG patients ($P < 0.001$). They suggested that PEG placement for longer periods of time was associated with protracted disuse of the muscle of deglutition, which may result in an increased incidence of pharyngeal stenosis after radiotherapy and may be associated with more persistent dysphagia. In the present study, four patients (4%) had an NG tube inserted some time during treatment for HPC, and none had a PEG tube inserted. In addition, 58 patients (60%) did not require a feeding tube and were able to continue oral intake during treatment. We suggest that these circumstances may be one reason for our lower rate of dysphagia. Among our 97 patients, only 27 patients (27%) underwent CCRT. Most patients underwent ICT or alternating CRT. Alternating CRT has the advantage of reducing toxicity due to reduced concurrent use of cytotoxic agents [16]. Therefore, mucosal toxicity may have been decreased in our series. With increasing treatment intensity, which includes docetaxel plus cisplatin and 5-FU-based sequential therapy, caution should be taken for severe late toxicity. It is necessary to provide attentive care to patients during and after treatment.

HPC patients are well known to have synchronous and metachronous malignancies, especially esophageal cancer. Kohmura *et al.* [17] reported that 18% of HPC patients investigated had esophageal cancer, which followed HPC in fewer than three years in all metachronous cases. Moreover, they reported that most hypopharyngeal cancers were at an advanced stage, but all of the esophageal cancers were at an early stage and were superficial. Morimoto *et al.* [18] reported that 41% of HPC patients investigated had esophageal cancer, and the 5-year OS rates with esophageal cancer were 83% in Stage 0, 47% in Stage I and 0% in Stage IIA–IVB. In this study, 29% of patients investigated had esophageal cancer and 52% of them were metachronous. Furthermore, all of the esophageal cancers following treatment for HPC were at an early stage, were superficial, and could be treated with EMR. We perform annual periodic endoscopic examinations of the upper aerodigestive tract for patients after treatment for HPC. Early detection of esophageal cancer enables successful minimally invasive treatment such as EMR or endoscopic submucosal dissection. To improve the clinical efficacy of HPC, early detection of metachronous malignancies is essential. Therefore, we believe that it is necessary to perform periodic endoscopic examination of HPC patients after treatment.

Recently, narrow band imaging has attracted attention as a screening examination for the head and neck region [19]. Late toxicity after CRT decreases the quality of life for HPC patients who are often first diagnosed at an advanced stage. Therefore, early detection and treatment of HPC in high-risk groups, such as heavy smokers and heavy alcohol consumers, with minimally-invasive screening examinations are expected to refine the clinical outcome of HPC patients.

In conclusion, the clinical efficacy of definitive CRT for HPC is thought to be promising not only for organ preservation but also disease control. Second primary cancer may have a clinical impact on the outcome for HPC patients, and special care should be taken when screening at follow-up.

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CLINICAL INVESTIGATION **Thoracic Cancer**

PROGNOSTIC IMPACT OF THE 6TH AND 7TH AMERICAN JOINT COMMITTEE ON CANCER TNM STAGING SYSTEMS ON ESOPHAGEAL CANCER PATIENTS TREATED WITH CHEMORADIOTHERAPY

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Purpose: The new 7th edition of the American Joint Committee on Cancer TNM staging system is based on pathologic data from esophageal cancers treated by surgery alone. There is no information available on evaluation of the new staging system with regard to prognosis of patients treated with chemoradiotherapy (CRT). The objective of this study was to evaluate the prognostic impact of the new staging system on esophageal cancer patients treated with CRT.

Methods and Materials: A retrospective review was performed on 301 consecutive esophageal squamous cell carcinoma patients treated with CRT. Comparisons were made of the prognostic impacts of the 6th and 7th staging systems and the prognostic impacts of stage and prognostic groups, which were newly defined in the 7th edition.

Results: There were significant differences between Stages I and III ($p < 0.01$) according to both editions. However, the 7th edition poorly distinguishes the prognoses of Stages III and IV ($p = 0.36$ by multivariate analysis) in comparison to the 6th edition ($p = 0.08$ by multivariate analysis), although these differences were not significant. For all patients, T, M, and gender were independent prognostic factors by multivariate analysis ($p < 0.05$). For the Stage I and II prognostic groups, survival curves showed a stepwise decrease with increase in stage, except for Stage IIA. However, there were no significant differences seen between each prognostic stage.

Conclusions: Our study indicates there are several problems with the 7th TNM staging system regarding prognostic factors in patients undergoing CRT. © 2012 Elsevier Inc.

Esophageal cancer, Chemoradiotherapy, American Joint Committee on Cancer, TNM, Prognostic factor.

INTRODUCTION

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

The TNM staging system was recently revised in the 7th edition of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) cancer staging manual, which was published in 2009 (2). The main differences between the 6th and 7th editions include: 1) T is was redefined and T4 was subclassified as T4A and T4B and 2) regional lymph nodes were redefined. N was subclassified according to the number of positive regional lymph nodes, and 3) M was redefined. In addition, prognostic staging, including histological grade and cancer site, was defined for T1-3N0M0 patients.

The 7th edition staging system for esophageal cancer was also revised and was based on retrospective analysis of pathologic data from patients treated only by primary surgical resection (3). However, because of poor outcomes with surgery alone, the current treatment for esophageal cancer incorporates neoadjuvant chemotherapy or chemoradiotherapy (CRT) (4–6). Definitive CRT has been established as a curative treatment for esophageal cancer, and its clinical utility has been recently expanded (7–9). To our best knowledge, the prognostic impact of the 7th edition staging system has been not evaluated in detail for esophageal cancer patients undergoing CRT.

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Therefore, the objective of the present study was to evaluate the prognostic impact of clinical staging in the 7th edition on esophageal squamous cell cancer patients treated with CRT. We performed two analyses: 1) the prognostic impacts of the TNM staging systems of the 6th and 7th editions were compared and 2) the prognostic impacts of stage and prognostic groups, which incorporate TNM, cancer site, and histological grade, on patients with Stage I and II cancers were also compared.

METHODS AND MATERIAL

Patients

This was a retrospective cohort study of esophageal cancer patients treated with CRT at the Aichi Cancer Center Hospital between January 2003 and January 2009.There were a total of 301 patients who met the following inclusion criteria: 1) carcinoma of thoracic esophagus; 2) histological diagnosis of primary esophageal squamous cell carcinoma; 3) total radiation dose ≥50 Gy; 4) concomitant chemotherapy consisting of 5-fluorouracil and platinum agents; 5) no previous thoracic radiotherapy (RT); 6) no previous thoracic surgery; and 7) no salvage surgery. Patients who received chemotherapy followed by CRT were also included in this analysis.

Pretreatment staging and treatment planning

Pretreatment staging evaluations included physical examination, laboratory tests, esophagogastroduodenoscopy, barium esophagography, and contrast-enhanced computed tomography scans (CT) from the neck to upper abdomen. Positron emission tomography (PET) scans were performed especially after 2005 if the clinician thought it necessary to reveal distant metastasis such as bone metastasis. PET scans were rarely performed until 2005 since it had not been approved in Japan. Pretreatment staging was performed according to the 6th edition of the AJCC Cancer Staging Manual during a team conference, which included thoracic surgeons, radiologists, gastroenterologists, and medical oncologists. The treatment strategy was also decided at this conference. In general, patients with Stage I disease were treated by surgery alone, or endoscopic mucosal resection, or CRT. Patients with Stage II-IV disease were treated by surgery plus chemotherapy or CRT.

Three-dimensional RT planning and treatment

During this study period, RT was delivered using a linear accelerator (Clinac 21EX, Clinac 2100C; Varian Medical Systems, Palo Alto, CA) with a 6- or 10-MV photon beam. In general, patients received 2 Gy/day for 5 days per week, to a total radiation dose of 60 Gy. The primary gross tumor volume (GTV-P) and volume for involved lymph nodes (GTV-N) were determined. The primary clinical target volume (CTV-P) included the GTV-P with a 20-mm margin (craniocaudal direction); the lymph node clinical target volume for (CTV-N) included the GTV-N without an additional margin (9). The regional nodal site was not added to the CTV for prophylaxis. The planning target volume (PTV) included both CTVs with lateral and anteroposterior 5- to 10-mm margins and 10- to 20-mm craniocaudal margins. In addition, 5- to 8-mm leaf margins were added to the PTV. All fields were treated each day. There were patients initially treated with 36–40 Gy using an anteroposterior field technique that included the PTV. A boost dose was given to the PTV for a total dose, using bilateral oblique or multiple fields to exclude the spinal cord from the field. Spinal cords never received more than 45 Gy. If the patients had distant organ metastases or had nonregional lymph node metastasis (with the exception of supraclavicular lymph node metastasis), the radiation fields were minimized to include only the primary lesion.

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 (9–12).

Follow-up

A 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 3–6 months for 3 years after initiation of treatment. Patient vital status and disease status were confirmed by checking medical records at the last follow-up visit. For a patient lost to follow-up, his or her vital status was confirmed from the annual census registration. In that case, if a patient was determined to have died, the cause of death was treated as unknown.

Data collection and restaging

The following information was recorded from the medical record and radiological images of each patient: treatment initiation date, age, sex, cancer site, tumor length, histological grade, clinical stage, total radiation dose, final date assessing survival, and date of death. TNM staging, including number of lymph nodes, was independently redetermined by two radiologists (M.N., T.K.) according to the 6th and 7th AJCC editions. A lymph node was considered positive for metastasis if the short axis was greater than 5 mm (13). If restaging was different from pretreatment staging, the redetermined stage was adopted for this analysis.

Statistical analysis

Overall survival was calculated from the time of treatment to the time of death from any cause, or to time of last follow-up. Survival curves were constructed using the Kaplan-Meier method. To evaluate the impact of each factor on overall survival, univariate and multivariate Cox proportional hazards modeling was applied. Therefore, the measure of association in this study was the hazard ratio along with the 95% confidence interval (95% CI). Statistical analyses were performed using the SPSS statistical software package version 11 (SPSS Inc., Chicago, IL), and a p value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Between January 2003 and January 2009, 513 consecutive patients with esophageal cancer received RT. There were 212 patients excluded from this analysis for the following reasons: adenocarcinoma (n = 15), small-cell carcinoma (n = 1), carcinoma of cervical esophagus (n = 40), total radiation dose <50 Gy (n = 45), underwent RT alone (n = 37), underwent primary endoscopic mucosal resection (n = 23), chemotherapy other than 5-fluorouracil and platinum (n = 18), and missing analysis data (n = 33). Thus, a total of 301 patients were analyzed in this study. Study patient characteristics are summarized in Table 1. The chemotherapy regimens with RT were 5-fluorouracil and cisplatin (n = 281, 93.4%) or 5-fluorouracil and nedaplatin (n = 20, 6.6%). Chemotherapy before CRT was performed in 31 (10.3%) patients. In the 6th edition, the 3-year survival rates

Table 1. Patient and tumor characteristics

Characteristic	Patients (n = 301)	%
Age (y)		
Median	65	
Range	39–82	
Gender		
Male	265	88
Female	36	12
PS		
0	88	29
1	210	70
2	3	1
Total dose		
Median	60 Gy	
Range	50–66.5 Gy	
Tumor length		
Median	5 cm	
Range	1–17 cm	
Cancer site		
Ut	61	20
Mt	168	56
Lt	72	24
T stage (7th)		
1	81	27
2	18	6
3	132	44
4	70	23
N stage (7th)		
0	92	31
1	116	39
2	76	25
3	17	6
M stage (7th)		
0	231	77
1	70	23
Histological grade		
Grade 1	49	16
Grade 2	128	43
Grade 3	28	9
Grade X	96	32

Abbreviations: PS = Eastern Cooperative Oncology Group performance status; Ut = upper thoracic portion; Mt = mid-thoracic portion; Lt = lower thoracic portion.

of Stage I, II, III, and IV were 88.6%, 64.5%, 37.1%, and 29.1%, respectively. In 7th edition, the 3-year survival rates of Stage I, II, III, and IV were 87.6%, 62.0%, 32.3%, and 24.6%, respectively. The median follow-up period was 52 months, with 148 patients dead at the time of analysis.

Comparison of 6th and 7th edition staging systems

Table 2 shows the distribution of patient classifications according to the TNM staging systems of the 6th and 7th AJCC editions. Two patients were shifted to a higher stage in the 7th edition compared with the 6th. One patient shifted from Stage IIB to IIIA, and the other patient went from Stage III to IV. Eighty-four patients were shifted to a lower stage, and most of these went from Stage IV to III (n = 74).

Table 3 shows the univariate and multivariate analyses for each prognostic factor. By multivariate analysis, T stages, which remained the same in both the 6th and 7th editions,

Table 2. Patient distribution according to 6th and 7th editions of TNM classifications

	6th edition					
	I	IIA	IIB	III	IVA	IVB
7th edition						
IA	52					
IB		5				
IIA		19				
IIB			17		4	6
IIIA			1	22	6	20
IIIB				3	2	18
IIIC				28	7	21
IV				1	7	62

had significant impact on prognosis. The difference for each N stage was not prominent compared with T stages. M1 had no significant impact on survival compared with M0 in multivariate analysis (p = 0.13). When the 7th-edition M was categorized according to nonregional lymph node metastasis (M1-lym: n = 34 with supraclavicular nodes, n = 4 with supraclavicular nodes and abdominal nodes, n = 2 with abdominal nodes, and n = 2 with cervical nodes) and distant organ metastasis (M1-organ), only distant metastasis was significantly associated with prognosis.

According to the 4 major stage classifications (Stage I, II, III, IV; Table 4), there were significant differences between Stages I and III (p = 0.05) for each edition (Fig. 1a, b). However, the 7th edition poorly distinguished between Stages III and IV (p = 0.36 by multivariate analysis, Table 4) in comparison to the 6th edition (p = 0.08, Table 4). In the 6th edition, the 3-year survival rates of Stage III, IV-lym, and IV-organ were 37.1%, 34.2%, and 9.1%, respectively. In 7th edition, the 3-year survival rates of Stages III, IV-lym, and IV-organ were 32.3%, 36.2%, and 9.1%, respectively. When Stage IV was subclassified into Stage IV-lym or Stage IV-organ in accordance with the M1 subclassifications, the survival impact of Stage IV-lym almost completely overlapped with Stage III (p = 0.59), although there were significant differences between Stage IV-lym and Stage IV-organ (hazard ratio 1.90, 95%CI 1.02–3.56, p = 0.044) (Table 4, Fig. 2a, b).

Comparison between stage group and prognostic group for patients Stages I and II by the 7th edition

By multivariate analysis (Table 3), no cancer site had significant impact on survival. For histological grade, there was a significant difference between grade 1 and grade 2 (p = 0.008) by univariate analysis; however, the difference was not significant by multivariate analysis (p = 0.1). Table 5 shows the distribution of patients according to stage and prognostic classifications. In stage group, the 3-year survival rates of Stage IA, IB, IIA, and IIB were 88.6%, 66.7%, 48.0%, and 71.6%, respectively. In prognostic group, the 3-year survival rates of Stage IA, IB, IIA, and IIB were 92.0%, 79.7%, 54.4%, and 66.5%, respectively. The survival curves of the prognostic groups show a stepwise decrease

Table 3. Univariate and multivariate analyses of factors

		Univariate analysis			Multivariate analysis		
	Patients n = 301	HR	95% CI	p	HR	95% CI	p
Age (y)							
<65	142	1.00	–	–	1.00	–	–
>65	159	0.92	0.67–1.27	0.62	0.96	0.69–1.35	0.83
Gender							
Male	265	1.00	–	–	1.00	–	–
Female	36	0.61	0.35–1.08	0.09	0.50	0.28–0.91	0.023
PS							
0	88	1.00	–	–	1.00	–	–
1 or 2	213	2.99	1.8–4.97	<0.001	0.76	0.36–1.56	0.45
Tumor length							
<Median	143	1.00	–	–	1.00	–	–
>Median	128	1.78	1.26–2.52	0.001	1.24	0.82–1.86	0.32
Cancer site							
Ut	61	1.00	–	–	1.00	–	–
Mt	168	0.88	0.59–1.30	0.51	1.27	0.82–1.96	0.28
Lt	72	0.73	0.45–1.18	0.20	1.30	0.75–2.28	0.35
Grade (7th)							
1	49	1.00	–	–	1.00	–	–
2	128	2.13	1.22–3.73	0.008	1.64	0.91–2.97	0.10
3	28	2.10	1.04–4.26	0.039	1.38	0.66–2.88	0.39
X	96	2.33	1.31–4.15	0.004	1.91	1.05–3.47	0.033
T stage (6th, 7th)							
1	81	1.00	–	–	1.00	–	–
2	18	2.60	1.11–6.09	0.027	2.67	1.02–7.00	0.046
3	132	4.71	2.74–8.09	<0.001	3.96	1.79–8.77	0.001
4	70	6.53	3.70–11.53	<0.001	6.09	2.52–14.69	<0.001
N stage (6th)							
0	112	1.00	–	–	1.00	–	–
1	189	2.43	1.68–3.51	<0.001	1.05	0.67–1.66	0.80
N stage (7th)							
0	92	1.00	–	–	1.00	–	–
1	116	2.78	1.76–4.40	<0.001	1.56	0.93–2.60	0.09
2	76	4.06	2.51–6.57	<0.001	1.71	0.97–3.02	0.063
3	17	4.76	2.33–9.69	<0.001	1.89	0.85–4.23	0.12
M stage (6th)							
0	148	1.00	–	–	1.00	–	–
1	153	2.88	2.04–4.05	<0.001	2.01	1.34–3.01	0.001
M stage (7th)							
0	231	1.00	–	–	1.00	–	–
1	70	2.06	1.45–2.92	<0.001	1.34	0.91–1.93	0.13
1 lym	42	1.63	1.04–2.54	0.032	1.01	0.64–1.61	0.96
1 organ	28	2.90	1.82–4.62	<0.001	2.17	1.30–3.60	0.003
Neoadjuvant chemotherapy							
No	270	1.00	–	–	1.00	–	–
Yes	31	1.21	0.73–2.00	0.47	1.09	0.65–1.82	0.75

Abbreviations: PS = Eastern Cooperative Oncology Group performance status; Ut = upper thoracic portion; Mt = mid-thoracic portion; Lt = lower thoracic portion; HR = hazards ratio; CI = confidence interval; lym = metastasis to nonregional lymph nodes.

with increase in stage, except for Stage IIA (Fig. 3b). However, there were no significant differences between each stage in either group (Fig. 3a, b).

DISCUSSION

Although neoadjuvant chemotherapy, CRT followed by esophagectomy, or CRT as definitive treatment have been standard therapies for resectable esophageal squamous cell cancer (4–9), the 7th edition of the AJCC/UICC cancer staging system for esophageal cancer was based on pathologic data from esophageal cancer treated by primary surgical resection alone (3). However, pathologic staging criteria have been thought to be inadequate for patients receiving neoadjuvant therapy, including CRT (14, 15). Thus, this study was conducted to evaluate the prognostic impact of the new TNM staging system on esophageal cancer treated with CRT.

In the 7th edition, the N factor, which is based on the number of positive regional lymph nodes, is one of the major changes from the 6th edition. With clinical N staging, the accurate number of positive lymph nodes is difficult to determine

Table 4. Comparison between the 6th and 7th editions of TNM classifications

	7th edition						6th edition					
	Univariate			Multivariate*			Univariate			Multivariate*		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Stage I	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
Stage II	3.04	1.31	7.04	0.01	3.15	1.30	7.65	0.01	3.81	1.48	9.82	0.01	3.78	1.41	10.69	0.01
Stage III	7.93	3.82	16.46	<0.001	8.15	3.45	19.30	<0.001	7.60	3.16	18.28	<0.001	7.24	2.62	20.00	<0.001
Stage IV	9.15	4.31	19.45	<0.001	9.61	4.02	22.97	<0.001	10.70	4.66	24.40	<0.001	10.87	4.20	28.12	<0.001
Stage III	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–
Stage IV	1.15	0.80	1.67	0.44	1.19	0.82	1.72	0.36	1.39	0.92	2.10	0.11	1.48	0.96	2.27	0.08
Stage IV lym	0.92	0.58	1.45	0.69	0.88	0.55	1.41	0.59	1.26	0.82	1.92	0.29	1.24	0.79	1.96	0.35
Stage IV organ	1.67	1.03	2.70	0.04	2.23	1.22	4.10	0.01	2.27	4.00	1.30	0.004	2.94	1.61	5.56	<0.001

Abbreviations: HR = hazards ratio; CI = confidence interval; lym = metastasis to nonregional lymph nodes.
* According to performance status, age, gender, tumor length, location, and grade.

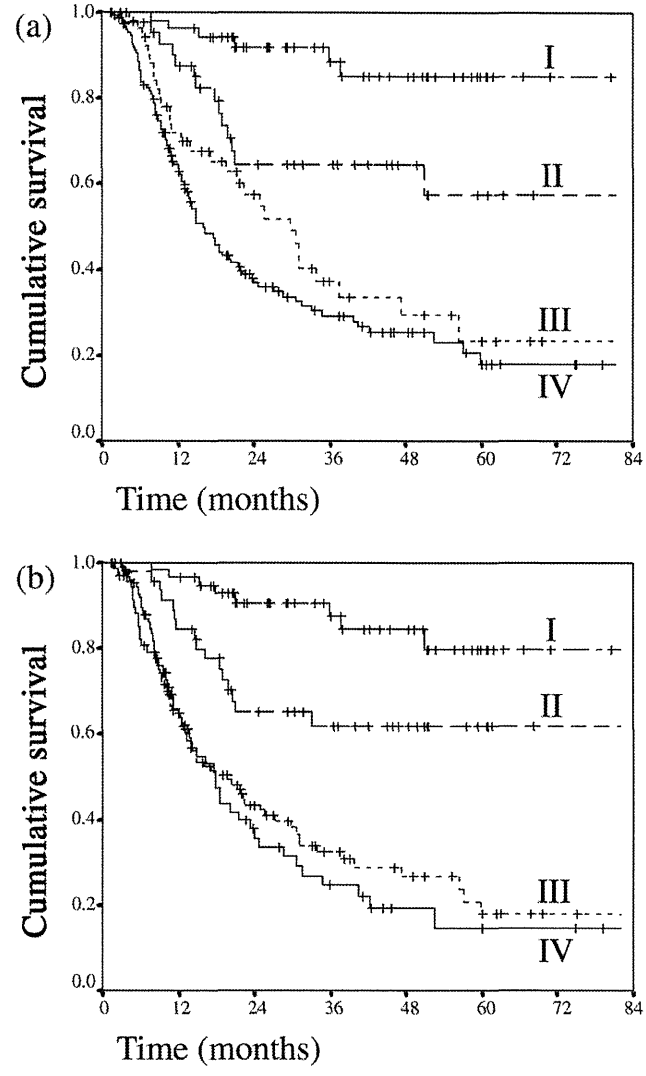

Fig. 1. Survival curves of patients stratified according to the 6th (a) and 7th (b) edition staging systems classified into four major stages. In 6th edition, the 3-year survival rates of Stage I, II, III, and IV were 88.6%, 64.5%, 37.1%, and 29.1%, respectively. In 7th edition, the 3-year survival rates of Stage I, II, III, and IV were 87.6%, 62.0%, 32.3%, and 24.6%, respectively. Statistical differences in survival between groups were analyzed by Cox proportional hazards model. By multivariate analysis, there were significant differences between Stages I and II ($p = 0.01$ in 6th and $p = 0.01$ in 7th), Stages II and III ($p = 0.014$ in 6th and $p = 0.006$ in 7th) for each edition.

before treatment. In our study, the number of lymph nodes was determined according to enhanced CT. Our results indicated that the difference between each N stage was not great compared with the difference between each T stage. In addition, the prognostic impact of N is generally lower than the prognostic impact of T. Our analysis of M factors shows that the survival curve of Stage IV-lym was significantly different from the curve for Stage IV-organ. There were 34 (81.0%) M1 lymph patients with metastatic supraclavicular nodes that were relatively small, and their radiation fields covered the entire PTV. However, in patients with metastasis to a distant organ, their limited radiation fields could not cover all tumor

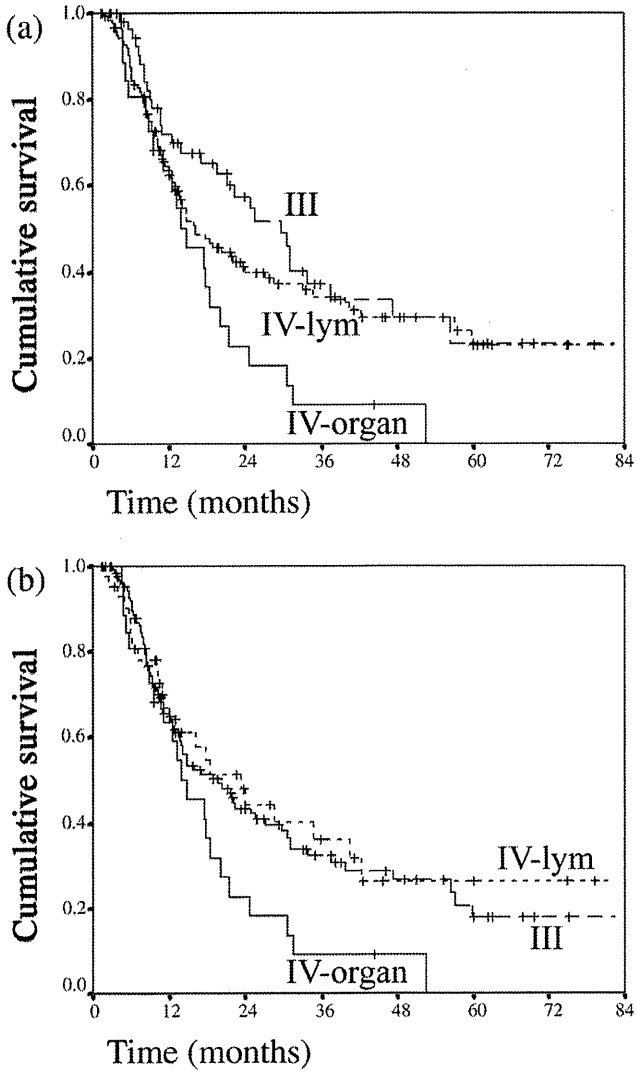

Fig. 2. Survival curves of patients stratified according to the 6th (a) and 7th (b) edition staging systems when Stage IV was subclassified as Stage IV-lym or Stage IV-organ. In the 6th edition, the 3-year survival rates of Stages III, IV-lym, and IV-organ were 37.1%, 34.2%, and 9.1%, respectively. In the 7th edition, the 3-year survival rates of Stage III, IV-lym, and IV-organ were 32.3%, 36.2%, and 9.1%, respectively.

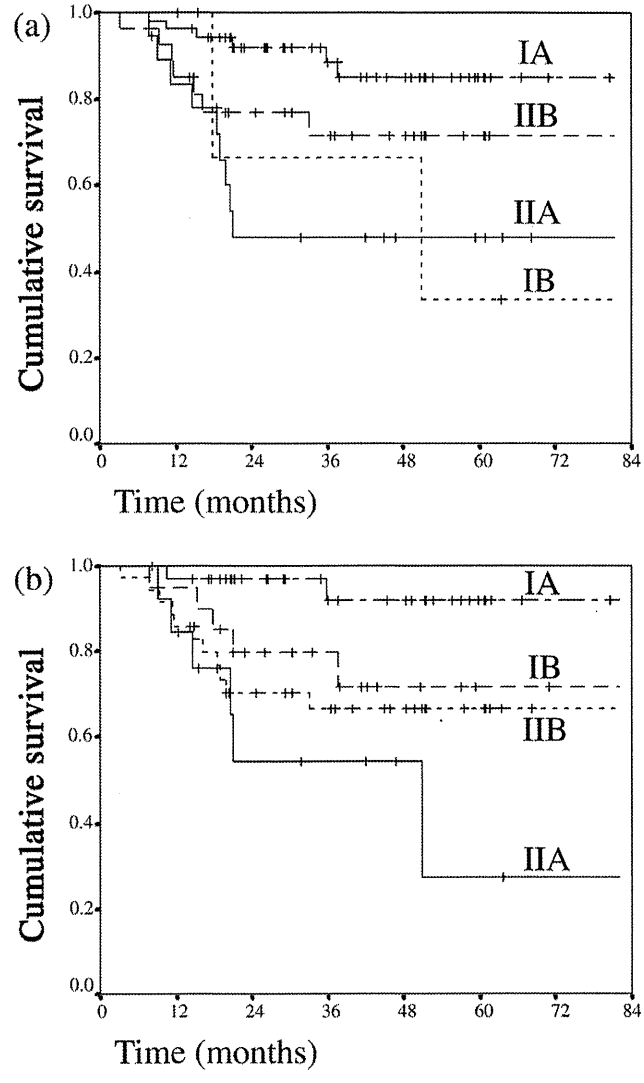

Fig. 3. Survival curves of patients stratified according to stage group (a) and prognostic group (b). In stage group, the 3-year survival rates of Stages IA, IB, IIA, and IIB were 88.6%, 66.7%, 48.0%, and 71.6%, respectively. In prognostic group, the 3-year survival rates of Stages IA, IB, IIA, and IIB were 92.0%, 79.7%, 54.4%, and 66.5%, respectively.

lesions. This may be the major reason why patients with M1-lym had significantly better survival compared with patients with M1-organ. Moreover, recent reports have indicated that early tumor response to CRT predicts improved survival of esophageal cancer (16). Therefore, prediction of esophageal cancer sensitivity to CRT may be more important for predicting prognosis after CRT.

Table 5. Distribution of the stage and prognostic groups

	Stage group			
	IA	IB	IIA	IIB
Prognostic group				
IA	34			
IB	18	1	2	
IIA		3	11	
IIB		1	7	27

For N0M0 cancer patients, incorporation of new prognostic factors, including histological grade and cancer site, are other major changes in the 7th edition. Studies have shown that histological grade and cancer site are prognostic factors for survival in esophageal carcinoma (17, 18). However, Hsu *et al.* reported results of comparisons between the prognostic impacts of the 6th and 7th TNM staging systems in esophageal squamous cell carcinoma treated with primary surgical resection alone, and did not find a significant prognostic role for these two factors (19). Our results also showed that these two factors were not significant for esophageal squamous cell carcinoma treated with CRT. Moreover, by multivariate analysis, the T factor was the most significant

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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ORIGINAL ARTICLE

Long-term outcomes of intraluminal brachytherapy in combination with external beam radiotherapy for superficial esophageal cancer

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Abstract
Background The aim of this study was to assess the long-term outcomes of combining high-dose-rate intraluminal brachytherapy (IBT) with external beam radiotherapy (EBRT) for superficial esophageal cancer (SEC).
Methods From 1992 to 2002, 87 patients with T1N0M0 thoracic esophageal cancer received IBT in combination with EBRT. Of these, 44 had mucosal cancer and 43 had submucosal cancer. For patients with tumor invasion within the lamina propria mucosa, IBT alone was performed ($n = 27$). IBT boost following EBRT was performed for patients with tumor invasion in the muscularis mucosa or deeper ($n = 60$). No patient received chemotherapy.
Results The median follow-up time was 94 months. For mucosal cancer, the 5-year locoregional control (LRC), cause-specific survival (CSS) and overall survival (OS) rates were 75, 97 and 84%, respectively, and 49, 55 and 31%, respectively, for submucosal cancer. Tumor depth was a significant factor associated with LRC ($p = 0.02$), CSS ($p < 0.001$) and OS ($p < 0.001$) by univariate analysis. Multivariate analysis revealed that tumor depth was the only significant predictor for OS ($p = 0.003$). Late toxicities of grade 3 or higher in esophagus, pneumonitis, pleural effusion and pericardial effusion were observed in 5, 0, 0 and 1 patients, respectively. Grade ≥3 events of cardiac ischemia and heart failure after radiotherapy were observed in 9 patients, and history of heart disease before radiotherapy was the only significant factor ($p = 0.002$).
Conclusion There was a clear difference in outcomes of IBT combined with EBRT between mucosal and submucosal esophageal cancers. More intensive treatment should be considered for submucosal cancer.

Keywords Esophageal cancer · Superficial esophageal cancer · Squamous cell carcinoma · Radiotherapy · Brachytherapy

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Introduction

Advances in endoscopic equipment have enabled the treatment of increasing numbers of patients with superficial esophageal cancer (SEC) [1–3], which can be divided into mucosal and submucosal cancers. In SEC patients treated by surgery, pathological analyses have shown significant differences in rates of lymph node (LN) metastasis according to tumor depth: 0–6% in the mucosa and 38–53% in the submucosa [4–9]. Among mucosal cancer patients, when tumor cells were found within the lamina propria mucosa there was almost no LN metastasis (0–1.4%), whereas in patients with tumors invading to the muscularis mucosa, a ratio of LN metastases of more than 10% was reported [4]. Endoscopic resection is generally indicated for patients with tumors invading within the lamina propria mucosa. For patients with tumors invading the muscularis mucosa or deeper, esophagectomy with systematic LN dissection is the main treatment. However, due to the extent of surgery, the alternative of radiotherapy (RT) is often selected for patients in poor medical condition or advanced age, and its efficacy has been reported by several authors [10–14].

Brachytherapy is a RT technique that can deliver a high dose to local tumors while sparing exposure to the surrounding normal tissues. Intraluminal brachytherapy (IBT) has been used mainly for SEC in Japan, while in Western countries IBT has been used with palliative intent for malignant esophageal strictures. The efficacy of IBT combined with external beam radiotherapy (EBRT) for SEC has been reported [15–19], and this method was considered an effective treatment in Japan in the 1990s. We performed IBT combined with EBRT for SEC patients until 2002, following the introduction in 1991 of the high-dose-rate iridium-192 remote afterloading system (micro-Selectron HDR from Nucletron, Netherlands). Subsequently, the protocol was changed and chemoradiotherapy (CRT) was introduced for SEC. In this study, the long-term outcomes of IBT combined with EBRT for SEC were evaluated.

Patients and methods

Patient and tumor characteristics

Patient and tumor characteristics are listed in Table 1. There were 87 patients eligible for this study with T1N0M0 (International Union Against Cancer TNM system, 1997) thoracic esophageal cancer who received IBT combined with EBRT between 1992 and 2002. The median age was 70 years (range 43–89), with 80 males and 7 females. Sixty-nine patients had Karnofsky performance status (KPS) of 90 or more. RT was selected in 54 patients who were judged medically inoperable and in 33 patients who declined surgery. Medically inoperable factors included concurrent illnesses, advanced age and coexisting malignancies. Main concurrent illnesses included heart disease in 14, hepatic disease in 18 and pulmonary disease in 9. Coexisting malignancies were observed in 28 patients, and 16 had malignancies within 5 years before the diagnosis of esophageal cancer. Among them, 12 had active malignancies. Taken together, these malignancies were distributed as follows: gastric cancer in 11, head and neck cancer in 10, hepatocellular carcinoma in 4, colorectal cancer in 3 and lung cancer in 2. Histologically, 86 patients had squamous cell carcinoma and one had adenocarcinoma. Tumor sites were upper thoracic in 8 patients, middle thoracic in 65 and lower thoracic in 14. Forty-four had mucosal cancer and 43 had submucosal cancer. Of the 44 mucosal cancer patients, 25 received incomplete endoscopic mucosal resection (EMR) for tumors within the lamina propria mucosa, i.e., positive margin or partial resection of multiple or large lesions for the purpose of diagnosing tumor depth.

Table 1 Patient and tumor characteristics

Characteristics	No. of patients (%)
Age (years)	
Range	43–89
Median	70
Gender	
Male	80 (92)
Female	7 (8)
KPS	
90–100	69 (79)
60–80	18 (21)
Reasons for selecting RT	
Medically inoperable	54 (62)
Patient refused surgery	33 (38)
Double cancer	
All	28 (32)
Within 5 years	16 (18)
Histology	
Squamous cell	86 (99)
Adenocarcinoma	1 (1)
Tumor sites	
Upper thoracic	8 (9)
Middle thoracic	65 (75)
Lower thoracic	14 (16)
Tumor depth	
Mucosal	44 (51)
Submucosal	43 (49)

KPS Karnofsky performance status, *RT* radiotherapy

Treatment

Intraluminal brachytherapy was performed using the high-dose-rate iridium-192 remote afterloading system. The double-balloon applicator was used for IBT. The outer diameter of the applicator was either 16 or 20 mm, and the latter was mainly used. A prescribed dose was calculated at a depth of 5 mm from the surface of the esophageal mucosa.

EBRT was administered with 6 or 18 MV X-rays. After irradiation with 45–46 Gy using a fractional dose of 1.8–2.0 Gy to the primary tumor and regional LN area with anterior–posterior opposed beams, a planned dose was delivered to the primary tumor with oblique opposed beams to spare the spinal cord.

For patients with tumors within the lamina propria mucosa who had almost no risk of LN metastases, IBT alone was performed ($n = 27$). IBT was performed 5 days per week and irradiation doses were 35 Gy/14 fractions in 15 patients, 36 Gy/18 fractions in 9, 30 Gy/15 fractions in 2 and 25 Gy/5 fractions in 1.

Intraluminal brachytherapy boost following EBRT was performed for patients with tumors in the muscularis mucosa or deeper who had risk of LN metastases ($n = 60$). Irradiation doses of EBRT were 50–58 Gy/25–29 fractions (median 54 Gy) in cases of tumors in the muscularis mucosa or inner one-third of the submucosa and 54–61 Gy/27–33 fractions (median 60 Gy) in cases of tumors in the outer two-thirds of the submucosa. The IBT boost was generally performed immediately after EBRT using a schedule of 5 days per week. IBT boost doses were 10 Gy/4 fractions in 29, 10 Gy/5 fractions in 25, 10 Gy/2 fractions in 3, 7.5 Gy/3 fractions in 1, and 15 Gy/3 fractions in 1.

In this study, no patient received chemotherapy.

Analysis

The data were updated in June 2009. The median follow-up time for survivors was 94 months (range 28–187) and for all patients 64 months (range 2–187). There were 3 patients who were lost to follow-up within 60 months from RT. The follow-up periods of these 3 patients were 28, 56 and 57 months. Complete response (CR) was defined as the disappearance of the primary tumor by endoscopic biopsy. Overall survival (OS) was defined as the time from the initiation of RT to death from any cause. Cause-specific survival (CSS) was defined as the time from the initiation of RT to death due to esophageal cancer. Locoregional control (LRC) was calculated from the initiation of RT to the earliest events of recurrences in esophageal primary site, esophageal metachronous cancers and regional LN metastases. OS, CSS and LRC rates were calculated using the Kaplan–Meier method. Comparison of data was analyzed by Fisher's exact test. Univariate (UVA) and multivariate analyses (MVA) were performed using the log-rank test and the Cox proportional hazards test. A p value of <0.05 was considered significant. Toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Results

Response and failures

Treatment outcomes are shown in Table 2. Initial response was evaluated 8–181 days (median 31 days) after RT. Two patients were not evaluated because one died in a traffic accident soon after treatment, and concurrent illness

Table 2 Treatment outcomes

Outcomes	No. of patients (%)		
	Mucosal ($n = 44$)	Submucosal ($n = 41$)	Total ($n = 85$)
Initial response (evaluable cases)			
Complete response	43 (98)	40 (98)	83 (98)
Partial response	1 (2)	1 (2)	2 (2)
Recurrences			
Locoregional	14 (32)	19 (46)	30 (39)
Esophagus—primary site	5 (11)	8 (20)	13 (15)
Esophagus—metachronous	8 (18)	4 (10)	12 (14)
Lymph node—in EBRT field	0 (0)	1 (2)	1 (1)
Lymph node—out of EBRT field	1 (2)	4 (10)	5 (6)
Distant	0 (0)	1 (2)	1 (1)
Unknown	1 (2)	1 (2)	2 (2)

EBRT external beam radiotherapy, *RT* radiotherapy

progressed after treatment in the other patient. In 85 evaluable patients, 83 (98%) achieved CR and residual cancer cells were confirmed in 2 patients. Failures were observed in 33: locoregional failures in 30, distant metastasis (malignant pleural effusion) in 1 and unspecified in 2. Among the 30 patients with locoregional failures, one had failure at the primary esophageal site and regional LN metastasis concurrently. Esophageal failures were observed in 25 patients: 13 were primary tumor failures and 12 were metachronous esophageal cancers. There were no differences according to tumor depth in the occurrence rate of all esophageal failures, primary site failures and metachronous esophageal cancers. Regional LN metastases were observed in 6 patients. Although submucosal cancer patients showed a high rate of regional LN metastasis compared with mucosal cancer patients, the difference lacked significance (2% in mucosal and 12% in submucosal cancer, $p = 0.10$). Furthermore, 5 failures were not in the EBRT field and one was in the EBRT field.

Among the 33 patients with failures, an early stage failure detected as a superficial esophageal lesion was observed in 15 patients and an advanced stage failure was observed in 18. According to the depth of tumor, the occurrence rate of advanced stage failures was significantly higher in submucosal cancer patients (7% in mucosal and 37% in submucosal cancer, $p < 0.01$). Regarding salvage treatments for 15 patients with early stage failures, 14 patients were salvaged by esophagectomy or endoscopic resection. For 18 patients with advanced stage failures, only one patient who received lymphadenectomy with adjuvant CRT for LN metastasis out of the EBRT field was salvaged.

Survival rates and prognostic factor

At the time of last follow-up, 49 of 87 patients had died. Seventeen patients had esophageal cancer deaths including one treatment-related death; 2 in mucosal and 15 in submucosal cancer patients. Submucosal cancer patients showed a higher rate of esophageal cancer deaths compared with mucosal cancer patients ($p < 0.01$). Eleven patients died of other malignancies: lung cancer in 3, hepatocellular carcinoma in 3, head and neck cancer in 2, and single cases each of malignant lymphoma, bile duct carcinoma and bladder sarcoma. Among these 11 patients, 3 had esophageal metachronous cancers and 1 had LN recurrence, however, all of them were controlled by salvage treatments. Twenty-one patients died of intercurrent diseases: pulmonary infection in 9, heart disease in 4, hepatic failure in 2, unknown cause in 2 and single cases each of renal failure, suicide, senility and cerebral thrombosis.

The 5-year OS, CSS and LRC for all patients were 58% [95% confidence intervals (CI) 48–69%], 78% (95% CI 69–88%) and 63% (95% CI 52–75%), respectively (Fig. 1). According to the depth of tumors, the 5-year OS, CSS and LRC for mucosal and submucosal cancers were 84% (95% CI 73–95%) and 31% (95% CI 17–46%), 97% (95% CI 92–100%) and 55% (95% CI 38–73%), and 75% (95% CI 62–89%) and 49% (95% CI 36–67%), respectively (Fig. 2a–c). There were significant differences in OS, CSS and LRC between mucosal and submucosal cancer ($p < 0.01$, $p < 0.01$ and $p = 0.02$, respectively). Prognostic factors according to UVA are summarized in Table 3. The significant factors for LRC were tumor depth ($p = 0.02$) and tumor length ($p = 0.01$), those for CSS were tumor depth ($p < 0.01$) and tumor length ($p = 0.02$), and those for OS were KPS ($p = 0.04$), operability ($p = 0.02$), double cancer within 5 years ($p < 0.01$) and tumor depth ($p < 0.01$). MVA for OS revealed that tumor depth was the only significant prognostic factor ($p < 0.01$).

Toxicity

Toxicities are summarized in Table 4. Grade ≥3 acute toxicities of esophagitis, leucopenia and thrombocytopenia occurred in 2, 1 and 0 patients, respectively. Grade ≥3 late toxicities of esophageal ulcers, pneumonitis, pleural effusion and pericardial effusion were observed in 5, 0, 0 and 1 patients, respectively. Details of Grade ≥3 late toxicities of the esophageal ulcers are shown in Table 5. All of them received IBT boost following EBRT and 3 patients developed esophago-mediastinal fistulas concurrently. One needed bypass surgery (Grade 4) and another died of mediastinitis (Grade 5). The other 3 patients recovered by conservative treatment. The lone patient with Grade 3 pericardial effusion, who was the same patient with Grade 3 esophago-mediastinal fistula, developed Grade 2 pleural effusion concurrently. Both pericardial and pleural effusion decreased after recovery from the fistula. Regarding

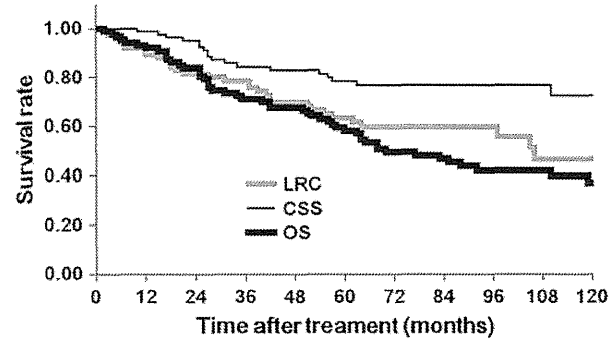

Fig. 1 Curves for overall survival (*OS*), cause-specific survival (*CSS*) and locoregional control (*LRC*) rates for all patients. The 5-year OS, CSS and LRC were 58% (95% CI 48–69%), 78% (95% CI 69–88%) and 63% (95% CI 52–75%), respectively

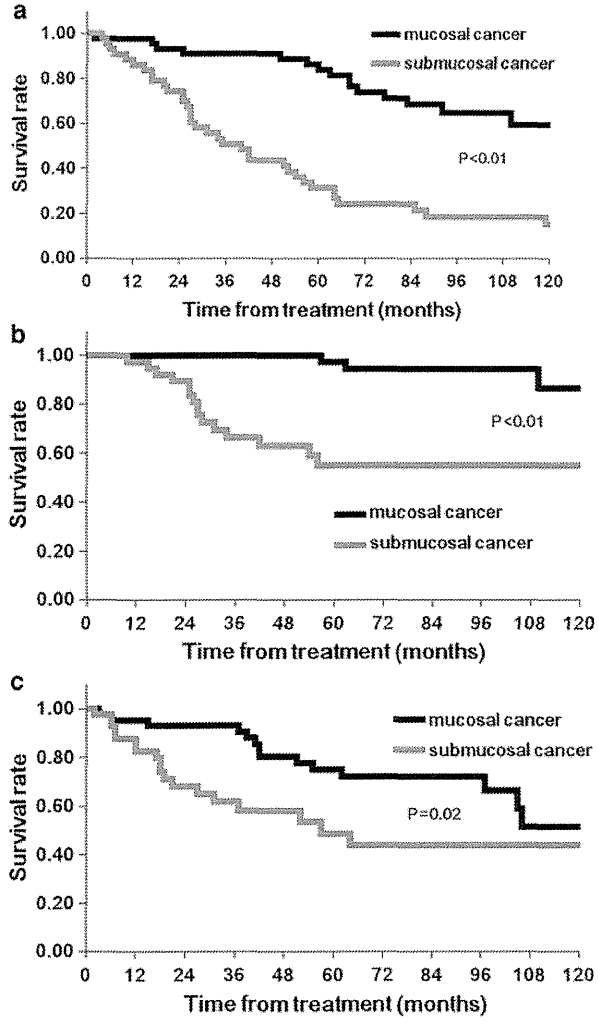

Fig. 2 **a** Curves for OS according to tumor depth. The 5-year OS for mucosal and submucosal cancer were 84% (95% CI 73–95%) and 31% (95% CI 17–46%), respectively ($p < 0.01$). **b** Curves for CSS according to tumor depth. The 5-year CSS for mucosal and submucosal cancer were 97% (95% CI 92–100%) and 55% (95% CI 38–73%), respectively ($p < 0.01$). **c** Curves for LRC according to tumor depth. The 5-year LRC for mucosal and submucosal cancer were 75% (95% CI 62–89%) and 49% (95% CI 36–67%), respectively ($p = 0.02$)

occurrence of Grade ≥3 esophageal ulcers, no significant factor emerged.

We also investigated cardiac ischemia and heart failure after RT (Grade ≥3 according to CTCAE v3.0) (Table 6). Cardiac ischemia occurred in 5 patients. Two patients died of acute myocardial infarction, at 2 and 6 months after RT. One had a history of angina and the other patient had a history of brain infarction and KPS of 60. The time to onset of the other 3 patients was 22, 76 and 151 months after RT. They received stent placement and were alive 65, 24 and 13 months later, respectively. Four patients suffered heart failure. One died of heart failure at 64 months after RT; he had a history of dilated cardiomyopathy. The time to onset of the other 3 patients was 42, 46 and 124 months. They received pacemaker placement; one of them died of malignant lymphoma 9 months later; the other 2 patients were alive 18 and 47 months later. Investigation of significant factors associated with cardiac ischemia and heart failure revealed that a history of heart disease before RT was the only significant factor ($p = 0.002$) (Table 7).

Discussion

With advances in endoscopic equipment, the number of SECs treated has increased. According to the report of the Registry of Esophageal Carcinomas in Japan, SEC accounted for 8.5% of esophageal cancer patients treated in 1979–1982 and 28% in 1998–1999 [1, 2]. In the data of the Japanese Patterns of Care Study, 21% of the esophageal cancer patients who were treated with RT in 1999–2001 had SEC [3].

In our study, there was a clear difference in treatment results depending on the depth of tumor invasion. Tumor depth was a significant factor for OS, CSS and LRC by UVA. Furthermore, tumor depth was the only significant factor for OS by MVA. Favorable treatment outcomes in mucosal cancer were achieved in this study. The CR rate was 98% and the 5-year OS, CSS and LRC were 84, 97 and 75%, respectively. These results were almost equivalent to that reported for surgery [4–9]. Most of the mucosal cancers in this study were large or multiple lesions that were difficult to completely resect by EMR or had margin-positive lesions after EMR. In the 1990s, surgery or radiotherapy was often considered for these lesions. However, remarkable progress in endoscopic techniques has resulted in significant changes. Recently, endoscopic submucosal dissection (ESD) has been increasingly used as a new technique of endoscopic resection. ESD facilitates en-bloc resection even in large lesions where piecemeal resection was needed by EMR. Takahashi et al. [20] reported that ESD reduced the local recurrence rate (0.9% in the ESD group and 9.8% in the EMR group) significantly and that the disease-free survival rate was significantly better with ESD than with EMR. Most mucosal cancers can now be cured by endoscopic treatment alone due to advances in the technique of endoscopic resection. Thus, surgery and RT in the treatment of mucosal cancer have been relegated to a limited role.

Initial response for submucosal cancer was considered equally good as that achieved for mucosal cancer. CR rate was 98% and high long-term LRC and survival rates were anticipated. However, the 5-year OS, CSS and LRC were 31, 55 and 49%, respectively. These results were obviously inferior to those of mucosal cancer, and little difference

Table 3 Prognostic factors

Patient characteristics	*n*	LRC		CSS		OS		
		5-year rate (%)	UVA	5-year rate (%)	UVA	5-year rate (%)	UVA	MVA
Age (years)								
≤70	49	61	n.s.	84	n.s.	65	n.s.	–
>70	38	67		72		51		
Gender								
Male	80	62	n.s.	77	n.s.	58	n.s.	–
Female	7	86		100		57		
KPS								
90–100	71	61	n.s.	79	n.s.	64	0.04	0.222
60–80	16	74		73		37		
Operability								
Operable	33	63	n.s.	86	n.s.	72	0.010	0.076
Inoperable	54	63		73		50		
Double cancer within 5 years								
Yes	16	69	n.s.	90	n.s.	64	0.007	0.485
No	71	63		77		31		
Tumor depth								
Mucosal	44	75	0.023	97	<0.001	84	<0.001	0.003
Submucosal	43	49		55		31		
Tumor length (cm)								
≤3.0	63	72	0.012	85	0.026	63	n.s.	–
>3.0	24	38		63		45		
Circumferential extent								
≤1/2	70	65	n.s.	79	n.s.	60	n.s.	–
>1/2	17	57		78		51		
Multiple Lugol-voiding regions								
Yes	59	58	n.s.	78	n.s.	58	n.s.	–
No	28	74		81		60		
Multiple cancer in esophagus								
Yes	21	69	n.s.	81	n.s.	52	n.s.	–
No	66	62		78		60		

KPS Karnofsky performance status, *LRC* locoregional control rate, *CSS* cause-specific survival rate, *OS* overall survival rate, *UVA* univariate analysis, *MVA* multivariate analysis, *n.s.* not significant

Table 4 Toxicity

	G2	G3	G4	G5	≥G3 (%)
Acute					
Esophagitis	22	2	0	0	2 (2%)
Leukopenia	3	1	0	0	1 (1%)
Thrombocytopenia	1	0	0	0	0 (0%)
Late					
Esophagus	3	3	1	1	5 (6%)
Pneumonitis	2	0	0	0	0 (0%)
Pleural effusion	3	0	0	0	0 (0%)
Pericardial effusion	–	1	0	0	1 (1%)

G grade

was seen when compared with previous reports of RT alone [10–16]. The main pattern of failures was locoregional failures (18 of 19 patients with failures). These outcomes suggest that treatment needs to be intensified to improve the locoregional control rate for submucosal cancer patients.

Table 5 Details of patients with esophageal ulcer (≥Grade 3)

	Depth	Treatment	Complication	Grade	Support
1	Mucosal	EBRT + IBT	Ulcer + perforation	3	TPN
2	Submucosal	EBRT + IBT	Ulcer	3	TPN
3	Submucosal	EBRT + IBT	Ulcer	3	TPN
4	Submucosal	EBRT + IBT	Ulcer + perforation	4	Bypass surgery
5	Submucosal	EBRT + IBT	Ulcer + perforation	5	Death

EBRT external beam radiotherapy, *IBT* intraluminal brachytherapy, *TPN* total parental nutrition

Table 6 Details of patients with heart disease (≥Grade 3)

	Sex	Age	History of HD	Tumor site	Treatment	Complication	Onset (months)	Outcome (months)	
1	Male	69	Angina	Mt	IBT	CI	2	Dead with AMI	2
2	Male	78	–	Mt	EBRT + IBT	CI	5	Dead with AMI	6
3	Male	61	–	Mt	EBRT + IBT	CI	22	Alive	87
4	Male	70	–	Mt	EBRT + IBT	CI	76	Alive	100
5	Male	73	AR	Mt	EBRT + IBT	CI	151	Alive	164
6	Male	84	–	Lt	EBRT + IBT	HF	42	Dead with ML	51
7	Male	65	DCM	Lt	EBRT + IBT	HF	50	Dead with HD	64
8	Male	71	OMI	Mt	EBRT + IBT	HF	46	Alive	64
9	Male	55	AF	Mt	EBRT + IBT	HF	124	Alive	171

HD heart disease, *EBRT* external beam radiotherapy, *IBT* intraluminal brachytherapy, *CI* cardiac ischemia, *HF* heart failure, *AR* aortic regurgitation, *DCM* dilated cardiomyopathy, *OMI* old myocardial infarction, *AF* atrial fibrillation, *AMI* acute myocardial infarction, *ML* malignant lymphoma, *Mt* middle thoracic esophagus, *Lt* lower thoracic esophagus

Intraluminal brachytherapy is a RT method that can deliver an isolated high dose to local tumors while sparing the surrounding normal tissues. Its efficacy for SEC has been reported by several authors [13–19]. However, a significant advantage of IBT in the treatment of esophageal cancer remains to be demonstrated. The Study Group of the Japanese Society of Therapeutic Radiology and Oncology reported no advantage when IBT was compared with EBRT alone [11]. Recently, some promising results of IBT combined with EBRT for submucosal cancer were reported by Ishikawa et al. [19] from Gunma University. Their study showed a significant difference in the 5-year CSS between the IBT + EBRT group and EBRT alone (86 vs. 62%, $p = 0.04$). However, there were no significant differences in LRC, OS and recurrence-free survival. Furthermore, according to the Japanese Patterns of Care Study, the performance rate of IBT in the treatment of esophageal cancer in Japan has been decreasing [3]. Concurrent CRT has become the standard therapy as a non-surgical treatment for locally advanced esophageal cancer, because randomized controlled trials revealed the efficacy of CRT [21–23]. Recently, the efficacy of CRT for SEC has been studied. Yamada et al. [24] reported that the 5-year OS of CRT for stage I esophageal cancer was 66.4%. Kato et al. reported the outcome of a phase II trial of CRT in patients with stage I esophageal cancer. In their study, the 4-year OS was 80.5% [25]. The survival rates from these studies were equivalent to those of surgery. There has thus been a shift from RT alone to CRT in the RT methods for SEC.

In this study, 13 primary site recurrences and 12 metachronous esophageal cancers were observed. Fifteen of these 25 lesions were detected as superficial lesions and 14 of these were successfully salvaged. Meanwhile, most of the patients who developed advanced recurrences died of esophageal cancer. This suggests that detection of esophageal failures or metachronous cancers as a superficial lesion by periodic endoscopy is very important.

In treating with IBT, avoiding the toxicity of treatment-related esophageal ulcer is of critical importance. Nemoto et al. [10] recommended that the IBT fractional dose should not exceed 5 Gy to prevent esophageal ulcers. Akagi et al. [26] have also recommended a small fractional dose of 2.0 or 2.5 Gy in high-dose-rate IBT to minimize esophageal complications. In our study, Grade ≥3 esophageal ulcer occurred in 5 patients (6%). This incidence rate was comparatively low; however, Grade 4 and 5 ulcers