10. Fuwa N, Kano M, Toita T *et al.* Alternating chemoradiotherapy for nasopharyngeal cancer using cisplatin and 5-fluorouracil: a preliminary report of phase II study. *Radiother Oncol* 2001;**61**:257–60.
11. Ou SH, Zell JA, Ziogas A *et al.* Epidemiology of nasopharyngeal carcinoma in the United States: improved survival of Chinese patients within the keratinizing squamous cell carcinoma histology. *Ann Oncol* 2007;**18**:29–35.
12. Kawashima M, Fuwa N, Myojin M *et al.* A multi-institutional survey of the effectiveness of chemotherapy combined with radiotherapy for patients with nasopharyngeal carcinoma. *Jpn J Clin Oncol* 2004;**34**:569–83.
13. Lee N, Harris J, Garden AS *et al.* Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. *J Clin Oncol* 2009;**27**:3784–90.
14. Kodaira T, Tomita N, Tachibana H *et al.* Aichi Cancer Center initial experience of intensity modulated radiation therapy for nasopharyngeal cancer using helical tomotherapy. *Int J Radiat Oncol Biol Phys* 2009;**73**:1129–34.
15. Kwong DL, Sham JS, Leung LH *et al.* Preliminary results of radiation dose escalation for locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2006;**64**:374–81.
16. Lorch JH, Goloubeva O, Haddad RI *et al.* Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX324 randomised phase 3 trial. *Lancet Oncol* 2011;**12**:153–9.

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2013;43(5)476–482
doi:10.1093/jjco/hyt030
Advance Access Publication 10 March 2013

Phase II Study of Cetuximab Plus Concomitant Boost Radiotherapy in Japanese Patients with Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Susumu Okano[1,2], Takayuki Yoshino[1,*], Masato Fujii[3], Yusuke Onozawa[4], Takeshi Kodaira[5], Hirofumi Fujii[6], Tetsuo Akimoto[7], Satoshi Ishikura[8], Masahiko Oguchi[9], Sadamoto Zenda[7,10], Barbara de Blas[11] and Makoto Tahara[1]

[1]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, [2]Department of Otorhinolaryngology, Jikei University School of Medicine, Tokyo, [3]Department of Otolaryngology, National Tokyo Medical Center, Tokyo, [4]Division of Clinical Oncology, Shizuoka Cancer Center, Shizuoka, [5]Department of Radiation Oncology, Aichi Cancer Center Hospital, Aichi, [6]Department of Clinical Oncology, Jichi Medical University Hospital, Tochigi, [7]Department of Radiation Oncology and Particle Therapy, National Cancer Center Hospital East, Chiba, [8]Department of Radiology, Juntendo University, Tokyo, [9]Radiation Oncology Department, Cancer Institute Hospital, Tokyo, [10]Department of Head and Neck Surgery, Tokyo Medical and Dental University, Tokyo, Japan and [11]Merck KGaA, Darmstadt, Germany

*For reprints and all correspondence: T. Yoshino, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. E-mail: tyoshino@east.ncc.go.jp

Received November 6, 2012; accepted February 11, 2013

Background: We investigated the tolerability of cetuximab plus radiotherapy in Japanese patients with untreated locally advanced squamous cell carcinoma of the head and neck.
Methods: Patients with epidermal growth factor receptor-expressing locally advanced squamous cell carcinoma of the head and neck received cetuximab (400 mg/m^2 initial dose then 250 mg/m^2 weekly) for 7 weeks plus concomitant boost radiotherapy (weeks 2–7: once daily [1.8 Gy] for 3.6 weeks, then twice daily [1.8 Gy morning and 1.5 Gy afternoon] for 2.4 weeks). The primary endpoint was treatment completion rate (the rate of treated patients completing $\geq$70% of the planned cetuximab dose and the full dose of radiotherapy within 2 weeks over the planned schedule).
Results: Twenty-two patients were evaluable. The treatment completion rate was 100% (95% confidence interval 85–100). The response rate 8 weeks post-radiotherapy was 82% (95% confidence interval 60–95). The most common grade 3/4 treatment-emergent adverse events were mucosal inflammation (73%); dermatitis (27%); and infection, radiation skin injury and stomatitis (23% each).
Conclusions: Cetuximab plus concomitant boost radiotherapy can be safely administered to Japanese patients with locally advanced squamous cell carcinoma of the head and neck. Tolerability and efficacy were in line with those reported in the Phase III Bonner trial in a Western population of patients with locally advanced squamous cell carcinoma of the head and neck.

Key words: cetuximab – concomitant boost – Japanese – locally advanced – radiotherapy – squamous cell carcinoma of the head and neck

INTRODUCTION

Globally, cancers of the lip, oral cavity, pharynx (other than nasopharynx) and larynx account for over 4% of all malignancies, with more than 500 000 new cases worldwide and 300 000 attributed deaths reported in 2008 (1). In Japan alone, in 2007, 7879 people died of head and neck cancer, representing 2.3% of all cancer deaths that year (2).

Patients with locally advanced squamous cell carcinoma (SCC) of the head and neck (LASCCHN) have a number of treatment options available, depending on regulatory authority approvals. These options include concurrently administered chemoradiotherapy with or without surgery and the combination of the EGFR-targeting IgG1 monoclonal antibody cetuximab and radiotherapy (3,4). The use of cetuximab in combination with radiotherapy grew out of the finding that epidermal growth factor receptor (EGFR) is expressed by almost all SCCs of the head and neck (SCCHN) (5,6) and the observation from *in vivo* models that this combination enhanced tumor regression compared with radiation or cetuximab alone (7). Regulatory approval of the combination of cetuximab and radiotherapy in the USA and the EU was based on the results of the large Phase III trial conducted by Bonner et al. in centers in the USA and 14 other countries (8). This trial reported that the addition of cetuximab to once-daily, twice-daily or concomitant boost radiotherapy significantly improved overall survival, progression-free survival and locoregional control compared with radiotherapy alone in patients with LASCCHN. Survival benefits were maintained long term, with 5-year overall survival rates of 46% in the cetuximab plus radiotherapy arm and 36% in the radiotherapy alone arm (9).

It was notable that the addition of cetuximab to radiotherapy in the Bonner trial did not exacerbate the adverse events commonly associated with radiotherapy of the head and neck, including mucositis, xerostomia and dysphagia (8). Among grade ≥ 3 reactions, only acneiform rash and infusion reactions, both with a known association to cetuximab, occurred with a higher incidence in the cetuximab plus radiotherapy arm compared with the radiotherapy arm of the trial.

The Phase II study reported here was initiated to assess the tolerability and feasibility of administering cetuximab together with the concomitant boost radiotherapy regimen used in the Bonner trial to Japanese patients with newly diagnosed LASCCHN. The concomitant boost radiotherapy regimen was chosen because it was the most frequently used in the Bonner trial and the results from our trial would therefore be appropriate for comparison with those from the Bonner trial. Tumor response to treatment was also evaluated in this study.

PATIENTS AND METHODS

Patient Selection

The inclusion criteria used in this study closely followed those used in the Bonner trial to ensure that the patient, disease and treatment characteristics were similar in the two studies. Japanese patients with Stage III or IV (Union for International Cancer Control TNM classification) pathologically proven SCC of the oropharynx, hypopharynx or larynx confirmed by magnetic resonance imaging (MRI) and computed tomography (CT) and with tumor EGFR expression and an expected survival of at least 12 months were eligible for inclusion in the study. Tumor EGFR expression was determined at a single reference laboratory (SRL Medisearch, Inc., Tokyo, Japan) by immunohistochemistry on formalin-fixed or paraffin-embedded tumor tissue using the DAKO pharmDx kit (Glostrup, Denmark). The minimum criterion required to confirm EGFR expression was any intensity of membrane staining above-background level by at least one cell. Other main criteria were: at least bi-dimensionally measurable disease; age ≥ 20 years; Karnofsky performance status (KPS) ≥ 60; adequate bone marrow, kidney and liver function; no distant metastases; no prior chemotherapy within the last 3 years; no prior radiotherapy to the head and neck; and no prior treatment with cetuximab.

The study protocol was approved by institutional review boards and the trial was conducted in accordance with the protocol and with the ethical principles of the Declaration of Helsinki, as well as with the International Conference on Harmonization (ICH) Note for Guidance on Good Clinical Practice (GCP) (ICH Topic E6, 1996), the Japanese ministerial ordinance on GCP, the standard stipulated in Articles 14-3 and 80-2 of the Japanese Pharmaceutical Affairs Law, and applicable regulatory requirements. A quality assurance review of the data was conducted and an independent Radiation Therapy Quality Assurance Committee was set up to ensure compatibility of the type of radiotherapy used at each center with that defined in the protocol. All patients provided written informed consent and were also asked to provide informed consent for investigation of biomarkers other than EGFR in their tumor tissue.

Study Design and Treatment

This was an open-label, Phase II study conducted in patients with newly diagnosed LASCCHN across four centers in Japan. The primary endpoint of the study was tolerability, the main variable of which was treatment completion rate: the rate of patients who completed $\geq 70\%$ of the cetuximab planned dose administration (in terms of relative dose intensity [RDI] of cetuximab) and the full dose of radiotherapy within 2 weeks over the planned schedule of ≤ 8 weeks. The RDI of cetuximab of $\geq 70\%$ was estimated to be equivalent to no more than one missed dose of cetuximab, which, based on calculations on dose intensity data from the Bonner trial, was considered to be the minimum dose level required for cetuximab clinical activity. The selection of an RDI of $\geq 70\%$ as a component of the treatment completion rate was therefore considered to represent tolerability at clinically effective doses. A secondary efficacy endpoint was the best

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.

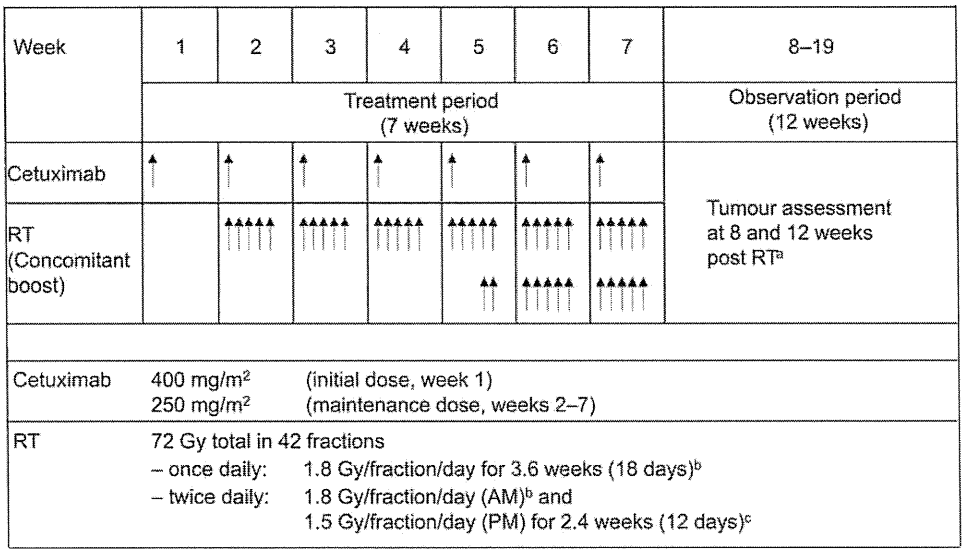

Figure 1. Schedule of irradiation treatment. [a]Imaging at week 12 (i.e. 4 weeks post-RT) was not to be performed for patients with progressive disease at week 8. [b]1.8 Gy/Fr (large field): The primary tumor, gross nodal area and uninvolved nodal area. [c]1.5 Gy/Fr (small field): The primary tumor and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

Acknowledgements

The authors acknowledge the valuable contributions of M. Tsukuda, Yokohama City University School of Medicine, Kanagawa, Japan, who is a coordinating investigator of the study, Y. Ariyoshi, Special Advisor (honorary director of Aichi Prefectural Cancer Center Aichi Hospital) Marumo Hospital, Chair of an Efficacy and Safety Evaluation Committee of the study and T. Seriu, Bristol-Myers Squibb, Japan, in reviewing the manuscript. The authors acknowledge the contribution of Jo Shrewsbury-Gee, Cancer Communications and Consultancy Ltd, Knutsford, Cheshire, who provided medical writing services on behalf of Merck KGaA.

Funding

This work was supported by Merck Serono Co, Ltd, Tokyo, Japan, an affiliate of Merck KGaA, Darmstadt, Germany.

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.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–917.
2. Japanese Society of Medical Oncology. *Clinical Oncology Update-Essentials for the Medical Oncologist.* 2nd edn. Tokyo, Japan: Nankodo 2009.
3. Budach V, Bernier J, Lefebvre J-L, et al. Trends in the treatment of locally advanced squamous cell carcinoma of the head and neck (LASCCHN) in Europe between 2006 and 2009. *Ann Oncol* 2010;21 (Suppl 8):viii321–2. Updated information presented at meeting.
4. Wong SJ, Harari PM, Garden AS, et al. Longitudinal Oncology Registry of Head and Neck Carcinoma (LORHAN): analysis of chemoradiation treatment approaches in the United States. *Cancer* 2011;117:1679–86.
5. Christensen ME, Therkildsen MH, Hansen BL, Albeck H, Hansen GN, Bretlau P. Epidermal growth factor receptor expression on oral mucosa dysplastic epithelia and squamous cell carcinomas. *Eur Arch Otorhinolaryngol* 1992;249:243–7.
6. Rubin Grandis J, Melhem MF, Barnes EL, Tweardy DJ. Quantitative immunohistochemical analysis of transforming growth factor-alpha and epidermal growth factor receptor in patients with squamous cell carcinoma of the head and neck. *Cancer* 1996;78:1284–92.
7. Huang SM, Harari PM. Modulation of radiation response after epidermal growth factor receptor blockade in squamous cell carcinomas: inhibition of damage repair, cell cycle kinetics, and tumor angiogenesis. *Clin Cancer Res* 2000;6:2166–74.
8. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;354:567–78.
9. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol* 2010;11:21–8.
10. Zenda S, Onozawa Y, Tahara M, et al. Feasibility study of single agent Cisplatin and concurrent radiotherapy in Japanese patients with squamous cell carcinoma of the head and neck: preliminary results. *Jpn J Clin Oncol* 2007;37:725–9.
11. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys* 2000;48:7–16.
12. Ghoshal S, Goda JS, Mallick I, Kehwar TS, Sharma SC. Concomitant boost radiotherapy compared with conventional radiotherapy in squamous cell carcinoma of the head and neck—a phase III trial from a single institution in India. *Clin Oncol (R Coll Radiol)* 2008;20:212–20.
13. Rathcke IO, Gottschlich S, Gorogh T, Lippert BM, Werner JA. [Incidence of point mutations in Ki-ras codon 12 and 13 in squamous epithelial carcinomas of the head-neck region]. *Laryngorhinootologie* 1996;75:465–70.
14. Weber A, Langhanki L, Sommerer F, Markwarth A, Wittekind C, Tannapfel A. Mutations of the BRAF gene in squamous cell carcinoma of the head and neck. *Oncogene* 2003;22:4757–9.
15. Sheikh Ali MA, Gunduz M, Nagatsuka H, et al. Expression and mutation analysis of epidermal growth factor receptor in head and neck squamous cell carcinoma. *Cancer Sci* 2008;99:1589–94.
16. Gregoire V, Lefebvre JL, Licitra L, Felip E. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21(Suppl 5):v184–6.
17. Pfister DG, Ang KK, Brizel DM, et al. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Head and neck cancers. *J Natl Compr Canc Netw* 2011;9:596–650.
18. Japan Society of Clinical Oncology. *Clinical Practice Guidelines*. http://jsco-cpg.jp/guideline/15_siryou.html (7 February 2012, date last accessed).
19. Levy AR, Johnston KM, Sambrook J, et al. Indirect comparison of the efficacy of cetuximab and cisplatin in squamous cell carcinoma of the head and neck. *Curr Med Res Opin* 2011;27:2253–9.

APPENDIX

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

Frank Beier, Global Biostatistics, Merck KGaA, Darmstadt, Germany.

Int J Clin Oncol (2014) 19:30–37
DOI 10.1007/s10147-013-0518-9

ORIGINAL ARTICLE

Neck dissection after chemoradiotherapy for oropharyngeal and hypopharyngeal cancer: the correlation between cervical lymph node metastasis and prognosis

Nobuhiro Hanai · Daisuke Kawakita · Taijiro Ozawa · Hitoshi Hirakawa · Takeshi Kodaira · Yasuhisa Hasegawa

Received: 9 October 2012 / Accepted: 3 January 2013 / Published online: 23 January 2013

Abstract
Background Recently, the role of chemoradiotherapy (CRT) for preserving organs in the treatment of head and neck cancer has been increasing. However, the indication for post-CRT neck dissection (ND) and its surgical extent is still controversial. The purpose of this study was to discuss the indications for post-CRT ND and the proper extent of the surgical procedure.
Methods We performed a retrospective analysis on N2–3 oropharyngeal and hypopharyngeal squamous cell carcinoma (OHSCC) patients treated with CRT in our institute from 1995 to 2008, and determined the prognostic impact of post-CRT ND and the distribution of cervical lymph node (CLN) metastasis based on the pathological results of ND.
Results The patients without pathological CLN metastases had good prognoses, whereas patients with pathological CLN metastases exhibited a significantly high recurrence rate ($P = 0.033$). Based on the pathological results of ND, performing selective ND at levels II–IV can contain 88 and 85 % of CLN metastasis of the oropharynx and hypopharynx, respectively. In all cases, when pathological CLN metastases were found at level V in ND following CRT, distant metastases developed.
Conclusions The presence of pathological CLN metastasis affects prognosis, but also a diffuse distribution of CLN metastasis worsens prognosis; that is, the presence of CLN metastasis at level V after CRT appears to be an indicator of distant metastasis. Post-CRT ND may not make sense as a salvage intervention for improving the prognosis in such situations. We concluded that the proper extent of post-CRT ND of OHSCC is selective ND including levels II–IV.

Keywords Chemoradiotherapy · Neck dissection · Squamous cell carcinoma · Cervical lymph node metastasis

N. Hanai · T. Ozawa · H. Hirakawa · Y. Hasegawa (✉)
Department of Head and Neck Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
e-mail: hasegawa@aichi-cc.jp

D. Kawakita
Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan

T. Kodaira
Department of Radiation Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan

Introduction

Recently, the role of chemoradiotherapy (CRT) in organ preservation treatment for advanced oropharyngeal and hypopharyngeal squamous cell carcinoma (OHSCC) has been increasing [1]. Cervical lymph node (CLN) metastasis is an important factor affecting the prognoses of head and neck cancer patients [2], and neck control greatly contributes to improving head and neck cancer treatment outcomes. Therefore, neck dissection (ND) is a principal treatment for CLN metastasis. However, one cannot overlook the problems associated with treatment complications occurring after CRT. For example, incomplete wound healing after ND following CRT may cause fatal complications [3], and the addition of ND after CRT can be a risk factor for dysphagia [4].

The concept of planned ND [5, 6], once recommended for all patients with N2–3 squamous cell carcinoma (SCC), after radiotherapy (RT) or CRT is no longer in favor [7], and cases should be carefully selected when determining the necessity of the procedure [8]. This is one of the

salvage operations used only for cases of persistent disease as judged by a post-treatment scan, so the procedure is no longer referred to as "planned" but as "early salvage" to distinguish it from "salvage" surgery to be performed for an evident recurrence or manifest residual disease.

In addition, reducing the surgical extent of ND should be considered in order to avoid complications [9, 10]. However, the indications for post-CRT ND and its extent remain controversial. Therefore, the therapeutic validity, indications and extent of ND must be clarified.

In the present study, we compared the addition of ND to the neck response observed after CRT using imaging examinations of OHSCC patients treated with CRT from 1995 to 2008 at Aichi Cancer Center and evaluated the prognoses of these patients. We also determined the presence and location of CLN metastasis in cases when ND was performed and examined the association between CLN metastasis and prognosis.

Materials and methods

We retrospectively evaluated the clinical outcomes of 102 OHSCC patients with N2–3 disease treated with CRT including induction chemotherapy (ICT) [11] between 1995 and 2008 at Aichi Cancer Center Hospital. We conducted this retrospective investigation among patients who had achieved a complete response (CR) in the primary lesion after receiving CRT with platinum-based agents. Regarding CLN metastasis, we reviewed the pathological results based on 42 patients who underwent ND after receiving CRT.

Chemo-selection [12–14]

In order to ensure organ preservation, we conducted two courses of ICT in the advanced OHSCC patients and applied concurrent CRT or RT in the responding patients (those showing >50 % response at the primary tumor).

Induction chemotherapy

All patients were treated with a platinum-based CRT regimen that included ICT and RT or concurrent CRT. The ICT regimen consisted of 24-h continuous infusion of 5-FU at 800 mg/m^2/day on days 1–5 and cisplatin at 80 mg/m^2/day on day 6. This was repeated every 3–4 weeks and two courses were administered.

Radiotherapy and chemoradiotherapy

Definitive RT was administered to all patients with a conventional fraction (2 Gy/fraction once a day and five times a week). Treatment with 60–70 Gy was delivered as a curative dose to primary lesions and metastasis-positive lymph nodes detected on imaging. At least 40–50 Gy were delivered as a prophylactic dose to the neck region. Concurrent chemoradiation (CCRT) therapy consisting of cisplatin at 25–30 mg/m^2/week was administered in 13 patients. This was repeated every week, and a total of one to six courses were administered.

Diagnostic imaging

To evaluate the clinical effects of CRT in the neck, we conducted imaging examinations with one of the following: CT, MRI or PET–CT. The criteria for a CR in the neck included the absence of any contrast effects and no CLN enlargement: the length of the CLN long axis should be <1.5 cm for levels I and II and <1 cm for other levels [15]. Imaging examinations with CT or MRI were performed approximately 4 weeks after the completion of CRT, while examinations with PET–CT were performed approximately 6–8 weeks after completion.

Neck dissection and disease status

We performed ND for early salvage intervention approximately 2–4 weeks after performing the imaging examinations. The indications for ND included the cases of persistent CLN disease that were suspected based on the findings of imaging examinations. If the CLN was judged to be a CR based on imaging examinations, we omitted ND. However, in the early subset of patients in this study, we performed ND even if there was a CR in the neck by imaging examination, based on a former policy of planned ND.

We examined the patients for the presence of metastasis according to the pathological diagnosis in those who underwent ND and followed the development of regional recurrence. In the patients who did not undergo ND, the course was observed, and if recurrence or progression were noted, salvage surgery was performed when possible. Survival and disease status were confirmed by checking the patient's medical records on the date of the last follow-up visit.

Statistical analysis

The duration of regional control and overall survival were defined as the interval between the beginning of treatment and the date of death, relapse or last follow-up. The associations between neck response (with or without ND) and regional control or overall survival were assessed using Kaplan–Meier survival curves. P values <0.05 were considered statistically significant according to the log-rank test. Comparisons between the hypopharynx and

oropharynx for the presence or absence of pathological metastasis were assessed using the chi-squared test, and P values <0.05 were considered statistically significant.

Results

Patient characteristics

In this study, 61 patients with oropharyngeal carcinoma and 41 patients with hypopharyngeal carcinoma with nodal stage N2–3 in whom a CR was achieved at the primary tumor received ICT followed by CRT/RT (Table 1). Fifty-six patients showed a CR in the neck on imaging examinations. Non-CR in the neck was observed in 46 cases. Ten patients who showed a CR in the neck after receiving CRT underwent ND followed by planned ND. We followed the remaining 46 cases of CR in the neck without ND, while 32 patients with non-CR in the neck underwent ND as an early salvage intervention. We followed the 14 other patients with non-CR in the neck who did not want ND, and we performed salvage surgery, if possible, when recurrence was noted. The follow-up period ranged from 6.9 to 89.6 months. The mean age of the patients was 62.3 years (range 36–78 years).

Table 1 Patient characteristics

	OPC ($n = 61$)	HPC ($n = 41$)
Age (years)		
Range	30–78	42–74
Median	60	62
Sex		
Male	55 (90 %)	39 (95 %)
Female	6 (10 %)	2 (5 %)
Primary tumor stage		
T1	4 (7 %)	6 (15 %)
T2	28 (46 %)	17 (41 %)
T3	17 (28 %)	12 (29 %)
T4	12 (20 %)	6 (15 %)
Clinical nodal stage		
cN2a	12 (20 %)	6 (15 %)
cN2b	22 (36 %)	20 (49 %)
cN2c	18 (30 %)	13 (32 %)
cN3	9 (15 %)	2 (5 %)
Nodal response		
CR	34 (56 %)	22 (54 %)
Observe	30	16
Neck dissection (planned ND)	4	6
PR	27 (44 %)	19 (46 %)
Neck dissection (early salvage ND)	20	12
Observe (reject)	7	7

ND neck dissection, *OPC* oropharyngeal carcinoma, *HPC* hypopharyngeal carcinoma, *CR* complete response, *PR* partial response

Prognostic impact of neck dissection after chemoradiotherapy

Figure 1 shows the regional control rate and Fig. 2 shows the overall survival rate. Even CR cases included regional recurrence, and all CR cases in the neck were salvaged successfully and the 5-year overall survival rate was 92.8 %. In cases of non-CR in the neck, the regional control rate was significantly better in the group that underwent ND ($P = 0.0358$).

During follow-up, 14 of 42 patients who underwent ND suffered a relapse: five involved locoregional recurrence (four of five cases were successfully salvaged) and nine involved recurrence with distant metastasis. The primary cause of a recurrence following post-CRT ND was distant metastasis.

Neck dissection and pathological results

A summary of cases in which ND was performed is shown in Table 2 according to the type of ND. We examined the

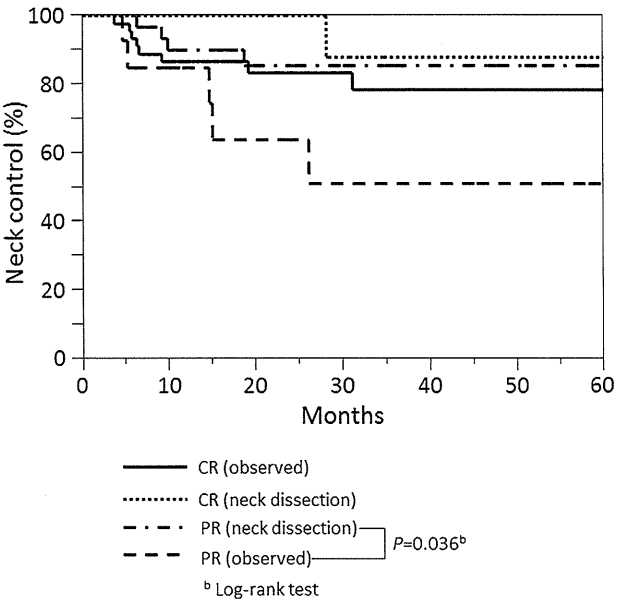

Fig. 1 Regional control rate. Kaplan–Meier survival curves for the associations between neck response (with or without ND) and regional control. In cases of CR of the neck, the 5-year regional control rate was 87.5 % for the ND group, and 78.2 % for the observed group, respectively. In cases of non-CR of the neck, the 5-year regional control rate was 85.8 % for the ND group, and 51.1 % for the observed group, respectively ($P = 0.036$)

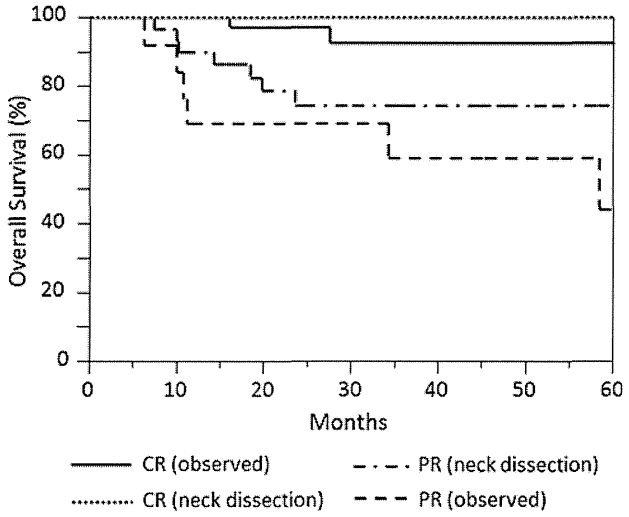

Fig. 2 Overall survival. Kaplan–Meier survival curves for the associations between neck response (with or without ND) and overall survival. In cases of CR of the neck, the 5-year overall survival was 100 % for the ND group, and 92.8 % for the observed group, respectively. In cases of non-CR of the neck, the 5-year overall survival was 74.6 % for the ND group, and 44.5 % for the observed group, respectively

Table 2 Type of neck dissection

	Total	OPC	HPC
Neck dissections: cases	42	24	18
Hemi neck dissection: sides	48	29	19
Comprehensive ND	25	21	4
Selective ND	23	8	15
II, III, IV	10	6	4
II, III, IV, V	11	–	11
I, II, III	1	1	–
I, II, III, IV	1	1	–

ND neck dissection, *OPC* oropharyngeal carcinoma, *HPC* hypopharyngeal carcinoma

results of pathological metastasis in ND cases. The presence or absence of pathological metastases as a result of ND is shown in Table 3. We also compared the hypopharynx and oropharynx for the presence or absence of pathological metastasis. There were no significant differences in the ratios of pathological metastasis depending on the primary site.

We analyzed the impact of the presence or absence of pathological metastasis on prognosis in cases of ND (Fig. 3). Patients without pathological CLN metastases had a significantly better recurrence-free survival than those with pathological CLN metastasis.

Table 3 Pathological findings after neck dissection

	pN(+)	pN(−)	*P* value
Neck response			0.28[a]
CR	3 (30.0 %)	7 (70.0 %)	
PR	18 (56.3 %)	14 (43.8 %)	
Primary site			0.76[a]
Oropharynx	11 (45.8 %)	13 (54.2 %)	
Hypopharynx	10 (55.6 %)	8 (44.4 %)	

CR complete response, *PR* partial response

[a] Chi square test

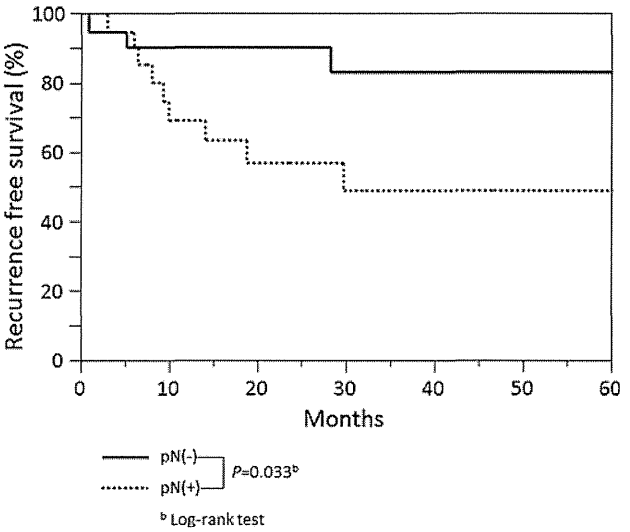

Fig. 3 Recurrence-free survival. Recurrence-free survival for patients who underwent ND depends on the pathological cervical lymph node (CLN) metastasis. The 5-year recurrence-free survival was 83.5 % for patients without pathological CLN metastases, and 49.3 % for patients with pathological CLN metastases, respectively ($P = 0.033$)

Distribution of cervical lymph node metastasis

The distribution of CLN metastasis in the oropharyngeal and hypopharyngeal cases is shown in Figs. 4 and 5, respectively. The percentage indicates the positive rate of pathological CLN metastasis in the dissection area (level or sublevel). The denominator indicates the number of the (sub)level at which the dissection was performed, and the numerator indicates the present (sub)level number of pathological metastases. No recurrence of ipsilateral CLN was found in these cases. Even when ND was selective, no cases of recurrence at the preserved ipsilateral neck level were observed in this study. CLN recurrence occurred in four cases: three cases involved CLN metastasis on the contralateral side, and the other case involved metastasis to the ipsilateral retropharyngeal node.

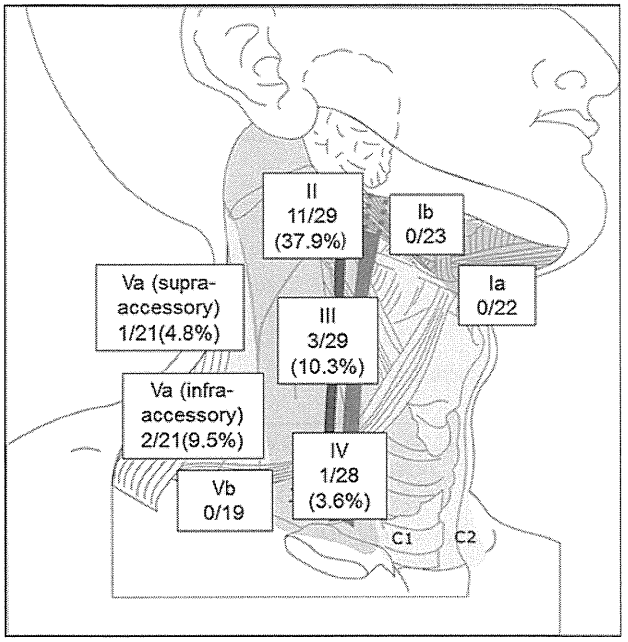

Fig. 4 Distribution of lymph node metastasis: oropharynx

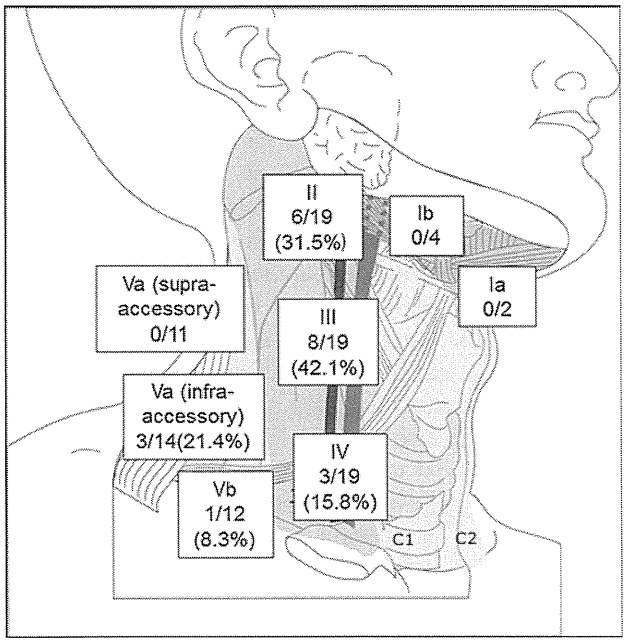

Fig. 5 Distribution of lymph node metastasis: hypopharynx

The location of CLN metastasis-positive levels is shown in Table 4. Histologically proven distribution to level V metastasis was detected in 12 % of oropharyngeal cases and 15 % of hypopharyngeal cases. Hence, performing selective ND at levels II–IV can contain 88 % of CLN metastases in oropharyngeal cases and 85 % of CLN metastases in hypopharyngeal cases.

Table 4 Location of positive levels

	Oropharynx	Hypopharynx
Level I	0	0
Level II	11 (65 %)	6 (30 %)
Level III	3 (18 %)	8 (40 %)
Level IV	1 (6 %)	3 (15 %)
Level V	2 (12 %)	3 (15 %)
SND (level II–IV)	15/17 (88 %)	17/20 (85 %)

SND selective neck dissection

Table 5 shows a list of cases with histologically proven CLN metastasis at level V. Although few in number, all of these cases involved distant metastasis.

Complications

Eight patients (19.0 %) experienced postoperative complications from ND: four cases of laryngeal edema, two cases of lymph fluid leakage, one case of lingual nerve paralysis and dysphagia and one case of wound infection. Three of the four patients with laryngeal edema underwent tracheostomy. Six of the eight complications were caused by comprehensive ND (24.0 %). Among patients who underwent selective neck dissection, two complications (laryngeal edema and wound infection) were seen (8.6 %).

Discussion

In the treatment of OHSCC, the use of CRT for the purpose of organ preservation has been increasing, especially in recent years. Therefore, ND may not be performed as first-line therapy, but rather as second-line therapy for CRT as part of combined modality therapy. The current way of thinking is to determine the need for ND after CRT based on imaging examinations [16, 17]. In this study, there were no significant differences in the regional control rates in cases judged to show a CR on imaging examinations. However, even when judged to show a CR on imaging examinations, CLN recurrence was found in a few cases, and performing salvage was possible in each case. In other words, even if planned ND was not performed in CR cases, the same treatment outcomes were obtained by performing salvage when recurrence or progression was noted. There is the problem, however, of difficulty in performing late salvage. In cases without a CR in the neck, performing early salvage intervention should be considered necessary.

It was also shown in this study that prognoses were poor in cases of pathological CLN metastasis. Earlier studies [18, 19] have previously shown similar results. We retrospectively examined the distribution of CLN metastasis in

Table 5 Summary of the cases with level V metastasis

Primary site	Clinical stage	Pre-operative findings	Modality	Type of ND	Pathology	Recurrence site	Disease-free interval (months)	Prognosis
Oropharynx	T2N3 (bilateral)	lt III(+)	PET–CT	bl CND (I–V)	rt V:1; lt II:1, V:2	Lung	14	NED (surgery)
Hypopharynx	T1N2b	lt III(+)	PET–CT	SND (II–V)	II:5, III:4, IV:1, V:1	Local, RPN, contra-neck, mediastinal LN, lung	10	DOD
Hypopharynx	T2N2b	CR	CT	SND (II–V)	III:1, V:1	Axillary LN	6	NED (CTx, RTx)
Hypopharynx	T4aN2b	PR	CT	SND (II–V)	II:3, III:3, IV:3, V:6	Trachea, mediastinal LN	11	AWD

lt left, *bl* bilateral, *rt* right, *CR* complete response, *PR* partial response, *CND* comprehensive neck dissection, *SND* selective neck dissection, *RPN* retropharyngeal node, *LN* lymph node, *AWD* alive with disease, *NED* no evidence of disease, *DOD* died of disease

dissected cases to clarify the appropriate surgical extent of ND. We found that the majority of CLNs can be contained by performing selective ND assuming levels II–IV as a basis [20, 21] after CRT. However, even though recommendations regarding the surgical extent of ND are the same for oropharyngeal and hypopharyngeal cancer, differences were found in the distribution and extent of metastasis between the oropharynx and hypopharynx; therefore, they cannot be discussed equally. Hypopharyngeal cancer often shows more extensive metastasis than oropharyngeal cancer. Careful examination is needed; however, performing super-selective ND [22, 23] might be possible in cases of oropharyngeal cancer. Super-selective ND is a new concept, not yet generally accepted, and is a more targeted neck dissection that involves removing the single neck level and its adjacent level in cases with clinical evidence of persistent nodal disease confined to a single neck level [24]. In this study, the distribution of persistent nodal disease of oropharyngeal cases was relatively confined, with almost all of the CLN metastases located in levels II and III. Therefore, super-selective ND removing level II and III for oropharyngeal cases might be effective.

We also found it necessary to take into account not only the CLN metastasis situation, but also the prognosis, in determining the indications for post-CRT ND and the appropriate surgical extent of ND.

When recurrence appears as a distant metastasis over a short period, the ND procedure itself is often considered to be ineffective for survival prognosis. Although we were able to contain the majority of CLN metastases by performing level II–IV selective ND in this study, metastasis to level V is not insignificant enough to be considered negligible. However, distant metastases occurred in all cases with pathological CLN metastasis at level V found during ND following CRT. This shows that, in disseminated lesions with metastatic persistence to level V, the likelihood that distant metastasis has already occurred is very high. In other words, the presence of CLN metastasis at level V after CRT appears to be an indicator of distant metastasis.

In this study, metastases to level V were found pathologically during and/or after post-CRT ND. Residual CLNs were not actually suspected at level V on imaging examinations performed just before ND. Prior to administering treatment in these cases, multiple CLN metastases were detected along the jugular chain: metastasis to the posterior neck developed in two cases; however, only equivocally sized LNs were detected at level V on imaging examinations in the other two cases. In one case, comprehensive ND had been planned beforehand and the presence of metastasis was proven after performing a histopathological examination; however, this was at a time when we had not yet performed selective ND. In the other cases, we extended the range of ND to level V based on intraoperative clinical findings. We should assume the existence of concomitant distant metastasis and consider subsequent treatment when metastasis is found in level V. In addition, if metastasis is detected in level V before performing ND, one must reconsider whether ND is indicated.

Additionally, the postoperative complication rate is obviously lower in selective ND cases than in comprehensive ND cases. Therefore, in this study, we consider the proper extent of post-CRT ND of OHSCC to include selective ND of levels II–IV.

This study had limitations, including its retrospective design and the conditions of CLN metastasis. Since ND is performed at a relatively early stage after the administration of CRT, there is a question as to the viability of persistent CLN metastasis on specimens [25]. It is unknown whether these cancers remain merely on the basis of observation. If the timing of ND is delayed a little, the proportion of metastases present may change. Imaging examinations were also performed in this study at earlier times than the current consensus [26, 27]. The diagnostic accuracy rate of PET–CT

improves 10 or 12 weeks after the completion of CRT [28, 29]. The usefulness of PET–CT will be improved by appropriately adjusting its timing. In this study, PET–CT was performed approximately 6–8 weeks after the completion of CRT. The rationale for early PET was based on the former policy of planned ND. Due the retrospective nature of the present study, we used to determine that the optimal timing for operative intervention before the occurrence of extensive fibrosis and scarring was approximately 6–8 weeks after the completion of CRT. This is one of the methodological limitations of this study. However, PET–CT has a high negative predictive value even if it is employed earlier [30]. Therefore, we did not perform ND in the cases that we could judge to be a CR by PET–CT, but did perform ND when the results were inconclusive. In cases judged to show a CR on imaging examinations, pathological CLN metastasis was found in 30 % of cases (false negative). When we performed ND in CR cases that conformed to planned ND, the residual rate of CLN metastasis was similar to the results of earlier studies of planned ND [31]. With regard to the pathologically negative CLN in the nodal PR cases (false positive), the early timing of imaging examinations influenced the results. In this study, the viable tumor rate in the nodal PR cases was 56.3 %. Similarly, the published literature suggests that the viable tumor rate is about 50 % in residual nodes [32].

It should also be noted that this study did not investigate the status of human papilloma virus (HPV). Because responses to CRT are different in HPV-positive cases, it is necessary to take this issue into account in the future. In recent cases, we assessed HPV status in oropharyngeal cases using multiplex PCR with sets of HPV genotype-specific primers. We also confirmed that HPV-positive oropharyngeal cancer patients showed good responses to CRT and that their clinical courses were superior to those of HPV-negative oropharyngeal patients.

In conclusion, this investigation of ND performed after CRT revealed not only that the presence of pathological CLN metastasis affects prognosis, but also that a diffuse distribution of CLN metastasis including level V after CRT worsens prognosis. Based on the results of this study, we showed that the proper extent of post-CRT ND of OHSCC is selective ND including levels II–IV. Because the presence of CLN metastasis at level V after CRT appears to be an indicator of distant metastasis, ND is not a realistic salvage treatment in such situations. New treatment strategies are needed in cases of precursors of distant metastasis.

Acknowledgments This work was supported by a Health and Labour Sciences Research Grant for Clinical Cancer Research (H20-Gannrinshou-Ippan-014) from the Ministry of Health, Labour and Welfare, Japan.

Conflict of interest No author has any conflict of interest.

References

1. Vokes EE, Kies MS, Haraf DJ et al (2000) Concomitant chemoradiotherapy as primary therapy for locoregionally advanced head and neck cancer. J Clin Oncol 18:1652–1661
2. Kutler DI, Patel SG, Shah JP (2004) The role of neck dissection following definitive chemoradiation. Oncology (Williston Park) 18:993–998
3. Maran AG, Amin M, Wilson JA (1989) Radical neck dissection: a 19-year experience. J Laryngol Otol 103:760–764
4. Machtay M, Moughan J, Trotti A et al (2008) Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol 26:3582–3589
5. Mendenhall WM, Million RR, Cassisi NJ (1986) Squamous cell carcinoma of the head and neck treated with radiation therapy: the role of neck dissection for clinically positive neck nodes. Int J Radiat Oncol Biol Phys 12:733–740
6. Mendenhall WM, Parsons JT, Amdur RJ et al (1988) Squamous cell carcinoma of the head and neck treated with radiotherapy: does planned neck dissection reduce the change for successful surgical management of subsequent local recurrence? Head Neck Surg 10:302–304
7. Ferlito A, Corry J, Silver CE et al (2010) Planned neck dissection for patients with complete response to chemoradiotherapy: a concept approaching obsolescence. Head Neck 32:253–261
8. Corry J, Peters L, Fisher R et al (2008) N2–N3 neck nodal control without planned neck dissection for clinical/radiologic complete responders—results of Trans Tasman Radiation Oncology Group Study 98.02. Head Neck 30:737–742
9. Nouraei SA, Upile T, Al-Yaghchi C et al (2008) Role of planned postchemoradiotherapy selective neck dissection in the multimodality management of head and neck cancer. Laryngoscope 118:797–803
10. Stenson KM, Huo D, Blair E et al (2006) Planned post chemoradiation neck dissection: significance of radiation dose. Laryngoscope 116:33–36
11. The Department of Veterans Affairs Laryngeal Cancer Study Group (1991) Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer: the Department of Veterans Affairs Laryngeal Cancer Study Group. N Engl J Med 324:1685–1690
12. Urba S, Wolf G, Eisbruch A et al (2006) Single-cycle induction chemotherapy selects patients with advanced laryngeal cancer for combined chemoradiation: a new treatment paradigm. J Clin Oncol 24:593–598
13. Worden FP, Wolf GT, Eisbruch A et al (2006) Chemo-selection of patients for organ preservation in advanced laryngeal cancer: failure of chemotherapy as the sole treatment for complete histologic responders to neoadjuvant chemotherapy. J Clin Oncol 24(suppl):18S (abstract 5560)
14. Worden FP, Moyer J, Lee JS et al (2009) Chemoselection as a strategy for organ preservation in patients with T4 laryngeal squamous cell carcinoma with cartilage invasion. Laryngoscope 119:1510–1517
15. Som PM (1992) Detection of metastasis in cervical lymph nodes: CT and MR criteria and differential diagnosis. Am J Roentgenol 158:961–969
16. Corry J, Peters L, Fisher R et al (2008) N2–N3 neck nodal control without planned neck dissection for clinical/radiologic complete responders—results of Trans Tasman Radiation Oncology Group Study 98.02. Head Neck 30:737–742

17. Lavertu P, Adelstein DJ, Saxton JP et al (1997) Management of the neck in a randomized trial comparing concurrent chemotherapy and radiotherapy with radiotherapy alone in resectable stage III and IV squamous cell head and neck cancer. Head Neck 19:559–566
18. Ahlberg A, Lagerlund M, Lewin F et al (2008) Clinical outcome following radiotherapy and planned neck dissection in N+ head and neck cancer patients. Acta Otolaryngol 128:1354–1360
19. Ganly I, Bocker J, Carlson DL et al (2011) Viable tumor in postchemoradiation neck dissection specimens as an indicator of poor outcome. Head Neck 33:1387–1393
20. Boyd TS, Harari PM, Tannehill SP et al (1998) Planned postradiotherapy neck dissection in patients with advanced head and neck cancer. Head Neck 20:132–137
21. Doweck I, Robbins KT, Mendenhall WM et al (2003) Neck level-specific nodal metastases in oropharyngeal cancer: is there a role for selective neck dissection after definitive radiation therapy? Head Neck 25:960–967
22. Robbins KT, Shannon K, Vieira F et al (2007) Superselective neck dissection after chemoradiation: feasibility based on clinical and pathologic comparisons. Arch Otolaryngol Head Neck Surg 133:486–489
23. Sandau A, Rao N, Giri S et al (2009) Role and extent of neck dissection for persistent nodal disease following chemo-radiotherapy for locally advanced head and neck cancer: how much is enough? Acta Oncol 47:948–953
24. Robbins KT, Dhiwakar M, Vieira F et al (2012) Efficacy of super-selective neck dissection following chemoradiation for advanced head and neck cancer. Oral Oncol 48:1185–1189
25. Strasser MD, Gleich LL, Miller MA et al (1999) Management implications of evaluating the N2 and N3 neck after organ preservation therapy. Laryngoscope 109:1776–1780
26. NCCN® Practice guidelines in oncology, v.2.2010: head and neck cancers. Principles of surgery (post chemoradiation or RT neck evaluation). http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
27. Wee JT, Anderson BO, Corry J et al (2009) Management of the neck after chemoradiotherapy for head and neck cancers in Asia: consensus statement from the Asian Oncology Summit 2009. Lancet Oncol 10:1086–1092
28. Isles MG, McConkey C, Mehanna HM (2008) A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy. Clin Otolaryngol 33:210–222
29. Ong SC, Schöder H, Lee NY et al (2008) Clinical utility of 18F-FDG PET/CT in assessing the neck after concurrent chemoradiotherapy for locoregional advanced head and neck cancer. J Nucl Med 49:532–540
30. Malone JP, Gerberi MA, Vasireddy S et al (2009) Early prediction of response to chemoradiotherapy for head and neck cancer: reliability of restaging with combined positron emission tomography and computed tomography. Arch Otolaryngol Head Neck Surg 135:1119–1125
31. Ganly I, Bocker J, Carlson DL et al (2011) Viable tumor in postchemoradiation neck dissection specimens as an indicator of poor outcome. Head Neck 33:1387–1393
32. Clayman GL, Johnson CJ 2nd, Morrison W et al (2001) The role of neck dissection after chemoradiotherapy for oropharyngeal cancer with advanced nodal disease. Arch Otolaryngol Head Neck Surg 127:135–139

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2013;43(7)719–725
doi:10.1093/jjco/hyt066
Advance Access Publication 9 May 2013

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

Yoko Goto[1,2], Takeshi Kodaira[1,*], Kazuhisa Furutani[1], Hiroyuki Tachibana[1], Natsuo Tomita[1], Junji Ito[1], Nobuhiro Hanai[3], Taijiro Ozawa[3], Hitoshi Hirakawa[3], Hidenori Suzuki[3] and Yasuhisa Hasegawa[3]

[1]Department of Radiation Oncology, Aichi Cancer Center Hospital, Aichi, Japan, [2]Department of Radiation Oncology and Image-applied Therapy, Kyoto University Graduate School of Medicine, Kyoto and [3]Department of Head and Neck surgery, Aichi Cancer Center Hospital, Aichi, Japan

*For reprints and all correspondence: Takeshi Kodaira, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan. E-mail: 109103@aichi-cc.jp

Received February 4, 2013; accepted April 8, 2013

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.

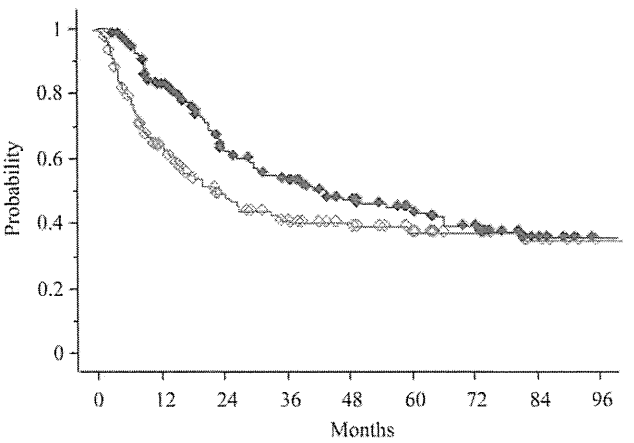

Figure 1. Overall survival (OAS) and progression-free survival (PFS) curves.

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