response 8 weeks after the completion of radiotherapy according to modified World Health Organization criteria as assessed by an independent review committee, the Efficacy and Safety Evaluation Committee (ESEC), and the investigators, using imaging. Tumor response at 8 weeks after completion of radiotherapy was to be confirmed at 12 weeks for the analysis of best tumor response. Determination of tumor *KRAS* mutation status was requested by the Pharmaceuticals and Medical Device Agency, Japan, in order to increase information on the incidence of this type of mutation among Japanese patients with LASCCHN, and response according to tumor *KRAS* mutation status was also assessed. Tumor DNA was screened for the presence of *KRAS* codon 12 and 13 mutations by pyrosequencing at a single laboratory (Biomarker Technologies, Merck Serono RBM, Ivrea, Italy) using a previously validated test (PyroMark KRAS kit; QIAGEN, Hilden, Germany).

All patients received a 7-week course of cetuximab plus concomitant boost radiotherapy. Cetuximab was administered at an initial dose of 400 mg/m^2 (over 120 min), with subsequent weekly doses of 250 mg/m^2 (over 60 min) as an intravenous infusion for 7 weeks of treatment, starting 1 week prior to radiotherapy. Radiotherapy treatment was determined using a 3D treatment planning system. Uninvolved nodal areas of the neck were treated with 54 Gy/30Fr. The primary tumor and gross nodal disease were treated with 72 Gy/42Fr. The irradiation schedule is shown in detail in Fig. 1.

On-study tumor response assessments were performed 8 and 12 weeks after completion of radiotherapy using MRI scanning of the neck and, at week 12, CT of the chest and abdomen. Where progressive disease (PD) was confirmed 8 weeks after completion of radiotherapy, imaging at 12 weeks was not performed. In cases where cetuximab therapy was discontinued before PD was confirmed, radiotherapy was to continue as planned, and assessments including imaging were to be performed at 8 and 12 weeks after completion of radiotherapy.

Treatment-emergent adverse events (TEAEs) (i.e. those events with an onset on or after the first dosing day of treatment and up until 60 days after the last treatment administration) were assessed weekly during treatment and at 4, 8 and 12 weeks after completion of radiotherapy. TEAEs were assessed by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0) and coded by the Medical Dictionary for Regulatory Activities (MedDRA version, 13.0): composite categories for the special adverse events skin reactions, acne-like rash and infusion-related reactions (IRRs), were based on MedDRA terms.

Statistical Considerations

All statistical analyses were performed on data recorded until the follow-up visit at week 12 after completion of the last radiotherapy dose for the last patient in the intention-to-treat (ITT)/safety population (defined as all patients receiving at least one dose of the study treatment). The clinical cut-off date was 11 June 2010.

Patients completing $\geq$70% of the cetuximab planned dose were those with a cetuximab RDI (from the second infusion onwards) $\geq$70%. Cetuximab RDI was calculated only for patients who received at least two doses of cetuximab. Patients receiving the full dose of radiotherapy within 2 weeks over the planned schedule were those receiving 42 fractions (thirty 1.8 Gy fractions [total dose 54.0 Gy] and twelve 1.5 Gy fractions [total dose 18.0 Gy]), at a total dose of 72.0 Gy and with a duration of exposure to radiotherapy of $\leq$56 days. The completion rate was defined as the proportion of patients who completed the planned cetuximab and radiotherapy schedules relative to the number of subjects in the ITT/safety population.

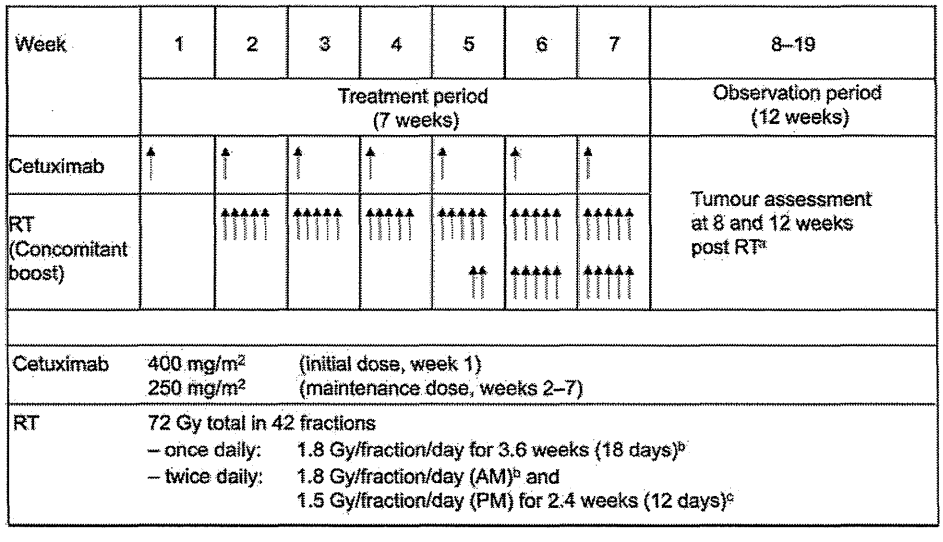

Figure 1. Schedule of irradiation treatment. [a]Imaging at week 12 (i.e. 4 weeks post-RT) was not to be performed for patients with progressive disease at week 8. [b]1.8 Gy/Fr (large field): The primary tumor, gross nodal area and uninvolved nodal area. [c]1.5 Gy/Fr (small field): The primary tumor and gross nodal area. Fr, fraction; Gy, Gray; RT, radiotherapy.

Descriptive statistics were used to summarize the data. A sample size of 20 patients was selected based on a completion rate of 94% reported for concomitant boost radiotherapy in the Bonner trial. The assumption was that at least 80% of the 20 patients would complete treatment, giving two-sided 95% confidence intervals of 68–99%, thereby encompassing the rate in the Bonner trial. The small sample size did not have any power to test statistical hypotheses but was considered to be sufficient for the evaluation of the tolerability (as primary endpoint), safety and efficacy in Japanese patients, in compliance with regulatory requirements. For completion and response rates, two-sided 95% confidence intervals (according to Clopper–Pearson) were calculated. All statistical analyses were performed using SAS® (SAS Institute, Inc., Cary, NC, USA), version 9.1.

RESULTS

Patient Characteristics

Between 6 March 2009 and 4 January 2010, 27 patients were enrolled. Five were ineligible for the study and therefore did not receive protocol-related treatment: due to investigator's decision, withdrawal of consent and interstitial lung disease ($n = 1$ patient each) and protocol-defined radiotherapy unable to be administered (because the required dose was out of the range of that defined by the protocol) ($n = 2$). Thus, 22 patients were enrolled and treated (ITT/safety population). Patient characteristics are summarized in Table 1. Most of the patients (95%) were male and 64% had a KPS of 100. The primary tumor sites were mainly the hypopharynx and larynx (36% each) and 45% of the patients had stage IV disease.

Table 1. Demographics and disease characteristics at baseline: ITT/safety population ($n = 22$)

Characteristic	
Age (years)	
Median	67
Range	(53–81)
Sex, *n* (%)	
Male	21 (95)
Female	1 (5)
Karnofsky performance status, *n* (%)	
100	14 (64)
90	8 (36)
Primary tumor site, *n* (%)	
Hypopharynx	8 (36)
Larynx	8 (36)
Oropharynx	6 (27)
Histology of squamous cell carcinoma, *n* (%)	
Well differentiated	5 (23)
Moderately differentiated	10 (45)
Poorly differentiated	3 (14)
Not known	4 (18)
TNM classification, *n* (%)	
T1–T2	9 (41)
T3–T4	13 (59)
N0	7 (32)
N+	15 (68)
UICC stage, *n* (%)	
Stage III	12 (55)
Stage IV	10 (45)

TNM, tumor node metastasis; UICC, Union for International Cancer Control.

Treatment Completion Rate

The treatment completion rate was 100% (95% CI 85–100) (Table 2). All 22 patients completed ≥70% of the cetuximab RDI and the full radiotherapy dose within 2 weeks over the planned schedule.

Treatment Exposure

One patient discontinued the study due to PD observed at 8 weeks after completion of treatment. The median duration of cetuximab treatment was 8 weeks, the median number of infusions administered was 8 and the median cumulative dose administered was 2169 mg/m^2 (Table 3). All but two patients (91%) received an RDI of ≥90%. The minimum observed cetuximab RDI was 80 to ≤90%. The dose of cetuximab was reduced in one patient, due to a TEAE (grade 3 dry skin). Most of the patients received cetuximab with fewer than 3 days delay in treatment, but two (9%) required cetuximab delays of 3–8 days (infection, $n = 1$; other reason, $n = 1$).

The median duration of radiotherapy was 44 days. All 22 patients received a total dose of 72.0 Gy radiotherapy divided into 42 fractions, i.e. 30 fractions of 1.8 Gy and 12 fractions of 1.5 Gy. The maximum radiotherapy delay which occurred in each patient is categorized as no delay or ≤5 days delay, 6–10 days delay, 11–15 days delay and ≥16 days delay. All patients were able to receive each fraction of radiotherapy with no or ≤5 days delay. In total, all patients completed their scheduled radiotherapy within ≤56 days, in accordance with the protocol-specified full radiotherapy dose criteria (Table 3).

Response Rate

According to the central review by the ESEC, the response rate 8 weeks after completion of radiotherapy was 82%, with a complete response rate of 41% (Table 4). The corresponding results based on the investigator assessment were 86 and 50%, respectively.

Table 2. Completion rate ($n = 22$)

Parameter	Patients, *n* (%)
Completion of ≥70% of cetuximab relative dose intensity	22 (100)
Completion of full dose of radiotherapy with a delay ≤2 weeks	22 (100)
Treatment completion rate [95% CI]	22 (100) [85–100]

CI, confidence interval.

Treatment completion rate and efficacy according to tumor *KRAS* mutation status

All 20 patients who underwent tumor *KRAS* mutation status testing had *KRAS* wild-type tumors. The completion rate among this group was 100% (95% CI 83–100). According to ESEC, 16 patients had a tumor response, giving a response rate of 80% (95% CI 56–94).

Safety

The most common TEAEs (≥50% patients) were mucosal inflammation (86%); dry mouth (77%); constipation, dry skin and dysgeusia (68% each); acne (64%); and dermatitis and pyrexia (50% each). Grade 3/4 TEAEs were reported in 21 (95%) patients. The most common (≥20% of patients) grade 3/4 TEAEs (Table 5) were mucosal inflammation (73%); dermatitis (27%); and infection, radiation skin injury and stomatitis (23% each). In terms of the special adverse events, all 22 patients experienced skin reactions and acne-like rash: three patients (14%) experienced a grade 3 reaction but there were no grade 4 TEAEs in these categories. There was one IRR (blood pressure increase, grade 1). No adverse events led to permanent discontinuation of either cetuximab or radiotherapy. No TEAE leading to death was reported.

DISCUSSION

In this study, we confirmed the feasibility of using a combination of cetuximab and concomitant boost radiotherapy for the treatment of Japanese patients with LASCCHN. The combination of cetuximab and concomitant boost radiotherapy has previously demonstrated efficacy benefits compared with concomitant boost radiotherapy alone in a subgroup of patients in the Phase III Bonner trial in a Western population. The characteristics of patients and their disease at baseline in the study reported here were generally similar to those observed in patients receiving cetuximab plus radiotherapy (once daily, twice daily and concomitant boost) in the Bonner trial, but with a few differences. In the present study, patients were slightly older versus those in the Bonner trial (8) (median age 67 versus 56 years), all had a good performance status (KPS ≥90, 100% versus 70%) and the proportion of patients with oropharynx as the primary tumor site was lower (27% versus 56%) whereas the proportion with primary hypopharyngeal tumors was higher (36% versus 17%). Patients with oropharyngeal tumors appeared to benefit particularly well from cetuximab plus radiotherapy in the Bonner trial (9).

Five patients enrolled to the trial were subsequently considered to be ineligible for protocol-defined treatment, and thus did not receive any study treatment. For two of these patients, the radiotherapy dose calculated to be required for effective treatment was outside the range specified by the

Table 3. Treatment exposure: ITT/safety population ($n = 22$)

Treatment	
Cetuximab	
Duration (weeks)	
Median	8
Range	7–9
Number of infusions	
Median	8
Range	7–9
Cumulative dose (mg/m^2)	
Median	2169
Range	1910–2415
Relative dose intensity,[a] *n* (%)	
≥90%	20 (91)
80 to <90%	2 (9)
Maximum dose delay, *n* (%)	
No delay or <3 days delay	20 (91)
3–8 days	2[b] (9)
Radiotherapy	
Duration[c] (days)	
Median	44
Range	40–52
Number of fractions	
Median	42
Range	42–42
Total dose administered (Gy)	
Median	72
Range	72–72
Maximum delay in each patient, [d] *n* (%)	
No delay or ≤5 days delay	22 (100)

[a]Relative dose intensity calculated only for patients who received at least two doses of cetuximab, with the initial cetuximab dose excluded from the calculation.
[b]One patient due to infection, one due to a reason other than an adverse event.
[c]Duration of radiotherapy exposure is defined as: the date of the last dose of radiotherapy − (date of the first dose of radiotherapy + 1).
[d]The maximum radiotherapy delay in each patient is categorized as follows: no delay or ≤5 days delay; 6–10 days delay; 11–15 days delay, and ≥16 days delay.

Table 4. Best response at 8 weeks after completion of radiotherapy: assessment by independent review committee and investigators: ITT/safety population ($n = 22$)

Response	Patients, *n* (%)	
	ESEC	Investigator
Complete response[a]	9 (41)	11 (50)
Partial response[a]	9 (41)	8 (36)
Stable disease	3 (14)	2 (9)
Progressive disease	1 (5)	1 (5)
Overall response rate [95% CI]	18 (82) [60–95]	19 (86) [65–97]

ESEC, Efficacy and Safety Evaluation Committee.
[a]Confirmed responses, whereby response at 8 weeks was confirmed at 12 weeks after the completion of radiotherapy.

Table 5. Most common grade 3/4 adverse events: ITT/safety population ($n = 22$)[a]

Adverse event	Patients, *n* (%)
Any	21 (95)
Mucosal inflammation	16 (73)
Dermatitis	6 (27)
Infection	5 (23)
Radiation skin injury	5 (23)
Stomatitis	5 (23)
Decreased appetite	4 (18)
Dysphagia	3 (14)
Lymphopenia	3 (14)
Pharyngeal inflammation	3 (14)
Diarrhoea	2 (9)
Dry skin	2 (9)
Pharyngitis	2 (9)

[a]Occurring in >1 patient.

protocol. For the other three patients, one was found to have interstitial lung disease (which was an exclusion criterion), one patient withdrew and the other was withdrawn at the decision of the investigator.

The completion rate of treatment was used as an indication of the tolerability of cetuximab plus radiotherapy in our study. The completion rate definition for cetuximab of ≥70% of the RDI represented no more than one missed dose of cetuximab, ensuring that tolerability was based on clinically effective levels of cetuximab. A treatment completion rate of 100% was reported, with all patients completing ≥70% of the cetuximab RDI and the full radiotherapy dose no later than 2 weeks after the planned end of treatment. The vast majority of patients received ≥90% of the cetuximab RDI and the lowest RDI was 80–90%. Only two patients required a cetuximab dose delay of more than 3 days. All patients were able to receive protocol-defined radiotherapy in combination with cetuximab.

The findings for treatment completion rate are in line with the data from the randomized Bonner trial, in which the treatment completion rate (according to the parameters defined in our study) of patients receiving cetuximab plus concomitant boost radiotherapy was 94% for patients receiving cetuximab in combination with radiotherapy (data on file, Merck KGaA). The results also compare favorably with data reported by Zenda et al. for the completion rate of cisplatin-based concurrent chemoradiotherapy in an exclusively Japanese population of patients with unresectable LASCCHN (10). In that study, in which patients received a 7-week course of radiotherapy (70 Gy at 2 Gy/day) combined with single-agent cisplatin (100 mg/m^2, days 1, 22 and 43), treatment completion was defined as administration of the planned dose of radiotherapy within 63 days and three courses of cisplatin no later than 14 days after the end of radiotherapy. The completion rate reported by Zenda et al. was 85%.

The adverse event profile in this study did not differ from that expected with the concomitant administration of cetuximab and radiotherapy for the treatment of LASCCHN. The overall incidence of grade 3 or 4 TEAEs in this study was similar to that seen in the cetuximab plus radiotherapy arm of the Bonner trial (95% versus 90%). The incidence of grade ≥3 mucosal inflammation was somewhat higher than that reported for mucositis in the cetuximab plus radiotherapy arm of the Bonner trial (73% versus 56%). This is probably due to the exclusive use of the concomitant boost radiotherapy regimen in our trial and the associated risk of an increase in mucositis severity with a concomitant boost compared with a once-daily regimen (11,12). Grade ≥3 acne-like rash, an adverse event associated with cetuximab, occurred with a similar incidence to acneiform rash in the cetuximab plus radiotherapy arm of the trial by Bonner et al. (14% versus 17%, respectively) (8).

In the study reported here, the response rate 8 weeks after completion of radiotherapy was 82% according to the independent review committee. This was in good agreement with the investigator-assessed analysis of response rate, which was 86%. It also compares well with the 74% response rate achieved after treatment with cetuximab plus radiotherapy in the Bonner trial (8). The finding that all of the 20 patients whose tumors were tested had *KRAS* wild-type disease supports data in the literature for the low incidence of *KRAS* mutations in SCCHN (13,14), including in an exclusively Japanese population (15). To our knowledge, this is the first time that *KRAS* mutation data have been obtained for LASCCHN from a prospective clinical trial.

Currently, concomitant chemoradiotherapy (16–18) and radiotherapy plus cetuximab (16,17) are accepted treatment approaches in a range of countries for patients with unresectable SCCHN. There are no trials directly comparing these two strategies, but a recently published quantitative analysis indirectly compared a meta-analysis of data from four randomized trials of cisplatin plus radiotherapy versus

radiotherapy alone and data from one meta-analysis with data from the Bonner et al. trial (19). The analysis indicated that cetuximab and cisplatin were equally effective when administered in combination with radiotherapy, in terms of locoregional control and overall survival in patients with LASCCHN. Given the estimated efficacy equivalence, the choice of whether to treat with concurrent chemoradiotherapy or with cetuximab plus radiotherapy should be based on the toxicity profiles of the two treatment approaches and which of them is considered by the treating physician to be the most suitable for the individual patient.

The study reported here demonstrated that the combination of cetuximab and concomitant boost radiotherapy was a feasible and well-tolerated approach for the treatment of Japanese patients with newly diagnosed LASCCHN. The tolerability of treatment, assessed using treatment completion rate as a surrogate measure, the safety and the antitumor activity observed, was similar to that reported in a pivotal Phase III randomized trial investigating the addition of cetuximab to radiotherapy in a Western population of patients with LASCCHN (8).

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Conflict of interest statement

Takayuki Yoshino received honoraria from Chugai, Takeda, Bristol-Myers Squibb, Yakult and Merck Serono, a research grant from Bayer, Taiho, Daiichi-sankyo and ImClone, and consulting fees from Takeda. Makoto Tahara received consulting fees from Merck Serono. Barbara de Blas is an employee of Merck KGaA. The other authors declare no conflict of interest.

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APPENDIX

In addition to the authors listed on the first page, the following author also contributed equally to this study:

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Original Articles

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Phase II Study of Concurrent Chemoradiotherapy at the Dose of 50.4 Gy with Elective Nodal Irradiation for Stage II–III Esophageal Carcinoma

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Objective: Definitive chemoradiotherapy is one of the curative options for resectable esophageal squamous cell carcinoma with organ preservation. We evaluated the efficacy and toxicity of radiotherapy at a dose of 50.4 Gy concurrent with chemotherapy for Stage II–III esophageal cancer.

Methods: Esophageal cancer patients with clinical Stage II–III (T1N1M0 or T2-3N0-1M0) were eligible. Radiotherapy was administered to a total dose of 50.4 Gy with elective nodal irradiation of 41.4 Gy. Concurrent chemotherapy comprised two courses of 5-fluorouracil (1000 mg/m^2/day) on days 1–4 and 2-h infusion of cisplatin (75 mg/m^2) on Day 1; this was repeated every 4 weeks. Two courses of 5-fluorouracil with cisplatin were added.

Results: Fifty-one patients were enrolled in the study from June 2006 to May 2008. The characteristics of the 51 patients enrolled were as follows: median age 64 years; male/female, 45/6; performance status 0/1, 32/19 patients; Stage IIA/IIB/III, 9/20/22 patients, respectively. A complete response was achieved in 36 patients (70.6%). The 1- and 3-year overall survival rate was 88.2 and 63.8%, respectively. The median 1- and 3-year progression-free survival rate was 66.7% (80% CI: 57–74%) and 56.6% (80% CI: 47.1–64.9%), respectively. Acute toxicities included Grade 3/4 anorexia (45%), esophagitis (35%) and febrile neutropenia (20%). Eight patients (15.6%) underwent salvage surgery due to residual or recurrent disease. There were no deaths related to salvage surgery.

Conclusion: Chemoradiation therapy at a dose of 50.4 Gy with elective nodal irradiation is promising with a manageable tolerability profile in esophageal cancer patients.

Key words: esophageal squamous cell carcinoma – chemoradiotherapy – elective nodal irradiation – 50.4 Gy – salvage surgery

INTRODUCTION

Esophageal cancer, a highly aggressive malignancy, is often refractory to current therapeutic approaches and has a poor outcome. Worldwide, almost 400 000 new cases of esophageal cancer are diagnosed annually—it is the eighth most common cancer and the sixth most common cause of cancer-related mortality (1). In Japan, esophageal cancer was responsible for 11 182 deaths in 2005, accounting for 3.4% of the country's total cancer deaths (2). In Japan, the standard treatment for Stage II–III esophageal squamous cell carcinoma is neoadjuvant chemotherapy followed by esophagectomy with three-field lymph node dissection. The 5-year survival rate is reported to be 36.8–61% (3–5), with a surgical mortality rate of 3–5%.

Chemoradiotherapy (CRT) is also a curative-intent treatment for esophageal cancer patients. Japan Clinical Oncology Group (JCOG) 9906, a Phase II study of evaluating CRT (5-fluorouracil (5-FU) 400 mg/m^2 on days 1–5, 8–12, 36–40 and 43–47 with cisplatin (CDDP) 40 mg/m^2 on days 1, 8, 36 and 43 plus concurrent 60 Gy radiotherapy with 2 weeks of planned interruption) for Stage II–III esophageal cancer, showed promising efficacy with a complete response (CR) rate of 62.2% and 5-year survival rate of 36.8% as a non-invasive treatment (6). However, four (5.3%) treatment-related deaths occurred due to late toxicity caused by an excessive radiation dose and extended radiation field corresponding to the dissected area in extended surgery. Long-term toxicity after CRT was known to be serious and sometimes life-threatening complications. Most of these events occurred several years after CRT. It is considered that reduction in the radiation dose and control of late toxicity may improve post-CRT survival. One more problem to solve was pointed out from JCOG9906. Salvage treatment was needed for the patients who had residual or recurrent disease after CRT. Patients with only locoregional disease had a potential to be cured if salvage surgery or endoscopic mucosal resection (EMR) were performed.

Radiation Therapy Oncology Group (RTOG) 94–05 demonstrated that a higher irradiation dose (64.8 Gy) in CRT offered no advantage in terms of survival and local control compared with the standard dose (50.4 Gy) (7), one reason being low tolerability in the high-dose arm due to toxicity. We speculated that the RTOG regimen will overcome the weak points of the JCOG9906 regimen, such as the high incidence of late toxicity, without compromising efficacy. However, retrospective analysis showed that elective lymph node irradiation was effective for regional lymph node failure (8).

We therefore performed a Phase I study to assess the optimal dose of 5-FU and CDDP with radiotherapy at a dose of 50.4 Gy (9). The radiation field included the primary tumor, metastatic lymph nodes and regional lymph nodes up to 41.4 Gy with a booster dose of 9 Gy administered to the primary tumor and metastatic lymph nodes. The recommended dose of 5-FU and CDDP was 1000 mg/m^2 on Days 1–4 and 29–32, and 75 mg/m^2 on Days 1 and 29, respectively, which were the same doses used in the RTOG regimen, while elective lymph node irradiation was added.

We conducted this Phase II study to evaluate the efficacy and toxicity of the modified RTOG regimen in Japanese esophageal cancer patients.

PATIENTS AND METHODS

PATIENTS

Patients were recruited on the basis of the following criteria: pathologically confirmed thoracic esophageal cancer (primary squamous cell carcinoma, adenosquamous cell carcinoma, adenocarcinoma); clinical Stage II–III, excluding T4 (T1N1M0 or T2-3N1-0M0; International Union Against Cancer [UICC] 2002), Eastern Cooperative Oncology Group (ECOG) performance status (PS), 0 or 1; and age, 20–70 years. Patients who had received previous therapy for esophageal cancer or chemotherapy/radiotherapy for other malignancies and who previously had other active malignancies were excluded. All patients were required to meet the following laboratory criteria within 14 days prior to registration: white blood cells (WBCs) $\geq$4000/mm^3; platelet (PLT) count $\geq$100 000/mm^3; hemoglobin level $\geq$10 g/dl; aspartate aminotransferase (AST), alanine aminotransferase (ALT) $\leq$100 IU/l; total bilirubin $\leq$1.5 mg/dl; serum creatinine $\leq$1.2 mg/dl; creatinine clearance $\geq$60 ml/min; SpO_2 $\geq$95%; and no major electrocardiogram abnormalities. Written informed consent was obtained from all patients. This study is registered with UMIN-CTR, number UMIN000000856.

CHEMOTHERAPY

Chemotherapy comprised two courses of infusion of 5-FU (1000 mg/m^2/day) on Days 1–4 and a 2-h infusion of CDDP (75 mg/m^2) on Day 1, with concurrent radiotherapy. Each cycle of chemotherapy was repeated every 28 days. Patients had a 4-week rest after the completion of radiation and then received an additional two cycles (Days 57 and 85) of chemotherapy (Figure 1).

The Common Terminology Criteria for Adverse Events Version 3.0 was used for acute chemotherapy toxicity (10). Each cycle of chemotherapy was held until toxicity was no longer present for any of the following toxicity conditions: WBC < 2500/mm^3; PLT < 75 000/mm^3, Grade 3 nausea, vomiting, anorexia, esophagitis or diarrhea; serum creatinine > 1.5; T-bilirubin > 2.5; AST > 100; ALT > 100; or any Grade 2 or higher radiation pneumonitis. If the WBC count was 2000/mm^3 or higher but lower than 2500/mm^3, the dose of 5-FU and CDDP was temporarily decreased by 50% at the beginning of the second course of CRT, and radiation therapy was continued. Doses were permanently reduced by 25% in the subsequent course for any of the following toxicity conditions: Grade 4 leukopenia, neutropenia or

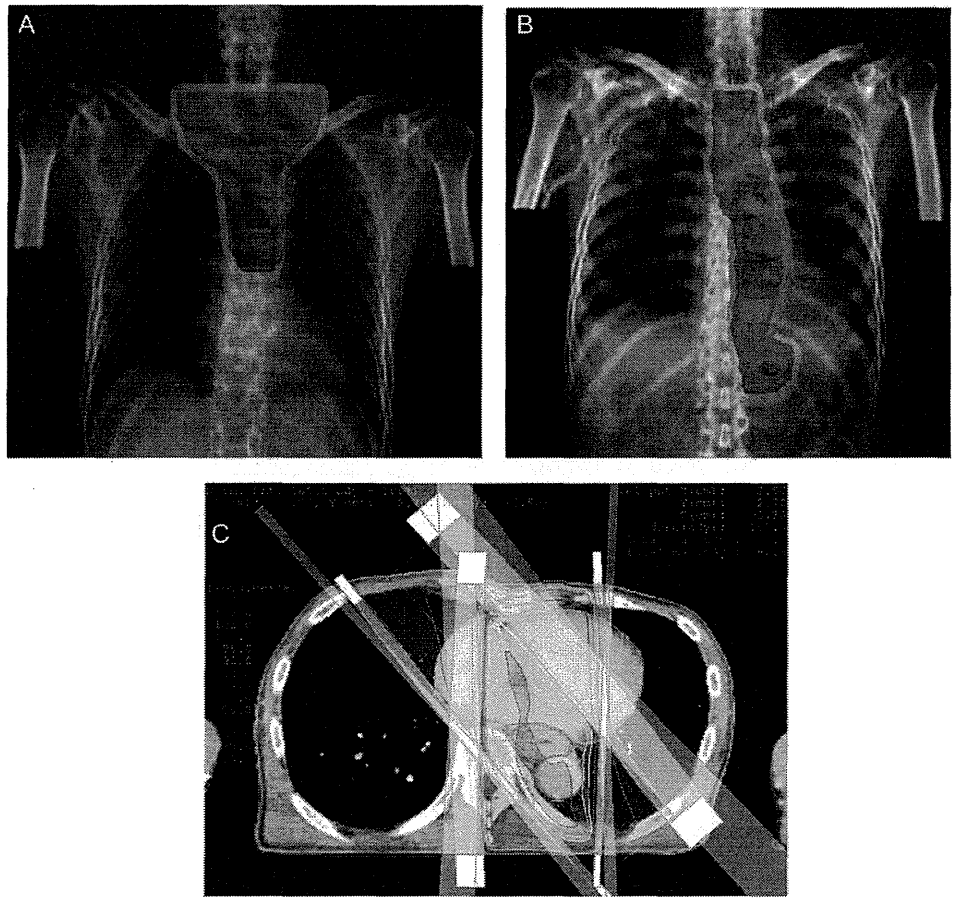

Figure 1. An example of the radiotherapy target volume and dose distribution. The gross tumor volume (GTV) of primary tumor, red; the GTV of metastatic lymph nodes, green; the CTV of primary tumor, pink; the CTV of elective nodal region, blue; the initial PTV, yellow and the boost PTV, orange and cyan. (A) For cancer of the upper thoracic esophagus, (B) for cancer of the middle or lower esophagus. (C) The dose distribution treated with a four-field technique for a middle thoracic esophagus tumor.

thrombocytopenia; or Grade 3/4 stomatitis or diarrhea. If Grade 4 leukopenia, neutropenia or thrombocytopenia, or Grade 3/4 febrile neutropenia or radiation pneumonitis were observed, administration of both chemotherapy and radiation was discontinued until recovery from toxicity. Treatment was terminated when disease progression was observed, evident residual disease was observed in any evaluation, the patient refused to continue or recovery from toxicity delayed the initiation of a course by >2 weeks from the planned schedule.

Radiotherapy

Radiotherapy was delivered with megavoltage equipment (≥6 MV) using a multiple-field technique. Three-dimensional treatment planning was required. The total dose was set at 50.4 Gy in 28 fractions over 6 weeks. A three- or four-field technique was strongly recommended for a middle or lower thoracic esophagus tumor. An opposite field technique was permitted for upper thoracic esophagus tumor. Primary tumor and metastatic lymph nodes were contoured as gross tumor volumes. The clinical target volume (CTV) included the primary tumor with a 2-cm craniocaudal margin, metastatic lymph nodes and regional lymph nodes. The regional lymph nodes included bilateral supraclavicular fossae and superior mediastinal lymph nodes for carcinoma of the upper thoracic esophagus, and mediastinal and perigastric lymph nodes for carcinoma of the middle or lower thoracic esophagus. Celiac axis lymph nodes were also included for carcinoma of the lower thoracic esophagus. Planning target volume (PTV) was defined as CTV plus a 1–2 cm margin in the craniocaudal direction and 0.5–1 cm margin in the lateral direction to account for respiratory organ motion and daily setup error. After treatment with 41.4 Gy to the PTV, a booster dose of 9.0 Gy was administered to the reduced PTV, including the primary tumor and metastatic lymph nodes up to a total dose of 50.4 Gy. The reference point of radiation doses was set at the center of the PTV. Lung inhomogeneity corrections were not used. The dose to spinal cord was maintained below 44 Gy, the percentage of pulmonary volume irradiated to >20 Gy (V20) was limited to <25% and the mean dose to the heart was limited to <40 Gy.

Assessment

Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors, version 1.0 (11) with endoscopy and computed tomography (CT) performed after each course to assess response. Primary tumor response was evaluated by endoscopy using the modified criteria of the 10th edition of the Japanese Society for Esophageal Diseases (12). Complete resolution of lymph node metastasis was defined as the disappearance of all visible lymph node metastases on CT imaging. CR was defined when both primary tumors and lymph node metastases had disappeared without the presence of ulceration or malignant cells in biopsy specimens. After CR was observed, CT and endoscopy were repeated every 3 months during the first year, every 4 months in the second year and every 6 months thereafter.

Acute toxicities were assessed weekly during CRT and every 2 weeks during additional chemotherapy for 90 days after CRT completion. The toxicities were evaluated based on the Common Terminology Criteria for Adverse Events (Version 3.0) (10).

Statistical Methods

The primary endpoint was the 1-year survival rate, defined as the proportion of patients who died by any cause during 1 year from registration. Progression-free survival (PFS) was defined as the time from the date of registration to that of disease progression, evidence of residual disease or death from any cause. Based on the results of the JCOG9906 trial, in which the 1- and 3-year survival rates were 73 and 46%, respectively, the results were considered as positive if the 1-year survival rate was estimated at around 75% with adequate precision. Based on this, a precision-based sample size calculation was performed so that the 80% confidence interval (CI) for the estimated 1-year survival would be no greater than $\pm$ 10% (1-year survival rate 65–85%). The total number of patients was set at 50 to allow for patients who might be ineligible for efficacy evaluation.

Secondary endpoints included rates of CR, PFS and acute and late adverse events. The study was analyzed according to an intention-to-treat principle. The time-to-event distribution was estimated using the Kaplan–Meier method, and CIs were calculated using Greenwood's formula. All analyses were performed using SAS Version 9.1.3 (SAS Institute, Cary, NC, USA). The final analysis was conducted in June 2010.

RESULTS

Patient Characteristics

Between June 2006 and May 2008, 51 patients were enrolled; their characteristics are summarized in Table 1. The median age was 64 years (range, 42–70 years). Thirty-two (62.7%) and 19 (37.3%) patients showed ECOG PS of 0 and 1, respectively. Thirty-one patients had T3 disease, while 42 had N1 disease. The clinical stages (UICC-TNM 6th Edition) were IIA for nine patients, IIB for 20 patients and III for 22 patients. Fifty patients were diagnosed with squamous cell carcinoma and one was diagnosed with adenosquamous cell carcinoma.

Table 1. Patient characteristics

Characteristic	Number of patients ($N = 51$)
Sex: male/female	45/6
Age: median (range)	64 (42–70)
PS: 0/1	32/19
Tumor location: upper/middle/lower	7/35/9
Histology: squamous cell carcinoma/ adenosquamous cell carcinoma	50/1
Clinical Stage: IIA/IIB/III	9/20/22
T: 1/2/3	15/8/28
N: 0/1	9/42

PS, performance status.

Treatment

Of the 51 patients, 34 (67%) completed the CRT and the two courses of additional chemotherapy. Of the 49 patients who received a second course of CRT, seven needed delay and 12 needed dose reduction (two for 25% reduction and 10 for 50% reduction) mainly due to hematological toxicity at the beginning of the second course of CRT. After completion of CRT, 10 patients discontinued the protocol treatment due to disease progression ($n = 3$), adverse event ($n = 6$) and patient refusal not related to any adverse event ($n = 1$). Details of adverse events were as follows: delay of recovery prolonged over 2 weeks of Grade 3 creatinine, Grade 3 appetite loss, gastric ulcer, pneumonia, Grade 3 esophagitis and patient refusal due to adverse events. Of the 39 patients who received the first course of additional chemotherapy, 17 needed delay and six needed dose reduction mainly due to appetite loss and esophagitis during the second course of CRT. After the first course of additional chemotherapy, four patients discontinued the protocol treatment due to disease progression ($n = 2$) and adverse events ($n = 2$: Grade 3 appetite loss and esophagitis). Of the 35 patients who received the second course of additional chemotherapy, 10 needed delay and seven needed dose reduction mainly due to hematological toxicity during the prior course. Totally, six (12%) patients discontinued the protocol treatment due to insufficient efficacy in terms of residual disease (5) and lung metastasis (1). All patients except two completed the radiotherapy at a dose of 50.4 Gy. Two discontinued the radiotherapy due to disease progression and infection.

Efficacy

All patients were included for efficacy analysis. At the final data cut-off date (June 30, 2010), the median duration of follow-up was 29.4 months. Twenty deaths were observed at the time of analysis; 16 patients died from esophageal cancer, three died from conditions other than esophageal cancer (lung cancer, pneumonia, subarachnoid hemorrhage) and one died from an unknown cause. Thirty-six patients achieved CR, resulting in a 70.6% CR rate (80% CI, 58.3–84.1%). The CR rate by stage was 89.7% for cStage II and 45.5% for cStage III, respectively.

The 1- and 3-year survival rate was 88.2% (80% CI: 81–92.9%) and 63.8% (80% CI: 54.3–71.8%), respectively. The lower limit of 80% CI for 1-year survival exceeded the threshold of 75%. The respective 1- and 3-year survival rates by clinical stage were 96.6 and 78.3% for Stage II and 77.3 and 44.6% for Stage III patients (Figure 2). The median 1- and 3-year PFS was 66.7% (80% CI: 57–74%) and 56.6% (80% CI: 47.1–64.9%), respectively (Figure 3).

Safety

For all 51 patients, no protocol-related deaths were observed. Grade 4 leukopenia, neutropenia, anemia and thrombocytopenia were observed in 7.8, 21.6, 3.9 and 2.0% of the patients, respectively, while Grade 3/4 esophagitis, anorexia, febrile neutropenia and hyponatremia were observed in 35.3, 45.1, 19.6 and 15.7% of the patients, respectively (Table 2). Late toxicity data are summarized in Table 3. Grade 3–4 late toxicities included gastric hemorrhage (2.0%), esophageal stenosis (3.9%) and pneumonitis (5.9%).

Pattern of Failure and Salvage Treatment

The pattern of failure is described in Table 4. Fourteen patients (27.4%) had residual or progressive disease, 10 with only residual disease and four with distant metastasis. Eight patients (15.7%) had recurrence, four of only a regional lesion and four with distant metastasis after CR. Salvage

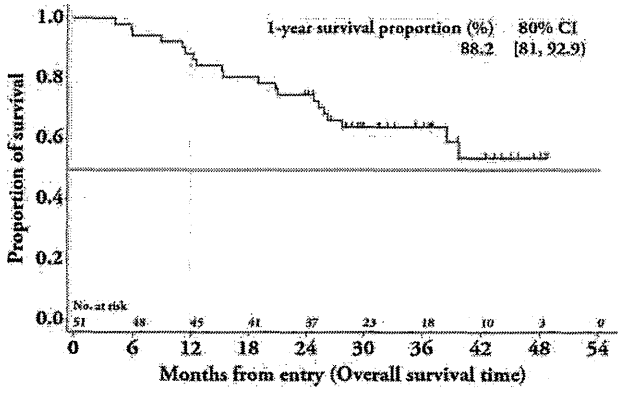

Figure 2. Overall survival of 51 eligible patients.

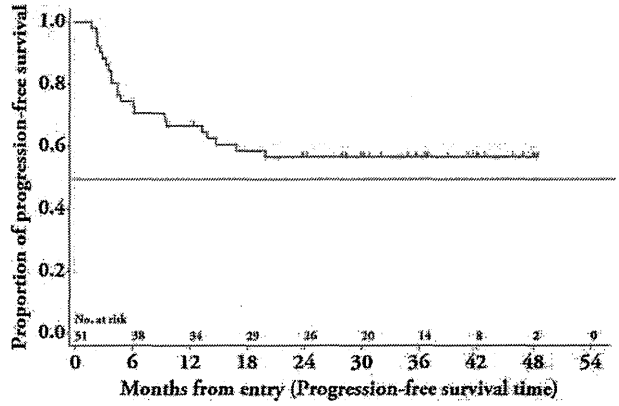

Figure 3. Progression-free survival of 51 eligible patients.

Table 2. Acute toxicity ($N = 51$)

Toxicity	CTC-AE Version 3.0				
	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)
Leukocytes	1	7	38	4	82.3
Neutrophils	3	7	29	11	78.4
Hemoglobin	8	31	10	2	23.5
Platelets	23	13	9	1	19.6
Esophagitis	6	17	18	0	35
Dysphagia	14	10	16	0	31
Anorexia	6	17	23	0	45
Nausea	19	18	6	-	12
Vomiting	9	11	3	0	6
Diarrhea	9	1	0	0	0
Stomatitis/pharyngitis	13	7	2	0	4
Febrile neutropenia	–	–	10	0	20
Hyponatremia	37	–	8	0	16
AST	21	2	3	0	6
ALT	16	3	2	0	4
Creatinine	26	9	1	0	2

CTC-AE Version 3.0, Common Terminology Criteria for Adverse Events Version 3.0; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

treatment was performed for these patients. Of the 14 patients who had residual disease, six patients underwent salvage surgery. Two refused to undergo salvage surgery and six patients were not candidates for salvage surgery due to inadequate organ function or the presence of distant metastasis. Of the eight patients with recurrent disease, one underwent salvage surgery, two underwent endoscopic submucosal dissection (ESD), one underwent both ESD and salvage surgery and four received chemotherapy and/or radiotherapy due to distant metastasis or tumor invasion. In total, 14 patients (27.4%) had locoregional residual and recurrent disease

Table 3. Late toxicity ($N = 51$)

Late toxicity	CTC-AE Version 3.0					
	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)	≥Grade 4 (%)
Pleural effusion (non-malignant)	6	1	0	0	0	0
Esophagus-related (dysphagia, stenosis, fistula)	6	9	2	0	3.9	0
Pericardial effusion	5	1	0	0	0	0
Pneumonitis	26	0	3	0	5.9	0
Hemorrhage-gastrointestinal	0	0	1	0	2.0	0
Spinal cord-related	0	0	0	0	0	0

Table 4. Pattern of failure

	N	%
Alive/no failure	27	53
Any failure	24	47
Dead by other cause	2	4
Persistent failure	14	27
Only local failure	10	20
With distant failure	4	8
Recurrence after complete response	8	16
Only local recurrence	2	4
Only regional recurrence	2	4
Any distant recurrence	4	8
Total local/regional persistence/failure	14	27

without distant metastasis, eight patients underwent salvage surgery and four underwent ESD with curative intent. There were no deaths related to salvage surgery (Table 5).

DISCUSSION

Our results showed that CRT for Stage II–III esophageal squamous cell carcinoma (ESCC) produced a 70.6% CR rate (80% CI: 58.3–84.1%), 88.2% (80% CI: 81–92.9%) 1-year survival rate and 63.8% 3-year survival rate. The 1-year survival rate, the primary endpoint of this study, met the decision criteria. The RTOG regimen has already been used as a standard in various countries; we set the primary endpoint to be able to confirm the efficacy of the RTOG regimen within a short time and with adequate precision. In the JCOG9906 trial, the 1- and 3-year survival rate was 72.4 and 45%, respectively. The short follow-up duration of our study makes it difficult to draw a comparison with JCOG9906, but the results of this study are promising.

Table 5. Characteristics and outcomes of patients who underwent salvage surgery

Characteristic	Number of patients ($N = 8$)	Characteristic	Number of patients ($N = 8$)
Male	7	Residual/recurrent	6/2
Female	1		
Age (years)		Surgical curability	
Range	49–70	R0	5
Median	60	R1 + R2	3
Tumor location			
Upper	1	Operative mortality or hospital death	0
Middle	4		
Lower	3	Relapse after surgery	1
Clinical stage[a]		No relapse	7
IIA	1		
IIB	3		
III	4		

[a]Clinical stage at the time of registration.

Esophagectomy with extended lymph node dissection is the standard treatment for local esophageal cancer patients in Japan. The control of disease to regional lymph nodes is considered critical for prolonging survival. In a randomized trial, extended transthoracic resection with en bloc lymphadenectomy demonstrated a trend toward improving survival for esophageal adenocarcinoma patients compared with transhiatal resection (13). Moreover, there was a discrepancy in the number of lymph nodes between clinical and surgical findings, and a higher number of lymph node sampling clinically associated with disease-specific survival even in lymph node-negative patients (14,15). In a retrospective study with CRT, extended radiation for regional lymph nodes improved survival compared with a normal radiation field (8). Therefore, we set the radiation field to cover regional lymph nodes (Figure 2). The original RTOG regimen includes only the primary tumor and metastatic lymph nodes. In our study, 27% of the locoregional residual and recurrent disease showed no distant metastasis, whereas 16% of patients had distant metastasis. In the RTOG94-05 trial, 55% of the locoregional residual and recurrent disease and 18% of any distant failure were seen in the standard dose (50.4 Gy) arm. It is difficult to compare the two trials whose characteristics and follow-up duration were slightly different. But among the failure patients, the patients with only locoregional failure were 58% in this trial compared with 73% in RTOG 9405. Even with limitations, these results may suggest that the extended radiation field increased locoregional control.

In JCOG9906, late toxicities included Grade 3/4 esophagitis (13%), pericardial (16%) and pleural (9%) effusions, and pneumonitis (4%), which caused four deaths. The radiation field of JCOG9906 was much wider and longer than this study. Late toxicity after thoracic radiotherapy has also been reported in patients with esophageal cancer, lung cancer and Hodgkin's lymphoma (16–21). In a previous report, two of 78 patients with CR after CRT died of myocardial infarction and eight (10.2%) died of pericardial or pleural effusion (21). Because an application of the multifield technique could reduce the dose to the heart of the respective patients in this study, a very low incidence of pericardial and pleural effusion was presently seen. It is difficult to fully evaluate late toxicity in this study due to the short follow-up, and so further follow-up and evaluation for late toxicity is needed.

In contrast, acute toxicity was relatively high in this study and presumably caused by the extended radiation field. Increase of the dose of 5-FU compared with the previous study and a wider radiation field may increase the esophagitis or gastrointestinal toxicities. It was necessary to provide supportive care, including total parenteral nutrition, analgesics including opioids for esophagitis and antibiotics for febrile neutropenia, when severe toxicity occurred. Although the incidence was relatively high, acute toxicity was manageable with recovery being achieved within a matter of weeks with sufficient support.

For non-responders, salvage surgery is a possible therapeutic option. Salvage treatment (e.g. salvage surgery (22–24) or salvage EMR (25)) was recently reported to have therapeutic potential for patients with local CRT failure. It has been reported that 6–34% of patients undergo salvage esophagectomy after definitive CRT (26,27). Although a high rate of hospital deaths (6–33%) is observed when compared with that after surgery without preoperative therapy, some patients achieve long-term survival with a 25–35% 5-year survival rate (28–30). In the present study, eight patients underwent salvage esophagectomy and there was no operative mortality and no hospital deaths. Some patients benefit from salvage surgery after definitive CRT; which types of patients receive benefit from salvage surgery and how the procedure is best performed after CRT requires further prospective evaluation. JCOG0909, Phase II trials of CRT for resectable ESCC followed by salvage surgery for residual or recurrent disease are underway. CRT apparently has the advantage of preserving the esophagus, which may provide a better quality of life than the strategy that includes surgery.

CRT by the RTOG regimen with an extended radiation field is effective with manageable toxicities and can be a non-invasive treatment option for Stage II–III ESCC.

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Conflict of interest statement

There exists no conflict of interest for any of the authors.

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Original Article

Clinical Outcome and Patterns of Recurrence of Head and Neck Squamous Cell Carcinoma with a Limited Field of Postoperative Radiotherapy

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Background: Postoperative radiotherapy is the standard treatment for head and neck squamous cell carcinoma having high-risk features in surgical specimens. However, its severe toxicity can be a significant problem. This study was undertaken to evaluate the efficacy of our limited-field postoperative radiotherapy with the aim of reducing morbidity by minimizing the radiation field.

Methods: Between 2000 and 2009, 154 patients with head and neck squamous cell carcinoma received limited-field postoperative radiotherapy. The reason for postoperative radiotherapy was close/positive margins in 33 patients and extracapsular extension in 91. The median radiation dose was 50 Gy (30–66.4). The radiation field covered the tumor bed without lymph node regions for close/positive margins and only involved sites of the neck region were irradiated for multiple nodes or extracapsular extension.

Results: With a median follow-up of 43 months for surviving patients, the 3-year overall survival and progression-free survival rates were 53.7 and 42.1%, respectively. The 3-year rates of progression-free survival of the group having major risks (i.e. close/positive margins and/or extracapsular extension) and the group with other risks were 34.7 and 62.8%, respectively ($P < 0.01$). Thirty-one local recurrences (20%), of which 22 were located out-of-field, and 44 regional recurrences (29%), of which 16 were located out-of-field, developed. Late toxicity of grade 3 or greater developed in only six patients (3.8%).

Conclusions: Although the toxicities associated with limited-field postoperative radiotherapy could be kept to lower levels, the locoregional control rate did not seem to be sufficient. We should arrange the radiation field depending on risk factors.

Key words: postoperative radiotherapy – limited field – squamous cell carcinoma of the head and neck

INTRODUCTION

The prognosis of locally advanced head and neck squamous cell carcinoma (HNSCC) patients is still poor. Initially, the combination of surgery and postoperative radiotherapy (PORT) for the treatment of advanced HNSCC was developed in an empirical manner because of the poor locoregional control rates achieved with either modality alone. Convincing evidence then emerged regarding the efficacy of PORT to significantly reduce the risk of locoregional recurrence to lower than that with surgery alone (1–3). PORT is now standard care for HNSCC having high-risk features in surgical findings. In addition, the approaches used to decide the optimal dose in

relation to clinical and pathological risk factors have been performed in a prospective setting (4,5).

However, because of this intensive bi-modality treatment, the rates of acute and late toxicities are relatively high. Ang et al. conducted a randomized trial to investigate the risk features and time factors of surgery plus PORT in advanced HNSCC patients. They reported that 5 (16.1%) and 25 (33.3%) patients in the 57.6 Gy/6.5week and 63 Gy/7week groups, respectively, developed one or more Grade 3–4 late morbidities (5). In addition, two randomized trials, European Organization Research and Treatment of Cancer trial #22931 (EORTC trial #22931) and Radiation Therapy Oncology Group trial #9501 (RTOG trial #9501), recently reported that adjuvant chemoradiotherapy (CRT) was more efficient than adjuvant radiotherapy (RT) alone for both disease control and/or survival in selected high-risk locally advanced HNSCC patients (6,7). In the RTOG trial, the rates of late adverse events greater than Grade 3 were 16.8 and 20.9% in the postoperative RT group and postoperative CRT group, respectively. Thus, efforts to reduce severe adverse events have become more essential.

In the Aichi Cancer Center Hospital, HNSCC patients with poor prognostic features who were treated with surgery were considered for limited-field (LF) PORT to reduce toxicities while maintaining efficacy of the treatment. Until now, few reports have attempted to reduce the radiation field. We limited the radiation field of neck lymph node sites with no pathologically involved lymph nodes or one lymph node without extracapsular extension (ECE). Regarding the primary site, we spared the primary tumor bed if there was no evidence of close/positive surgical margins. The indication criteria for PORT were two or more histopathologically involved lymph nodes, the presence of ECE or close/positive surgical margins.

This study was undertaken to evaluate the efficacy of our LF-PORT with the aim of reducing morbidity by minimizing the radiation field.

MATERIALS AND METHODS

Patient Characteristics

Between 2000 and 2009, 154 patients with HNSCC received LF-PORT in the Aichi Cancer Center Hospital. All patients underwent magnetic resonance imaging (MRI) or computed tomography (CT) to assess the extension of primary and cervical lymph nodes before surgery. An evaluation of distant metastasis was performed using chest X-rays, cervico-thoracic CT, liver ultrasonography and/or bone scintigraphy before surgery. All patients had previously undergone radical surgery. If the pathological report showed positive/close surgical margins, multiple lymph node metastases or the presence of ECE after surgery, patients were considered for adjuvant LF-PORT. Tumor staging was decided based on pathological findings according to the American Joint Committee on Cancer staging criteria 2002 version 6.

Treatment Schedule

External beam radiotherapy was started using a 6–10 MV photon beam from a linear accelerator. At the 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 radiation field covered the tumor bed to 40–50 Gy for close/positive surgical margins, then cone down to the high-risk area to 60 Gy. For CTV nodes without ECE, the involved site of the neck region was irradiated up to 40–50 Gy. In the case of high-risk CTV related to ECE, a boost dose up to 60 Gy was added.

For the boost up to 60 Gy, we kept enough margins of surgically close/positive sites or ECE lesions from the edge of field. PTV margins were basically 5–10 mm. However, if needed those margins were reduced dependent on proximity to critical organs such as spinal cord.

Since 2003, concurrent CRT consisting of platinum was administered in the case of close/positive surgical margins or ECE. During the treatment period, complete blood counts and biochemical examinations were performed approximately once a week in CRT patients.

Treatment Contents

The median radiation dose was 50 Gy (range, 30–66.4 Gy) and the median period between the surgical procedure and the start of radiation was 27 days (range, 11–84 days). Thirty-four patients (22%) received concurrent CRT. Regarding the contents of chemotherapy, 29 patients received weekly administration of cisplatin (CDDP) at a dose of 20–30 mg/m^2. Other chemotherapy regimens were tri-weekly CDDP at a dose of 80 mg/m^2 or combination of nedaplatin (CDGP) and 5-fluorouracil (5-FU).

There were four patients who received <40 Gy. One patient received 30 Gy because of patient's refusal of radiation treatment even though adverse effects were not severe. The other three patients received 36–39.6 Gy. The reasons for the dose <40 Gy were mainly dependent on the radiation oncologists' judgement to avoid severe adverse effects because of the usage of whole neck irradiation or concurrent intensive chemotherapy such as combination of CDGP and 5-FU.

Follow-up and Statistical Considerations

Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. After the completion of PORT, the clinical status of the patient was assessed by fiberoptic pharyngoscopy, MRI and/or PET/CT. The frequency of follow-up was approximately every month for the first year, once every 3 months between the second and third post-treatment year and once every 6 months after the third post-treatment year. The survival period was calculated from the start of treatment to death or the last

follow-up examination, and progression-free survival (PFS) was defined as the period from the start of treatment to the progression of tumors or death by any cause. Statistical analyses were performed using StatView-J5.0. Overall survival (OAS) and PFS curves were calculated by the Kaplan–Meier method (8). The log-rank test was used to compare survival curves. A Cox-proportional hazard model was used for multivariate analysis (MVA). A probability value of <0.05 was defined as significant.

RESULTS

Patient Characteristics

Between 2000 and 2009, 154 patients with HNSCC received LF-PORT in the Aichi Cancer Center Hospital. Table 1 shows the patient characteristics in this cohort. The median age was 61 years old (range, 21–85). The oral cavity, oropharynx, hypopharynx and larynx were primary sites in 87, 17, 47 and 3 patients, respectively. Fifteen patients (9.7%) had histopathology with poorly differentiated squamous cell carcinoma. One hundred and eighteen patients (76.6%) had pN2b-3 disease. The treatment status of untreated or recurrence was 128 and 26, respectively. Ninety-one patients had ECE lesions, while 63 patients had lymph node lesions without ECE or no lymph node lesions.

The reason for PORT is positive/close margin as 17/16 patients, while ECE for 91 patients. One hundred and fourteen patients had multiple involved lymph nodes. The reason for PORT is positive/close margin or ECE as 113 patients, while other reasons such as multiple involved lymph nodes for 41 patients.

Table 1. Patient characteristics

Characteristics		*n*
Age (year)	Median	61 (21–85)
Gender	Male/female	116/38
Primary site	Oral cavity/OPC/HPC/larynx	87/17/47/3
Differentiation	Well/moderate/poor/unknown	69/60/15/10
pTstage	T0-1/2/3/4	45/43/27/39
pNstage	N0/1/2a/2b/2c/3	8/19/9/86/24/8
Surgical margin	Positive/close/negative	17/16/121
Extracapsular extension	Yes/no	91/63
Treatment status	Untreated/recurrence	128/26
Radiation dose (Gy)	Median	50 (30–66.4)
Time between surgery and radiation (days)	Median	27 (11–84)
Concurrent chemotherapy	Yes/no	34/120

OPC, oropharyngeal carcinoma; HPC, hypopharyngeal carcinoma.

Treatment Outcomes

With a median follow-up of 43 months for surviving patients (24 months for all patients), the 3-year rates of OAS and PFS were 53.7 and 42.1%, respectively (Fig. 1). The 3-year rates of OAS and PFS of 128 patients who were treated with initial therapy were 55.0 and 47.5%, respectively.

Fifty-six patients were alive without disease, 21 were alive with disease, 64 died from the disease, 12 died from other diseases (including 5 who died by other cancers such as esophageal cancer, hepatocellular cancer and ureteral cancer and 2 who died by pneumonia without any evidence of recurrence or difficulty in swallowing) and 1 died because of the acute toxicity associated with RT.

The 3-year rates of locoregional PFS (LRPFS) and distant metastasis-free survival (DMFS) were 57.4 and 75.5%, respectively.

Univariate Analysis

The results of univariate analyses (UVAs) for LRPFS and OAS were listed in Table 2.

Poorly differentiated squamous cell carcinoma and pN2b-3 were revealed to be significant unfavorable prognostic factors of OAS. The 3-year rate of OAS of the group with poorly differentiated squamous cell carcinoma was significantly lower than that with moderately and well differentiated (16.2 vs. 57.8%, $P < 0.0001$). The group with pN2b-3 lesions had a significantly worse 3-year rate of OAS (47.5%) than that with pN0-2a (72.6%, $P = 0.035$). Regarding concurrent chemotherapy, there was no significant difference in the 3-year rates of OAS between the RT and CRT group (56.1 vs. 47.5%, $P = 0.11$).

Poorly differentiation ($P = 0.034$), pN2b-3 ($P = 0.0079$) and ECE ($P = 0.039$) were revealed to be significant unfavorable prognostic factors for LRPFS. The 3-year rate of LRPFS of the group with ECE was significantly lower than that of the group without ECE (47.7 vs. 72.0%, $P = 0.039$).

Similar to LRPFS, significantly unfavorable factors for PFS were revealed to be poorly differentiation, pN2b-3 and ECE.

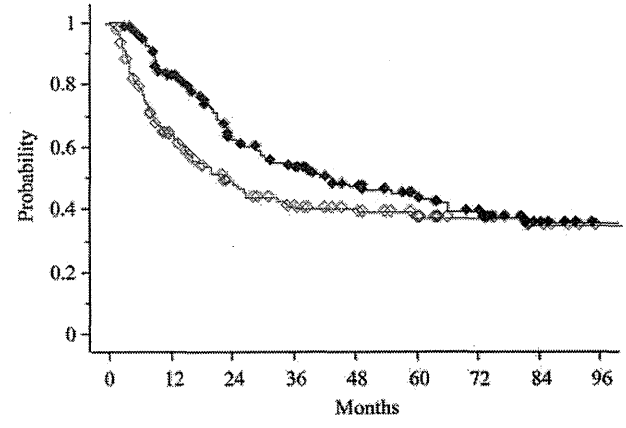

Figure 1. Overall survival (OAS) and progression-free survival (PFS) curves.

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

Factors	No. of patients	3-year LRPFS (%)	*P* value	3-year OAS (%)	*P* value
Age					
<61 or ≥61	75/79	57.7/57.1	0.88	58.1/49.4	0.22
Gender					
Male or female	116/38	60.3/49.5	0.093	55.4/49.2	0.31
Site					
Oral cavity or others	87/67	55.9/60.3	0.27	45.9/63.3	0.16
Differentiation					
Poorly or others	15/139	29.0/60.0	0.034	16.2/57.8	<0.0001
pTstage					
pT0-2 or pT3-4	88/66	59.5/54.7	0.30	59.5/46.3	0.26
pNstage					
pN0-2a or pN2b-3	36/118	76.5/51.5	0.0079	72.6/47.5	0.035
Margin					
Positive/close or negative	33/121	64.5/55.4	0.38	59.8/52.3	0.69
ECE					
Yes or no	91/63	47.7/72.0	0.039	47.3/63.9	0.18
Major risk					
High or intermediate	113/41	52.0/71.2	0.10	47.7/69	0.051
RT dose					
≤50 or >50 Gy	94/60	63.8/49.2	0.059	57.1/47.7	0.42
Concurrent chemotherapy					
Yes or no	34/120	62.1/57.7	0.46	47.5/56.1	0.11

LRPFS, locoregional progression-free survival; OAS, overall survival; ECE, extracapsular extension; RT, radiotherapy.

The 3-year rates of PFS of the group having major risks (i.e. close/positive margins and/or ECE) and group with other risk features were 34.7 and 62.8%, respectively ($P < 0.01$).The 3-year rates of LRPFS of the group having major risks and the group with other risk features were 52.0 and 71.2%, respectively ($P = 0.10$).

Multivariate Analysis

The results of MVAs for LRPFS and OAS were listed in Table 3.

On MVA, pN2b-3 ($P = 0.014$), poorly differentiation ($P < 0.0001$) and the presence of major risks ($P = 0.044$) were revealed to be significant unfavorable prognostic factors of OAS. As for LRPFS, pN2b-3 ($P = 0.069$), poorly differentiation ($P = 0.012$) and the presence of major risks ($P = 0.042$) showed a significantly worse impact.

Patterns of Failures

Eighty-five patients (55%) developed treatment failure at one or more sites. Patterns of failures were listed in Table 4. The most frequent site was nodal only in 28 patients (33%), followed by distant only in 23 (27%).

Forty-four regional recurrences developed, of which 16 were located out-of-field. In the group with regional recurrences, the rates of the presence of ECE were 71 and 69% in the in-field recurrence group and out-of-field recurrence group, respectively.

There were 28 in-field regional recurrences, of which 20 were with ECE lesions, and 2 and 26 were pN1-2a and pN2b-3, respectively. In 16 out-of-field regional recurrence patients, 11 patients had ECE lesions, and 2 and 14 patients were pN1-2a and pN2b-3, respectively.

Thirty-one local recurrences (20%) developed, of which 22 (71%) were located out-of-field. There were nine in-field local recurrences, of which 4 were with ECE lesions and 6 were pT3-4 lesions. In 22 out-of-field local recurrences, 17 patients had ECE lesions.

Treatment Toxicity

Acute and late toxicities were listed in Table 5. Acute toxicities of Grade 3 or greater developed in 13 patients (8.4%). The most common toxicity was mucosal inflammation. One

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

Factors	*N*	LRPFS		OAS	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender					
Male	116	0.572 (0.309–1.060)	0.758	0.663 (0.365–1.202)	0.1758
Female	38				
Age					
<61	75	0.988 (0.581–1.678)	0.9640	0.772 (0.484–1.232)	0.2784
≥61	79				
Site					
Oral cavity	87	1.375 (0.781–2.418)	0.2697	1.597 (0.968–2.634)	0.0666
Others	67				
pTstage					
pT0-2	88	0.688 (0.399–1.187)	0.1786	0.705 (0.435–1.145)	0.1582
pT3-4	66				
pNstage					
pN0-2a	36	0.352 (0.165–0.751)	0.0069	0.475 (0.262–0.860)	0.0141
pN2b-3	118				
Differentiation					
Poorly	15	2.720 (1.249–5.921)	0.0117	3.905 (2.075–7.348)	<0.0001
Others	139				
Major risks					
High	113	1.982 (1.026–3.820)	0.0418	1.792 (1.016–3.163)	0.044
Intermediate	41				

HR, hazard ratio; CI confidence intervals.

Table 4. Patterns of failures

Site	*n*		*n*
Local only	14 (16%)	Local recurrence	31
Local and nodal	12 (14%)	In-field	9
Local and distant	4 (5%)	Out-of-field	22
Local, nodal and distant	1 (1%)		
Nodal only	28 (33%)		
Nodal and distant	3 (4%)	Regional recurrence	44
Distant only	23 (27%)	In-field	28
Total	85	Out-of-field	16

Table 5. Acute and late toxicities of grade 3 or greater

	Gr3	Gr4	Gr5
Acute			
Skin	1	0	0
Mucous membrane	7	0	0
Infection	4	0	1
Late			
Bone	3	0	0
Skin	2	0	0
Pharynx and esophagus	1	0	0

patient developed Grade 5 acute toxicity due to DIC caused by infection.

Late toxicity of Grade 3 or greater developed in six patients only (3.8%). There were three patients with osteonecrosis of the jaw bone, two with skin necrosis and 1 with a Grade 3 pharyngeal stricture.

DISCUSSION

Locally advanced HNSCC patients have poor prognoses. Fletcher et al. first reported on the benefits of PORT in 1970 (9). Since the 1970s, many reports have shown that PORT improved locoregional control (LRC) over that of historical control groups or surgery alone (1–3,10–12). In addition,

several risk features and prognostic factors regarding combined treatment with surgery and PORT such as surgical margins, ECE, T stage, N stage or the interval between surgery and PORT have also been described (13–18).

A multi-institutional, prospective, randomized trial was also undertaken in patients with advanced HNSCC to investigate the validity of using pathologic risk features and determine the need for, and dose of PORT (5). In that phase III trial, patients were categorized into low-, intermediate- and high-risk groups according to pathological features. Study designs were no PORT for the low-risk group ($n = 31$), 57.6 Gy for 6.5 weeks for the intermediate-risk group ($n = 31$), and by random assignment, 63 Gy for 5 weeks ($n = 76$) or 7 weeks ($n = 75$) for the high-risk group. Intermediate-risk patients (i.e. 1 adverse feature other than ECE) who received 57.6 Gy PORT had 5-year actuarial LRC and survival rates of 94 and 66%, respectively. In contrast, high-risk patients with ECE or more than one other adverse feature had 5-year actuarial LRC and survival rates of 68 and 42%, respectively.

Although several prospective randomized trials established evidence of the need for, and dose of PORT in patients with advanced HNSCC, the relatively high rates of severe toxicities are still problematic. Peters reported that a total of 17 (7.1%) patients sustained one or more moderate-to-severe late complications (Grade 3–4 on the modified RTOG scale) (4). The most frequent complication was pharyngo-esophageal stricture, followed by bone exposure or necrosis, fistula and severe neck fibrosis/edema. In addition, a dose–response relationship was identified when complications were analyzed in terms of the maximum target dose delivered. Ang et al. reported that 5 (16%) and 25 (33%) patients in the 57.6 Gy/6.5 week and 63 Gy/7 week groups, respectively, developed one or more Grade 3–4 late morbidities (5). The head and neck regions are important for a number of processes including respiration, chewing and swallowing. Therefore, adverse events have a direct impact on the quality of life. The rate of adverse events should be reduced while maintaining the therapeutic effects of the treatment to improve the outcome of advanced HNSCC patients.

In our institute, we treated advanced HNSCC with surgery and PORT according to pathological risk features. To reduce adverse events, we adopted LF-PORT with a focus on moderate- to high-risk regions. For this kind of treatment it is essential to have mutual trust and good communication between head and neck surgeons and radiation oncologists. For these purposes, we have conferences among head and neck surgeons and radiation oncologists once a week to discuss about treatment strategies for HNSCC patients.

In the present study, the rates of acute and late toxicities were quite low. Acute toxicities of Grade 3 or greater developed in 13 patients (8.4%), and late toxicities of Grade 3 or greater developed in six patients only (3.8%). Regarding the therapeutic effect, the 3-year rates of OAS and PFS were 53.8 and 42.1%, respectively. The 3-year rates of PFS in the high-risk group (i.e. close/positive margins and/or ECE) and intermediate-risk group were 34.7 and 62.8%, respectively ($P < 0.01$). The 3-year rates of LRPFS in the high- and intermediate-risk groups were 52.0 and 71.2%, respectively ($P = 0.10$). We think that the results of efficacy in intermediate-risk patients were comparable with those of other groups; therefore, it is reasonable to apply LF-PORT. However, the results of efficacy in the high-risk group were worse than those in the intermediate-risk group and historical controls (Table 6).

In 2004, two randomized trials, EORTC and RTOG, reported that adjuvant CRT was shown to be more efficient than adjuvant RT alone for both disease control and/or survival in selected high-risk locally advanced HNSCC patients (6,7) In a systematic review with meta-analysis of four RCTs including EORTC and RTOG trials (6,7,19,20), pooling trials confirmed the benefit of adjuvant CRT in LRC and OAS (19)

In the present study, there was no significant difference in the 3-year rates of OAS between the adjuvant RT and CRT groups (56.1 vs. 47.5%, $P = 0.11$). In addition, there was no significant improvement in the 3-year rates of OAS between RT and CRT even in high-risk patients (52.5 vs. 42.3%, $P = 0.10$). However, there were several selection biases to decide whether we strongly recommended patients to receive CRT depending on their general condition even though they had major risks.

In order to improve outcomes, we noted the pattern of recurrences. Initially, the most frequent recurrent pattern was only regional recurrence in 28 patients, and the total number of patients who had regional recurrence with or without other site recurrences was 44 (29%). Of these patients, 16 (36%) were located out-of-field. Sixty-nine percent of patients who had out-of-field regional recurrence had ECE lesions. Therefore, we need to be careful when shrinking the regional radiation field especially in patients with ECE. In other words, it is appropriate to apply an entire neck irradiation field in high-risk patients. In addition, of the 28 in-field regional recurrences, 20 patients (71%) had ECE, which suggests that a higher dose may be necessary to control ECE lesions. Peters et al. reported that there was better LRC with doses of 63 Gy than at lower doses in a subset of patients with ECE (4). On the other hand, we observed 31 local recurrences with or without other site recurrences, of which local recurrences without other sites were 14. Of 31 local recurrences, 22 were located out-of-field. We believe that it is reasonable to include the primary tumor bed in the radiation field if patients have high-risk features such as ECE, even if they do not have close/positive surgical margins.

We evaluated the efficacy of our LF-PORT with the aim of reducing morbidity by minimizing the radiation field. LF-PORT is a promising strategy for patients who have intermediate risk features without close/positive surgical margins and/or ECE because of the comparative tumor control rate and low adverse effects. However, the present study used retrospective analysis in a single institution. Therefore, it is important to evaluate the efficacy of LF-PORT in an intermediate risk group in a prospective clinical study.

We need to adopt a whole neck irradiation field including the primary tumor bed in high-risk patients who have surgical close/positive margins and/or ECE. For such high-risk

Table 6. Results of the treatment outcome for HNSCC patients treated with surgery and PORT with or without chemotherapy

Author, year	Treatment	Risk category	No. of patients	Close/ positive margin (%)	ECE (%)	LRC or LRR (%)	PFS or DFS (%) (years)	OAS (%) (years)
Huang (1992) (10)	no RT		71	19	15	31 (5 years LRC)	NA	41 (3)
	RT		54			59 (5 years LRC)	NA	72 (3)
Ang (2001) (5)	RT	Low risk	31	14	75	90 (5 years LRC)	NA	83 (5)
		Intermediate	31			94 (5 years LRC)	NA	66 (5)
		High	151			68 (5 years LRC)	NA	42 (5)
Langendijk (2005) (18)	RT	Class I	234	35	51	92 (5 years LRC)	65 (5)	67 (5)
		Class II	336			78 (5 years LRC)	47 (5)	50 (5)
		Class III	231			58 (5 years LRC)	32 (5)	36 (5)
Bernier (2004) (6)	RT		167	26	53	31 (5 years LRR)	36 (5)	40 (5)
	CRT		167	31	61	18 (5 years LRR)	47 (5)	53 (5)
Cooper (2004) (7)	RT		210	19	81 (including multiple LN)	33 (3 years LRR)	36 (3)	47 (3)
	CRT		206	17	83 (including multiple LN)	22 (3 years LRR)	47 (3)	56 (3)
Present	RT/CRT	Intermediate	41	0	0	71.2 (5 years LRC)	62.8 (5)	58.8 (5)
		High	113	29	81	46 (5 years LRPFS)	29.5 (5)	39 (5)
		All	154	21	59	58.3 (5y LRPFS)	38.1 (5)	44.5 (5)

LRR, locoregional recurrence; PFS, progression-free survival; DFS, disease-free survival; CRT, chemoradiotherapy.

patients, depending on their risk factors, a higher dose or in some cases, chemotherapy may be needed.

Conflict of interest statement

None declared.

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