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Clinical Trial Note

Randomized Phase II/III Trial of Post-operative Chemoradiotherapy Comparing 3-Weekly Cisplatin with Weekly Cisplatin in High-risk Patients with Squamous Cell Carcinoma of Head and Neck: Japan Clinical Oncology Group Study (JCOG1008)

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A randomized Phase II/III study was launched in Japan to evaluate the non-inferiority of concurrent chemoradiotherapy with weekly cisplatin (40 mg/m^2) compared with concurrent chemoradiotherapy with 3-weekly cisplatin (100 mg/m^2) for post-operative high-risk patients with locally advanced squamous cell carcinoma of head and neck. This study began in October 2012, and a total of 260 patients will be accrued from 18 institutions within 5 years. The primary endpoint of the Phase II part is proportion of treatment completion and that of the Phase III part is overall survival. The secondary endpoints are relapse-free survival, local relapse-free survival, nutrition-support-free survival, non-hospitalized treatment period during permissible treatment period and adverse events. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000009125 [http://www.umin.ac.jp/ctr/].

Key words: head and neck cancer – post-operative chemoradiotherapy – high-risk patients – clinical trials – Phase II/III

INTRODUCTION

Head and neck cancer is relatively rare but increasing steadily in Japan. Squamous cell carcinoma is the most common histological type and comprises ~90% of head and neck cancer.

The prognosis of post-operative Stage III/IV locally advanced squamous cell carcinoma of head and neck (SCCHN) is still poor. Integrated analysis of RTOG95-01 (1) (Radiation Therapy Oncology Group) and EORTC22931 (2) (European Organisation for Research and Treatment of Cancer) demonstrated that microscopically positive resection margin and extracapsular nodal extension are high-risk factors for recurrence in post-operative locally advanced SCCHN. Moreover, these two trials revealed that the standard therapy for post-operative locally advanced SCCHN with high-risk factors for recurrence is surgery followed by chemoradiotherapy (CRT) with 3-weekly cisplatin (CDDP) at 100 mg/m^2 (3-weekly CDDP + RT); this adjuvant 3-weekly CDDP + RT showed 5-year survival of ~50% (1–4).

Meanwhile, concurrent CRT with weekly CDDP at 40 mg/m^2 (weekly CDDP + RT) is a promising regimen for post-operative locally advanced SCCHN with high-risk factors for recurrence. CDDP is expected to have a radiosensitizing effect when it is administered every week during radiation therapy and the dose intensity of weekly CDDP (40 mg/m^2/week) is higher than that of 3-weekly CDDP (33 mg/m^2/week). In fact, promising results of post-operative weekly CDDP + RT were reported in two prospective trials (5,6). In addition, weekly CDDP + RT has several advantages over 3-weekly CDDP + RT in terms of safety and toxicity. First, hematological toxicity tends to be milder in weekly CDDP + RT than in 3-weekly CDDP + RT. In particular, most published reports described that the incidence of Grade 3/4 neutropenia was ~30% in 3-weekly CDDP + RT compared with ~10–15% in weekly CDDP + RT (1,7–14). Second, auditory disorders are a problem associated with 3-weekly CDDP + RT, and weekly CDDP + RT is superior to the former due to the lower likelihood of neurotoxicity. In particular, CDDP-related auditory disorder is a dose-limiting toxicity; it occurs dose-dependently and is irreversible in most cases (15–18). In fact, in the RTOG95-01 study, the incidence of neurotoxicity including Grade 3 or more auditory disorders was 10% after 3-weekly CDDP + RT for head and neck cancer (1). In addition, in a feasibility study led by the National Cancer Center Hospital East, Grade 2 or more auditory disorder was observed in 8% of patients (7). On the other hand, there have been no reports on Grade 3 or more auditory disorders with weekly CDDP + RT. Hokkaido University and National Cancer Center Hospital East also reported that the incidence of Grade 2 or more auditory disorders was 0% in a retrospective study of weekly CDDP + RT in Japanese (8). Third, renal disorders rarely occur with weekly CDDP + RT, which is a major additional merit. In a retrospective overseas study reported by Uygun et al. (14), the incidence of Grade 3/4 renal disorder was lower with weekly CDDP + RT than with 3-weekly CDDP + RT. CDDP-related renal disorder is also dose-dependent and weekly CDDP + RT is superior in this regard. In fact, a Japanese study reported that, although no difference was observed in the incidence of Grade 3/4, the incidence of Grade 2 or more, for which dose reduction or discontinuation of CDDP must be considered, was 30–32% in 3-weekly CDDP + RT compared with 2–15% in weekly CDDP + RT, showing a significantly lower incidence with the latter (7–9). Finally, these potential merits of safety and toxicity for weekly CDDP + RT may lead to a shorter hospitalization period than for 3-weekly CDDP + RT. Therefore, we planned to test the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT.

In this randomized controlled study, we set 3-weekly CDDP + RT as the standard treatment arm and weekly CDDP + RT as the experimental treatment arm. For safety and feasibility data in Japanese post-operative high-risk patients with locally advanced SCCHN, only one feasibility study ($N = 25$) led by the National Cancer Center Hospital East is available for 3-weekly CDDP + RT. In addition, for weekly CDDP + RT, few safety and feasibility data have been accumulated in Japan, Europe and the USA Considering the above circumstances together, we evaluate the feasibility and safety of both treatment arms in the Phase II part at first and then proceed to the Phase III part to test the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT as a standard treatment.

The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in August 2012 and the study was activated in October 2012. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000009125 [http://www.umin.ac.jp/ctr/index.htm].

PROTOCOL DIGEST OF THE JCOG 1008

Purpose

The aim of this study is to evaluate the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT for post-operative high-risk patients with locally advanced SCCHN.

Study Setting

A multi-institutional randomized Phase II/III study.

Resources

This study is supported by National Cancer Center Research and Development Funds (23-A-16 and 23-A-21).

Endpoints

The primary endpoint of the Phase II part is the proportion of treatment completion in all eligible patients. The definition of complete treatment is as follows: 3-weekly CDDP + RT arm, completion of radiation therapy within 66 days and administration of two out of three courses of 3-weekly CDDP during the radiation treatment period or within 14 days from the last day of completion of radiation; weekly CDDP + RT arm, completion of radiation therapy within 66 days and administration of five out of seven courses of weekly CDDP during the radiation treatment period.

The primary endpoint of the Phase III part is overall survival, which is defined as days from randomization to death from any cause and censored at the latest day without an event. The secondary endpoints are relapse-free survival, local relapse-free survival, nutrition-support-free survival, non-hospitalized treatment period during the permissible treatment period and adverse events. Relapse-free survival is defined as days from randomization to any disease relapse or death from any cause and censored at the latest date when the patient is alive. Local relapse-free survival is defined as days from randomization to local and regional disease relapse or death from any cause and censored at the latest date when the patient is

evaluated as event-free. Nutrition-support-free survival denotes the percentage of surviving patients not requiring any nutrition support at the time of treatment start and then 2, 6, 12, 24, 36, 48 and 60 months after registration. The non-hospitalized treatment period during the permissible treatment period is defined as the difference between the duration of actual hospital stays and the permissible treatment period (66 days).

Eligibility Criteria

Inclusion Criteria

For inclusion in the study, the patient must fulfill all of the following criteria:

(1) Histologically proven squamous cell carcinoma in resected specimen.
(2) Primary lesion located in the oral cavity, oropharynx, hypopharynx or larynx.
(3) Pathological Stages III, IVA or IVB (UICC seventh edition).
(4) High risk of locoregional recurrence, defined as fulfilling (i) and/or (ii):
  (i) microscopically positive resection margin;
  (ii) extracapsular nodal extension.
(5) Within 56 days of surgery.
(6) No distant metastasis in head and neck contrast CT or MRI, chest contrast CT or upper abdominal contrast CT within 28 days before registration.
(7) Aged 20–75 years old.
(8) ECOG performance status of 0 or 1.
(9) No prior radiation therapy, chemotherapy or hormonal therapy for target or non-target cancers.
(10) Adequate organ function.
(11) Normal electrocardiogram.
(12) Written informed consent.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria:

(1) Active multiple primary cancers; synchronous or metachronous (within 5 years) double cancers except carcinoma *in situ* or intramucosal tumor.
(2) Infection requiring systemic treatment.
(3) Fever exceeding 38°C at registration.
(4) Women who are or may be pregnant, or who are nursing.
(5) Psychosis or psychiatric symptoms/signs that are judged to make participation in the study difficult.
(6) Long-term use of systemic steroidal treatment (oral/intravenous).
(7) Uncontrolled diabetes mellitus.
(8) Complication with unstable angina, or history of myocardial infarction within the last 6 months.
(9) Uncontrolled hypertension.

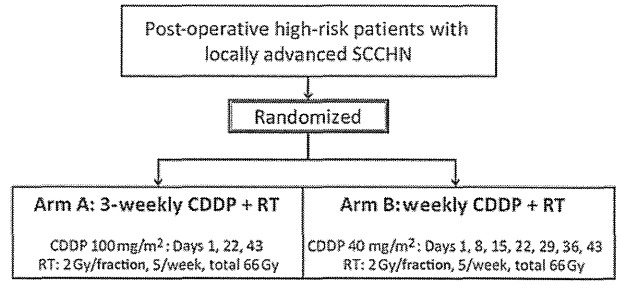

Figure 1. Schema of the study.

(10) Pleural effusion, pericardial effusion or ascites that requires drainage.
(11) Hepatitis B antigen-positive.
(12) Judged to have difficulty in abstaining from smoking or alcohol during the protocol treatment.

Treatment Methods

The protocol treatment consists of 3-weekly CDDP + RT and weekly CDDP + RT (Fig. 1).

Chemotherapy

Patients in the 3-weekly CDDP + RT arm receive concurrent CRT with CDDP at 100 mg/m^2. CDDP is administered on Days 1, 22 and 43, repeated every 3 weeks for three cycles. Patients in the weekly CDDP + RT arm receive concurrent CRT with CDDP at 40 mg/m^2. CDDP is administered on Days 1, 8, 15, 22, 29, 36 and 43, repeated every week for seven cycles.

Radiation Therapy

Radiation therapy is administered with high-energy photons of 4–10 MV X-rays to a total dose of 66 Gy in 33 fractions over 6.5 weeks. The gross tumor volume is not defined in this trial because macroscopic sites of the disease were resected before registration. The clinical target volume (CTV) initial includes locally resected lesion and potential lymph node metastasis area, and CTV boost is defined as a high-risk area with a positive node with extracapsular extension and/or a positive surgical margin with a 1–1.5 cm margin. The planning target volumes (PTV) for CTV initial and CTV boost (PTV initial and PTV boost) are defined as 0.5–1 cm margins around CTV initial and CTV boost to compensate for setup variations and internal organ motion. A total of 46 Gy is delivered to PTV initial, and then an additional 20 Gy is provided to PTV boost.

Follow-up

All enrolled patients are followed up for at least 5 years. The efficacy and the safety are to be evaluated at least every 3 months during the first year, at least every 4 months during

the second year, every 6 months during the third year, and every 12 months during the fourth and fifth years. Data on the use and methods of nutrition support are reported at 2, 6, 12 and then every 12 months until 60 months after registration.

Study Design and Statistical Analysis

This trial is designed to evaluate the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT for post-operative high-risk patients with locally advanced SCCHN. The planned accrual period is 5 years, and the follow-up period is 5 years after completion of accrual.

In the Phase II part, the planned sample size is 66 patients, which was calculated based on an expected proportion of complete treatment of 80% and a threshold of 50%, with a one-sided alpha of 0.025 and a beta of 0.1.

In the Phase III part, the primary analysis is carried out at 5 years after accrual completion. The hazard ratio between the treatment arms and its confidence interval, estimated by the Cox proportional hazard model stratified by the high-risk factors for recurrence (microscopically positive resection margin and extracapsular nodal extension), is used to test the non-inferiority of the weekly CDDP + RT arm in terms of overall survival. The significance level is set at 0.05 in a one-sided test because of the non-inferiority design of the study. One hundred and sixty-one events would be required to demonstrate, with a statistical power of 75%, that the weekly CDDP + RT arm is not inferior to the 3-weekly CDDP arm in terms of overall survival, with a non-inferiority margin of 10% at 5-year overall survival. Non-inferiority will be concluded if the upper limit of the confidence interval of the hazard ratio does not exceed the limit of 1.32, which is in accord with the non-inferiority margin. According to Schoenfeld and Richter's method (19), a sample size of 260 patients is necessary to observe 161 events, considering the accrual and follow-up periods and that the estimated 5-year overall survival rates of the 3-weekly CDDP + RT arm and the weekly CDDP + RT arm are 49 and 52%, respectively.

Interim Analysis and Monitoring

In this Phase II/III trial, three interim analyses are planned. The first interim analysis is planned at the time of protocol treatment completion of all registered patients in the Phase II part to evaluate the feasibility and safety of both treatment arms and to determine the progression to the Phase III part. The second interim analysis is planned when half of the planned sample size is registered to determine whether the registration of the Phase III part should be continued. The third interim analysis is planned after the registration completion to determine the continuation to the follow-up. The trial will be terminated when the primary objective is accomplished at each interim analysis.

The Data and Safety Monitoring Committee of the JCOG will independently review the interim analysis reports and recommend that the trial either be continued or terminated early. Central monitoring will be performed every 6 months by the JCOG Data Center to evaluate study progress and improve study quality.

Participating Institutions (from North to South)

Hokkaido University Hospital, Miyagi Cancer Center, Tohoku University Hospital, Jichi Medical University Hospital, National Cancer Center Hospital East, Tokyo Jikei Medical University Hospital, National Hospital Organization Tokyo Medical Center, Cancer Institute Hospital, Tokai University, Shizuoka Cancer Center, Aichi Cancer Center, Nagoya University Hospital, Kinki University Hospital, Osaka Prefectural Hospital Organization, Osaka Medical Center for Cancer and Cardiovascular Diseases, Kobe University Hospital, Hyogo Cancer Center, Nara Medical University, Shikoku Cancer Center.

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Conflict of interest statement

None declared.

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Evaluating positional accuracy using megavoltage cone-beam computed tomography for IMRT with head-and-neck cancer

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Accurate dose delivery is essential for the success of intensity-modulated radiation therapy (IMRT) for patients with head-and-neck (HN) cancer. Reproducibility of IMRT dose delivery to HN regions can be critically influenced by treatment-related changes in body contours. Moreover, some set-up margins may not be adaptable to positional uncertainties of HN structures at every treatment. To obtain evidence for appropriate set-up margins in various head and neck areas, we prospectively evaluated positional deviation (δ values) of four bony landmarks (i.e. the clivus and occipital protuberance for the head region, and the mental protuberance and C5 for the neck region) using megavoltage cone-beam computed tomography during a treatment course. Over 800 δ values were analyzed in each translational direction. Positional uncertainties for HN cancer patients undergoing IMRT were evaluated relative to the body mass index. Low positional accuracy was observed for the neck region compared with the head region. For the head region, most of the δ was distributed within ±5 mm, and use of the current set-up margin was appropriate. However, the δ values for the neck region were within ±8 mm. Especially for overweight patients, a few millimeters needed to be added to give an adequate set-up margin. For accurate dose delivery to targets and to avoid excess exposure to normal tissues, we recommend that the positional verification process be performed before every treatment.

Keywords: positional accuracy; body mass index; head and neck; IMRT; MV-CBCT

INTRODUCTION

Accurate dose delivery is essential for the success of intensity-modulated radiation therapy (IMRT) in patients with head-and-neck (HN) cancer, due to the steep dose gradient between the planning target volume (PTV) and the adjacent organs at risk (e.g. spinal cord and parotid glands). Reproducibility of the patient's position during IMRT is critically important. In general, the patient is immobilized with a customized thermoplastic mask and pillows. The body is positioned on a couch by matching external marks on the mask to the isocenter indicated by lasers. Skin marks on the patient's shoulders and chest are used to assist set-up.

Researchers have used various imaging procedures [1], such as orthogonal mega- or kilovoltage (kV) X-ray radiographic imaging [2–4], computed tomography (CT) on rails [5], and 3D cone-beam computed tomography (CBCT) [4, 6, 7], to verify patient positioning during set-up for IMRT. A recent study evaluated the positional accuracy of HN cancer patients using 3D imaging procedures, revealing positional deviations of 3 mm and ≥5 mm in 18.7 and 4.1% of set-ups, respectively, with kV-CBCT, compared with 11.2 and 1.7%, respectively, with 2D kV radiographic imaging [4]. Differences between the procedures were mainly attributed to the relative flexibility and possible rotation of the HN structures. Complex patterns of set-up errors resulting from these complications were also observed when CT on rails, which found a difference of 2–6 mm for the distance between two bony landmarks at the second or sixth cervical vertebra and the palatine process of the maxillary bone [1]. Various magnitudes of set-up errors among multiple regions-of-interest, which were frequently larger than those detected at the isocenter, were observed using kV-CBCT [7]. When 3D imaging procedures were used, geometrical uncertainties caused by the rotation/flexibility of HN structures became apparent. These findings imply that a variety of set-up margins are required for the different portions of the head and neck during IMRT planning.

Reproducibility of HN IMRT delivery could be critically influenced by changes in body contours derived from e.g. malnutrition or loss of postsurgical edema during treatment [8, 9]. In addition to loose fitting of immobilization masks and pillows, such changes may cause unexpected over- or under-IMRT dosing to targets and critical organs, which should be corrected with replanning of IMRT [10–12]. Set-up margins applied for the clinical target volume (CTV) and the risk organs are decided on the basis of clinical experiences and reported values. Thus, these margins may not be adaptable to the geometrical uncertainties of patient positioning during IMRT, such as the rotation/flexibility of HN structures and changes in body contours.

To obtain evidence for appropriate set-up margins for various HN portions, using 3D megavoltage (MV)-CBCT, we prospectively evaluated the positional deviation for four bony landmarks (clivus, occipital protuberance, mental protuberance, and C5) during a course of HN IMRT. Additionally, because obese patients generally have difficulty maintaining their weight during treatment and tend to have low positional reproducibility, positional uncertainties were evaluated relative to the body mass index (BMI).

MATERIALS AND METHODS

Patient characteristics and set-up

A total of 67 patients with HN cancer who underwent IMRT were included in this study. The study was approved by our institution's protocol review board, and patients gave their written consent prior to their participation. Characteristics for the patients are listed in Table 1. As defined by the World Health Organization, patients with BMI < 18, 18 ≤ BMI < 25, and 25 ≤ BMI were classified as underweight, normal weight and overweight, respectively. For set-up, all patients were immobilized in a supine position, with thermoplastic fixation masks and customized vacuum pillows extended to the shoulders from the back of the head (Fig. 1). Fixation devices were attached to the treatment couch by an index bar.

Volume acquisition

Once patients were positioned on a treatment couch using their personal masks and vacuum pillows, they were scanned by MV-CBCT mounted on an Oncor linear accelerator (Siemens Medical Solutions, Concord, CA). An amorphous-silicon flat panel detector with an active detector area of 41 cm × 41 cm and a spatial resolution of 1024 × 1024 pixels was used for volumetric acquisition of the MV-CBCT. The voxel size of the reconstructed images was 1.07 mm × 1.07 mm × 1 mm. The maximum field of view (FOV) was 27.4 cm × 27.4 cm at a source-to-axis distance of 100 cm. CT images were reconstructed using 200 projections during 200° of gantry rotation. The CBCT image reconstruction process has been described elsewhere [13–15]. Geometrical distortion of the reconstructed images was evaluated using a phantom with 1-cm square grids. Exposure corresponded to 2.1 cGy at a depth of 10 cm in solid water slabs measured with an ionization chamber.

To avoid clinical overloading and excess exposure to patients, volume acquisition was scheduled as follows: continuously during the first 5 d to confirm reproducibility of the isocenter marking on the masks, and once every 5 d

Table 1. Patient characteristics

Characteristics	
Sex (*n*)	
Male	51
Female	16
Total	67
Age (y)	
Median (Min.–Max.)	59 (18–82)
BMI classification (*n*)	
Underweight (BMI < 18)	10
Normal weight (18 ≤ BMI < 25)	37
Overweight (25 ≤ BMI)	12
Unknown	8
Irradiated site (*n*)	
Nasopharynx	13
Oropharynx	15
Hypopharynx	7
Parotid	3
Paranasal sinus	6
Oral cavity	15
Neck	6
Unknown	2

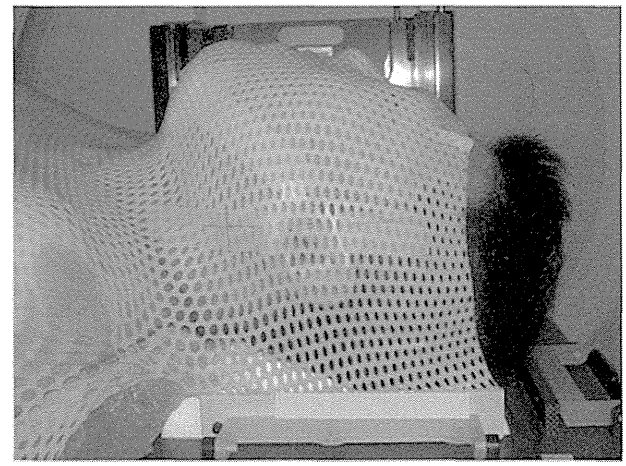

Fig. 1. Patient immobilization for HN IMRT.

thereafter. When a set-up error ≥3mm was detected, another volume acquisition was performed the next day.

Verification of patient position

Figure 2 shows the four bony landmarks used for the verification of patient position. The clivus was used for positional verification in the skull because, in many cases, a steep dose gradient is observed at this site to spare the brain stem. The occipital/mental protuberances and C5 were selected to evaluate deviation due to HN flexibility/rotation. For each landmark, discrepancy of the position between treatment and treatment planning (δ) was measured by manual registration between MV-CBCT and simulation-CT (Toshiba Medical Systems, Tokyo, Japan) using MVision software (Siemens Medical Solutions, Concord, CA). Simulation-CT had a voxel size of 1 mm × 1 mm × 1 mm. Since the edge of bony structures was detected simply in the CT images compared with the center of bony structures, the edge of bony structures was used in the manual registration. To improve reproducibility of the positional verification, the manual registration was performed changing the contrast of the CT images variously and widely, and prevented the edge of bony structures from being missing on CT images. Therapists were trained in the manual to reduce variations between individuals.

Statistical analysis

For each landmark, > 800 δ values were analyzed in the three translational directions of left–right (LR), craniocaudal (CC), and anteroposterior (AP). The mean and range (minimum to maximum) of δ values were obtained. To evaluate positional accuracy for HN IMRT, 1σ of δ values were calculated. The statistical analysis was performed for all patients, and patients were categorized by BMI.

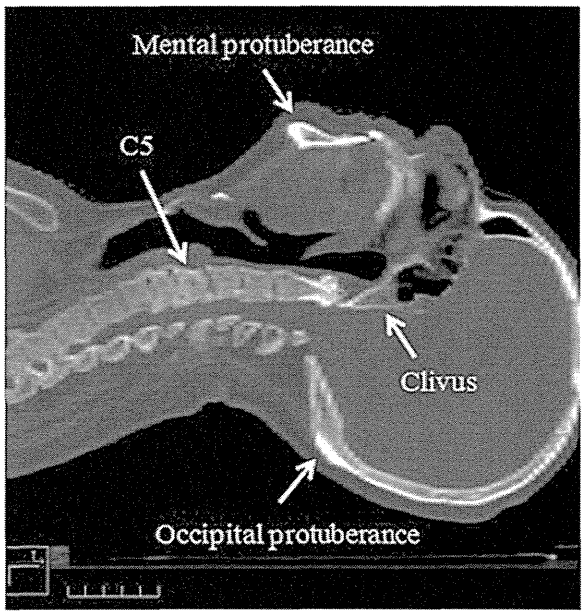

Fig. 2. Verification of patient position in HN IMRT. Positional reproducibility was evaluated with four body landmarks: the clivus, the occipital protuberance, the mental protuberance, and C5.

RESULTS

Table 2 shows statistics of the δ values for each landmark. Overall, patients tended to shift to the left, caudal and dorsal side within 2 mm. The 1σ values for the clivus and occipital protuberance (range, 1.2–1.7 mm) were less than those for the mental protuberance and C5 (range, 1.5–2.3 mm). Thus, the neck region (mental protuberance and C5) had lower positional accuracy than the head region (clivus and occipital protuberance). The mental protuberance had maximum δ and 1σ of 1 cm and 2.8 mm, respectively, which were found in overweight patients.

To evaluate differences in positional accuracy by BMI, δ values were plotted with the frequency distributions (Fig. 3). The positive side of the horizontal axis in Fig. 3 represents the right, caudal and dorsal side of the patients, and the vertical axis represents frequencies. For the clivus (a), occipital protuberance (b), mental protuberance (c), and C5 (d), the δ values were distributed in a near-normal distribution. Generally, most of the δ values for the clivus and occipital protuberance were distributed within ±5 mm, whereas those for the mental protuberance and C5 were distributed within ±8 mm. Compared with normal weight patients, overweight patients had a wider and more even distribution of δ values in the mental protuberance and C5. In underweight patients, the mental protuberance was shifted to the right side, whereas it was left-shifted for normal weight and overweight patients. To evaluate equality of the positional accuracy among the patient groups, an F-test was performed on the δ values classified by the patient's BMI. The significance level was determined to <0.02 by using a Bonferroni correction for the multiple comparison. In the neck region, (including mental protuberance and C5), the variances of δ values were more significantly different among the patient groups than in the head region (including the clivus and the occipital protuberance). Therefore, it was implied that the positional accuracy for the neck region, including the mental protuberance and C5, tended to be affected by the patient's BMI.

In the time trend of δ values, patients tended to shift slightly to the right and foot side during a course of treatment. A maximum shift of 0.8 mm to the foot direction was observed for the mental protuberance. No shift along the AP direction was observed in any landmark. Patients maintained constant positional accuracy during a course of treatment.

DISCUSSION

In this study, lower positional reproducibility was found in the neck region compared with the head region of HN cancer patients, and the patient's BMI affected the positional

Table 2. Statistical analysis of δ[a]

		Clivus			Occipital protuberance			Mental protuberance			C5		
		LR	**CC**	**AP**	**LR**	**CC**	**AP**	**LR**	**CC**	**AP**	**LR**	**CC**	**AP**
All patients	Number of δ values	867	858	858	824	824	824	813	813	813	831	831	831
	Median (mm)	−1	1	0	−1	0	1	0	1	0	0	1	2
	(Range)	(−4 to 3)	(−4 to 6)	(−3 to 4)	(−6 to 3)	(−7 to 6)	(−4 to 5)	(−4 to 5)	(−7 to 8)	(−8 to 10)	(−8 to 6)	(−6 to 6)	(−7 to 9)
	1σ (mm)	1.2	1.4	1.2	1.4	1.7	1.3	1.5	2.3	1.9	1.9	1.7	2.3
Underweight	Number of δ values	123	123	123	123	123	123	112	112	112	112	112	112
	Median (mm)	−1	1	1	−1	1	1	1	1	0	0	1	2
	(Range)	(−3 to 2)	(−3 to 6)	(−1 to 4)	(−5 to 3)	(−4 to 6)	(−2 to 4)	(−3 to 4)	(−2 to 4)	(−2 to 4)	(−5 to 5)	(−2 to 5)	(−2 to 7)
	1σ (mm)	1.3	1.5	0.9	1.4	1.6	1.1	1.6	1.5	1.2	1.7	1.5	1.8
Normal-weight	Number of δ values	512	512	512	501	501	501	501	501	501	501	501	501
	Median (mm)	−1	1	0	−1	0	1	0	2	0	0	1	1
	(Range)	(−4 to 2)	(−4 to 5)	(−3 to 4)	(−6 to 3)	(−5 to 5)	(−4 to 5)	(−4 to 5)	(−6 to 7)	(−8 to 6)	(−7 to 4)	(−4 to 6)	(−4 to 8)
	1σ (mm)	1.1	1.4	1.2	1.3	1.7	1.3	1.5	2.2	1.7	1.6	1.7	2.2
Overweight	Number of δ values	158	158	158	147	147	147	158	158	158	158	158	158
	Median (mm)	0	0	1	−1	−1	1	1	1	0	−1	0	2
	(Range)	(−4 to 2)	(−4 to 5)	(−3 to 4)	(−4 to 2)	(−7 to 4)	(−3 to 4)	(−4 to 4)	(−7 to 8)	(−4 to 10)	(−8 to 6)	(−6 to 3)	(−4 to 9)
	1σ (mm)	1.2	1.5	1.2	1.4	1.9	1.2	1.5	2.8	2.6	2.3	1.8	2.1

Translational directions are expressed in left–right (LR), craniocaudal (CC), and anteroposterior (AP) directions. [a]Discrepancy of the position between treatment and treatment planning.

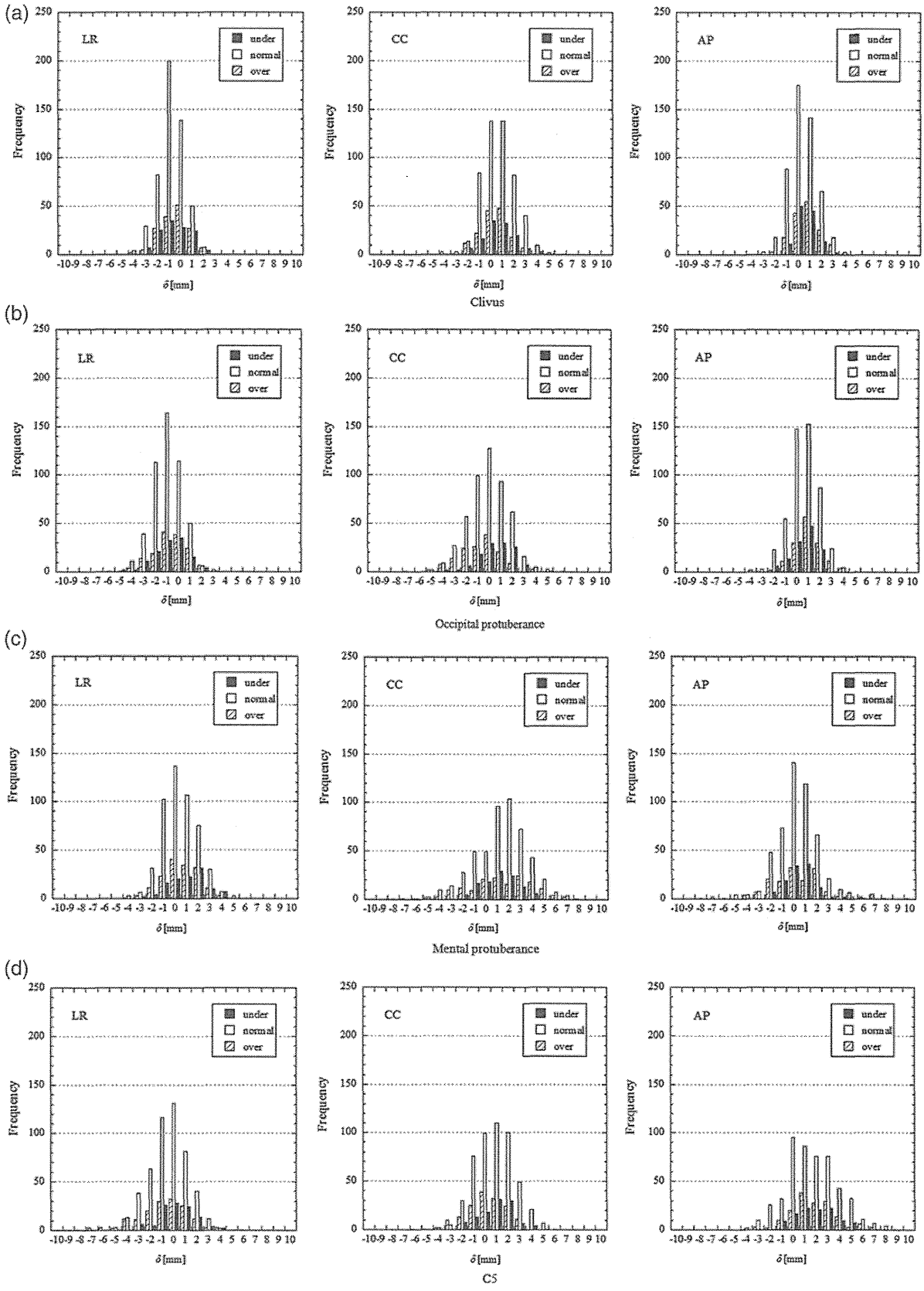

Fig. 3. Frequency distribution of positional deviation for four bony landmarks: (**a**) the clivus, (**b**) the occipital protuberance, (**c**) the mental protuberance, and (**d**) C5. Positional reproducibility was evaluated in three translational directions of left–right (LR), craniocaudal (CC) and anteroposterior (AP). Moreover, patients were classified into underweight (under), normal weight (normal), and overweight (over).

Table 3. Evaluation of the current set-up margin for HN IMRT

	Number of $\|\delta^{a}\|$ >5 mm (%[b])											
	Clivus			Occipital protuberance			Mental protuberance			C5		
	LR	CC	AP	LR	CC	AP	LR	CC	AP	LR	CC	AP
All patients	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	23 (2.8)	14 (1.7)	12 (1.4)	2 (0.2)	43 (5.2)
Underweight	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)
Normal weight	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	13 (2.6)	5 (1.0)	1 (0.2)	1 (0.2)	22 (4.4)
Overweight	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	10 (6.3)	9 (5.7)	8 (5.1)	1 (0.6)	10 (6.3)

[a]Discrepancy of the position between treatment and treatment planning. [b]Percentage of $|\delta|$ >5 mm in patient groups.

accuracy of HN IMRT. Overweight patients generally lose fat easily from under the lower jaw, the back of the neck, and the shoulders. The resulting looseness of the fixation mask markedly reduced the reproducibility of patient positioning. It will be very interesting to evaluate the relation between patients' surfaces and positional accuracy among the patient groups using volume data such as CBCT. In addition, it is potentially difficult to make fixation masks that will adjust to rapid differences in shape between the lower neck and upper chest.

In treatment planning for HN IMRT, a set-up margin of 5 mm was applied to any portion of the HN region. Most of the δ values for the clivus and occipital protuberance were distributed within ±5 mm. Thus, the current set-up margin for the head region was reasonably adequate. On the other hand, most of the δ values for the mental protuberance and C5 were within ±8 mm, suggesting that the set-up margin for the neck region should be expanded by a few millimeters. Furthermore, the frequency of $|\delta| > 5$ mm was evaluated (Table 3). In particular, the percentage of $|\delta| > 5$ mm out of the number of δ values for overweight patients was > 5% in the CC and AP directions for the mental protuberance, and the LR and AP directions for C5.

It was reported that the positional deviation of patients decreased the dose delivered to the PTV by 3–14% and caused excess exposure to critical organs [4]. Thus, positional verification before beam delivery is essential for successful HN IMRT. However, many facilities schedule specific days for the positional verification and do not perform such verification at every treatment. Therefore, we strongly suggest that the positional verification process be repeated frequently, preferably before every treatment, to prevent excess radiation exposure to adjacent critical organs by expansion of the PTV. In this context, the use of recent low-exposure 3D imaging devices in image-guided radiation therapy may be very useful.

CONCLUSION

Deviation of the patient position during a course of treatment was evaluated in HN IMRT. The positional deviation was locally different in the HN regions, with lower positional reproducibility being observed in the neck. Overweight patients had the lowest positional accuracies. An increase in the set-up margin of a few millimeters was required if the CTV and critical organs were located in the neck region. For accurate dose delivery to targets and to spare normal tissues, we recommend repeating the positional verification process often and using image-guided radiation therapy.

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Review Article

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Review Article

Adjuvant treatment for post-operative head and neck squamous cell carcinoma

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Abstract

One of the mainstays of treatment for locally advanced head and neck squamous cell carcinoma is surgery. However, for post-operative patients with high-risk factors for recurrence, surgery alone is insufficient and improving survival requires adjuvant treatment after surgery. Unlike with most other malignancies, the standard adjuvant treatment for post-operative head and neck cancer patients with high-risk factors for recurrence is radiotherapy concurrent with chemotherapy. This review article focuses on the history and future perspectives of adjuvant treatment for post-operative head and neck squamous cell carcinoma.

Key words: head and neck cancer, high-risk factors for recurrence, adjuvant treatment, chemoradiotherapy

Introduction

According to cancer statistics in Japan, 8120 Japanese died from head and neck cancer in 2012, accounting for 2.2% of cancer deaths (1). About half of head and neck cancer patients have Stage III/IV at diagnosis disease and the prognosis of these patients remains poor. Previously, surgery was one of the mainstays of treatment for resectable locally advanced head and neck squamous cell carcinoma (HNSCC), while post-operative radiotherapy (RT) was standard treatment in patients with high-risk factors for recurrence in pathological specimens (2). However, local relapse and distant metastasis relapse rates after post-operative RT were as high as 30 and 25%, respectively, and 5-year survival rate was as low as 40% (3). To improve the prognosis of post-operative HNSCC with high-risk features, the addition of cisplatin to RT was developed, and showed a survival benefit over RT alone. Now chemoradiotherapy (CRT) with cisplatin (CDDP) at a dose of 100 mg/m^2 is the standard of care for post-operative HNSCC with high-risk factors for recurrence. This review article focuses on the history and future perspectives of adjuvant treatment for post-operative HNSCC.

Adjuvant treatment for post-operative HNSCC

Which patients should receive adjuvant treatment?

The prognosis for Stage III/IV resectable locally advanced HNSCC is poor. Known risk factors for recurrence are: microscopic resection margin-positive, extracapsular nodal extension-positive, multiple cervical lymph node metastasis (≥2), lymph node metastasis with a diameter of 3 cm or more, perineural invasion, Level 4 (inferior internal jugular lymph node) or Level 5 (accessory nerve lymph node) lymph node metastasis in oropharyngeal cancer/oral cavity cancer and signs of vascular tumor embolism. For patients with none of these risk factors, 5-year local relapse rate is only 10%, and post-operative adjuvant treatment is therefore not usually performed. For patients with risk factors for recurrence, post-operative RT has been used as a post-operative adjuvant treatment. However, patients positive for extracapsular nodal extension or those with two or more risk factors for recurrence were reported to have a 5-year local relapse rate of 32% and 5-year survival rate of 42%, showing poor prognosis even after post-operative radiotherapy (4,5). Surgery with post-operative RT is therefore considered insufficient, and more effective treatment has been sought (6).

It is therefore necessary to identify the most important risk factors for recurrence in patients receiving post-operative radiotherapy. A combined analysis was conducted using data from the RTOG 85-03 study (randomized study to compare post-operative radiation with chemotherapy with 5FU + CDDP followed by post-operative radiotherapy in post-operative patients with locally advanced hypopharynx squamous cell carcinoma) and RTOG 88-24 study (Phase II study of post-operative chemoradiotherapy with CDDP in patients after surgery of locally advanced head and neck squamous cell carcinoma) conducted by the Radiation Therapy Oncology Group (RTOG) (6). Results showed that patients with risk factors for recurrence including (i) microscopically positive resection margin, (ii) extracapsular nodal extension-positive and (iii) multiple lymph node metastases (≥2) had a higher 5-year local relapse rate (microscopically positive resection margin vs. extracapsular nodal extension/multiple cervical lymph node metastasis vs. no relapse risk factor: 61 vs. 27 vs. 17%) and decreased 5-year survival rate (microscopically positive resection margin vs. extracapsular nodal extension/multiple cervical lymph node metastasis vs. no relapse risk factor: 27 vs. 34 vs. 53%) compared with patients with none of the above factors. On this basis, improving prognosis in patients with any of these three risk factors for recurrence is particularly important.

In addition to (i) microscopic resection margin positivity and (ii) extracapsular nodal extension positivity, the European Organization for Research and Treatment of Cancer (EORTC) also suggests that Stage III/IV disease, perineural infiltration, Level 4/5 lymph node metastasis in oropharyngeal cancer/oral cavity cancer, and signs of vascular tumor embolism are also risk factors for recurrence (7–10). Despite some differences in the definition of post-operative risk factors for recurrence between the EORTC and RTOG, the two key trials (Table 1), namely the EORTC22931 study (7) and RTOG95-01 study (11), were conducted, as described later. To account for these differing definitions, data from the two studies were consolidated in a combined analysis (8). This indicated not only that CRT with CDDP was generally superior to RT alone as post-operative adjuvant treatment, with the difference between them being significant [hazard ratio (HR), 0.776], but also that post-operative CRT with CDDP is more advantageous than RT alone for patients with either of the common high-risk factors for recurrence observed in the two studies, namely (i) microscopic resection margin positivity or (ii) extracapsular nodal extension positivity (HR = 0.702). In contrast, post-operative CRT with CDDP showed no advantage over RT alone in patients with risk factors for recurrence that were not common between the two studies (e.g. multiple lymph node metastases) in either the EORTC22931 study or the RTOG95-01 study.

Therefore, major high-risk factors for recurrence are presently defined as (i) microscopic resection margin positivity and (ii) extracapsular nodal extension positivity, and patients with either of these major risk factors should receive post-operative CRT with CDDP. Other risk factors for recurrence which were not common between the two studies, including multiple cervical lymph node metastases, are termed intermediate risk factors. The provision of post-operative RT to patients with these intermediate risk factors is based on the results of this combined analysis.

Table 1. Differences in risk factors for recurrence between RTOG and EORTC

Risk factor only in RTOG	Common risk factors with RTOG and EORTC	Risk factors only in EORTC
Multiple lymph node metastases (≥2)	Microscopic resection margin positivity, extracapsular nodal extension positivity	Stage III/IV disease, perineural infiltration, level 4/5 lymph node metastasis in oropharyngeal cancer/ oral cavity cancer, vascular tumor embolism

What is the optimal adjuvant treatment for post-operative high-risk HNSCC patients?

Radiotherapy

Prognosis of Stage III/IV resectable locally advanced head and neck squamous cell carcinoma is poor, and post-operative RT after radical resection has remained the standard treatment for this type of cancer since 1970, when Fletcher et al. (2) published a report on prognosis after post-operative radiotherapy. In conventional post-operative radiotherapy for resectable locally advanced head and neck squamous cell carcinoma, a total dose of 60–66 Gy is commonly used and administered once daily, five times per week at 2.0 Gy as conventional fractionated irradiation with no interval period (7,11). However, local relapse and distant metastasis relapse rates after post-operative radiotherapy were as high as 30 and 25%, respectively, and 5-year survival rate was as low as 40% (3). Thus, post-operative RT is now indicated for patients with intermediate risk factor for recurrence and those at high risk for recurrence who are unsuitable for post-operative CRT due to poor organ function (renal impairment etc.).

Chemoradiotherapy

As described above, post-operative CRT has been developed for the treatment of locally advanced HNSCC in patients at high risk of recurrence. Pivotal randomized trials of post-operative CRT for HNSCC patients at high risk of recurrence are listed in Table 2.

Bachaud et al. reported the results of a randomized comparative study in 83 HNSCC patients with high post-operative risk (extracapsular nodal extension-positive). The RT-alone group had a 5-year overall survival (OS) of 13% whereas that in the CRT (CDDP 50 mg/body every week) group was 36% ($P < 0.01$), showing the statistically significant superiority of post-operative CRT (12).

Smid et al. compared RT alone with CRT using mitomycin (MMC) and bleomycin (BLM) in 114 HNSCC patients with high post-operative risk (microscopic resection margin positivity, extracapsular nodal extension positivity, perineural invasion or signs of vascular infiltration). Although this was a small randomized study, 2-year OS was 64% in the RT-alone group versus 74% in the CRT group, showing that post-operative CRT was significantly superior ($P = 0.036$) (13).

The EORTC22931 study registered 334 patients with any of the risk factors for recurrence of microscopic resection margin positivity, extracapsular nodal extension positivity, Stage III/IV disease, perineural invasion, Level 4 or Level 5 lymph node metastasis (in oropharyngeal/oral cavity cancer), and signs of vascular tumor embolism. Five-year disease-free survival (DFS) was 36% in the RT alone vs. 47% ($P = 0.04$) in the CRT with CDDP groups, and 5-year OS was 40% vs. 53% ($P = 0.02$), showing the superiority of post-operative CRT (7).

The RTOG95-01 study registered 416 patients with any of the post-operative risk factors for recurrence (microscopic resection margin positivity, extracapsular nodal extension positivity or multiple cervical lymph node metastases (≥2). The 2-year local control rate (LCR), the primary endpoint, in the RT alone and CRT groups was 72 vs.

Table 2. Pivotal randomized trials of post-operative chemoradiotherapy

Author		Disease status	*N*	Chemo	RT total, Fr size	LRR	DFS	OS
Bachaud (1996)	5-year data (2-year data)	High risk	39	W-CDDP	65–74 Gy,	23%	45% (68%)	36% (72%)
			44	None	1.7–2 Gy/Fr	41%	23% (44%)	13% (46%)
						$P = 0.08$	$P < 0.02$	$P < 0.01$
Smid (2003)	2-year data	High risk	59	MMC,BLM	56–70 Gy,	14%	76%	74%
			55	None	2 Gy/Fr	31%	60%	64%
						$P = 0.037$	NS	$P = 0.036$
Bernier (2004)	5-year data	High risk	167	3W-CDDP	66 Gy,	18%	47%	53%
			167	None	2 Gy/Fr	31%	36%	40%
						$P = 0.007$	$P = 0.04$	$P = 0.02$
Cooper (2004)	3-year data	High risk	206	3W-CDDP	60–66 Gy,	18%	47%	56%
			210	None	2 Gy/Fr	28%	36%	47%
						$P = 0.01$	$P = 0.04$	$P = 0.19$
Fietkau (2006)	5-year data	High risk	226	5FU,CDDP	50–64 Gy	11%	62%	58%
			214	None	2 Gy/Fr	28%	50%	49%
						$P = 0.0006$	$P = 0.023$	NS
Argiris (2008)	5-year data	High risk	36	CBDCA	59.4 Gy	22%	49%	51%
			36	None	1.8 Gy/Fr	28%	53%	44%
						NS	NS	NS

Chemo, chemotherapy; LRR, local relapse rate; DFS, disease-free survival; OS, overall survival; NS, not significant; Gy, gray; Fr, fraction.

82% ($P = 0.003$) (Gray's test), respectively, showing the superiority of post-operative CRT. In addition, the 3-year progression-free survival (PFS) rate was 36 vs. 47% ($P = 0.04$), again showing the superiority of post-operative CRT. However, 3-year OS was 47 vs. 56%, showing only a trend for the superiority of post-operative CRT, without statistical significance ($P = 0.19$) (11).

At the American Society of Clinical Oncology (ASCO) meeting of 2006, Fietkau et al. (14) presented the results of ARO 96-3, a Phase III study, which compared two post-operative adjuvant treatments: RT alone and CRT with 5-FU + CDDP. This study targeted 440 HNSCC patients with high post-operative risk [microscopic resection margin positivity, extracapsular nodal extension positivity or multiple cervical lymph node metastases (≥3)]. Five-year DFS in the RT alone and CRT groups was 50 vs. 62%, respectively ($P = 0.023$), showing the statistically significant superiority of post-operative CRT, whereas 5-year OS was 49 vs. 58%, respectively, showing no significant difference.

In 2008, Argiris et al. (15) reported the results of a Phase III study on post-operative adjuvant treatment which compared RT alone and CRT with carboplatin in 72 HNSCC patients with high-risk factors (microscopic resection margin positivity, extracapsular nodal extension positivity, perineural invasion or signs of vascular infiltration). In this study, the CRT group showed no superiority to the RT-alone group in either 5-year DFS or 5-year OS, and thus the usefulness of post-operative CRT with carboplatin was not demonstrated.

Regarding the toxicities, acute/late toxicities and statistical comparisons were not consistently reported. Cooper et al. (11) reported that severe acute toxicities in RTOG95-01 study were significantly higher in CRT than RT alone (77 vs. 34%, $P < 0.001$). Moreover, Bachaud et al. (12) also reported that severe acute toxicities tended to be higher in CRT than RT alone (41 vs. 16%) (16). But, in terms of severe late toxicities, there were no significant differences between CRT and RT alone (RTOG95-01; 21 vs. 17%, EORTC22931; 38 vs. 49%) (7,11,16).

Based on the above results and combined analysis of RTOG95-01 study and EORTC22931 study (8), post-operative CRT has been the standard post-operative adjuvant treatment for HNSCC patients at high risk of recurrence (microscopic resection margin positivity or extracapsular nodal extension positivity). CDDP 100 mg/m^2 every 3 weeks, which was used in both the EORTC22931 and RTOG95-01 studies, is believed to be the most common standard regimen for concurrent monotherapy. Regarding the feasibility of post-operative CRT with CDDP at a dose of 100 mg/m^2 in Japanese patients, a Phase II feasibility study (17) reported that 80% (20/25) of patients completed per-protocol treatment. In addition, the safety profile of the study was almost the same as that of the previous studies (7,11) of post-operative CRT with CDDP at a dose of 100 mg/m^2. Thus, post-operative CRT with CDDP at a dose of 100 mg/m^2 is feasible and is the standard of care for Japanese HNSCC patients with high post-operative risk.

Chemotherapy

The role of adjuvant chemotherapy remains to be determined. Concurrent administration of chemotherapy with RT has been investigated since the 1970s, and a few randomized studies of adjuvant chemotherapy for post-operative HNSCC (18–21) have appeared. However, all of these randomized studies comparing treatment for post-operative HNSCC with or without adjuvant chemotherapy failed to show efficacy in this setting. Reports on post-operative adjuvant chemotherapy are also limited in Japan, with only a single study by Tsukuda et al. (22) in 1994, which reported that post-operative adjuvant chemotherapy with UFT significantly decreased distant relapse rate but did not contribute to survival prolongation. Thus, adjuvant chemotherapy is not indicated for post-operative HNSCC patients.

When should post-operative RT or CRT be started?

Appropriate timing to start post-operative RT or CRT is important because theoretically, excessive time from surgical resection will allow the repopulation of microscopic residual tumors, and the efficacy of adjuvant treatment will accordingly decrease. Ang et al. randomized post-operative high-risk HNSCC patients to a total dose of 63 Gy delivered over 5 or 7 weeks. In the 7-week schedule, a prolonged interval between surgery and post-operative RT was associated with significantly lower local control and survival. Overall treatment time from surgery to completion of post-operative RT had a major influence on the 5-year locoregional control rate: for an overall time of <11

weeks, locoregional control was achieved in 76%, compared with 62% for 11–13 weeks and 38% for >13 weeks ($P = 0.002$) (5). This result indicated that post-operative RT should preferably start within 6 weeks after surgery.

Future perspectives for adjuvant treatment for post-operative HNSCC

Adjuvant CRT with CDDP is the current standard treatment for high-risk post-operative HNSCC patients. Despite this treatment strategy, 5-year overall survival in this setting is still ~50% (7,11). Moreover, only 60% of patients in pivotal Phase III trials (7,11) received three cycles of CDDP at a dose of 100 mg/m^2. These findings indicate the need for more efficacious and less toxic adjuvant CRT.

Regarding investigations for more efficacious adjuvant CRT, Harrington et al. reported the final results of a randomized Phase III trial of adjuvant CRT with or without lapatinib for post-operative high-risk HNSCC patients. Lapatinib is a tyrosine kinase inhibitor with targets both EGFR and HER2. Primary endpoint of this study was DFS. Results showed no significant difference in DFS between arms (HR 1.10, 95% CI: 0.85–1.43) and no significant difference between arms in OS, the secondary endpoint (HR 0.96, 95% CI: 0.73–1.25). Taking this result together with that of the RTOG0522 trial, which compared CRT with or without cetuximab in locally advanced HNSCC and also failed to show a survival benefit for cetuximab, the addition of a molecular targeting agent to CRT provides no superiority over CRT. Other approaches may be necessary.

One of the concerns of adjuvant CRT with CDDP at dose of 100 mg/m^2 is insufficient compliance with CDDP delivery, and the use of CRT with weekly CDDP in adjuvant settings has been poorly investigated (12,23,24). CRT with weekly CDDP at 40 mg/m^2 has already shown a survival benefit for nasopharyngeal cancer (25). CRT with weekly CDDP at this dose appears to be safer and more feasible than CRT with CDDP at 100 mg/m^2. However, a small randomized trial (26) showed significantly higher rates of radiation mucositis and overall toxicities for CRT with CDDP at 40 mg/m^2. To clarify these discrepant findings for the safety and efficacy of 3-weekly and weekly schedules, we are now conducting a Phase II/III trial of post-operative chemoradiotherapy comparing 3-weekly with weekly cisplatin in high-risk patients with squamous cell carcinoma of the head and neck, the JCOG1008 study (UMIN Clinical Trial Registry number: 000009125) (27).

Conclusions

Standard adjuvant treatment for post-operative high-risk HNSCC patients is CRT with 3-weekly CDDP at dose of 100 mg/m^2. However, both compliance and treatment outcomes with this schedule are unsatisfactory, and further investigation for more efficacious and feasible adjuvant CRT is warranted.

Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

Clinical results of definitive-dose (50 Gy/25 fractions) preoperative chemoradiotherapy for unresectable esophageal cancer

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Abstract
Background The clinical results of definitive-dose preoperative chemoradiotherapy (CRT) of 50 Gy/25 fractions/5 weeks for unresectable esophageal cancer were analyzed.
Methods Inclusion criteria were unresectable esophageal squamous cell carcinoma with T4b or mediastinal lymph nodes invading to the trachea or aorta. Radiation therapy of 50 Gy/25 fractions/5 weeks was combined concurrently with two courses of FP therapy (CDDP 70 mg/m^2 + 5-FU 700 mg/m^2/d × 5 days: day 1–5, day 29–33). Tumor response was evaluated 4 weeks after completion of RT. Subtotal esophagectomy was planned 6–8 weeks after RT.
Results Thirty patients (26 male and 4 female) aged from 50–78 years (median 66) were enrolled between 2008 and 2011. The clinical stages according to the 7th edition of UICC were stages II/III/IV, 1/23/6; T1/2/3/4, 1/1/4/24; and N0/1/2/3, 3/25/1/1. All 30 patients completed RT of 50 Gy/25 fractions. Initial tumor responses were 21 patients with resectable disease, 7 with unresectable disease, and 2 with progressive disease. Subtotal esophagectomy was performed in 18 (60 %) of the 30 patients. Pathological complete response was obtained in five (28 %) patients. There were two patients with hospitalization death after surgery (11 %). Six of the 7 patients who still had unresectable disease were treated with 1–3 courses of docetaxel, CDDP and 5-FU. Three patients treated without surgery showed long-term survival. The 3-year locoregional control rate and the 3-year overall survival rate for the 30 patients were 70 and 49 %, respectively.
Conclusions Definitive-dose preoperative CRT was feasible, and is a promising treatment strategy for unresectable esophageal cancer.

Keywords Unresectable esophageal cancer · Preoperative treatment · Chemoradiotherapy

Introduction

Definitive chemoradiotherapy (CRT) is the standard treatment for locally advanced unresectable esophageal cancer [1]. In the United States, a phase III trial comparing standard-dose radiotherapy (RT) (50.4 Gy) and high-dose RT (64.8 Gy) concurrently combined with 5-FU/cisplatin was conducted for T1–T4, N0/1, M0 esophageal cancer [2]. In the INT0123 trial, the high-dose arm did not offer a survival benefit compared with the standard-dose arm. Thus, at present, four cycles of definitive-dose 5-FU/cisplatin combined with 50 Gy of RT is the standard CRT regimen for esophageal cancer in the USA. In Japan, concurrent CRT with RT of 60 Gy/30 fractions/6–8 weeks and FP therapy (cisplatin and 5-FU) has been applied, especially for unresectable T4 esophageal cancer. In prospective studies of definitive CRT for unresectable esophageal cancer, the complete response (CR) rate of T4 tumors ranged from 15–32 %, and 3-year overall survival rates of approximately 20 % have been reported [3–5]. A retrospective survey of 9 major Japanese institutions revealed median 3- and 5-year overall survival rates of 21 % (range 10–36 %) and 19 % (range 0–31 %), respectively, for unresectable stage III-IVA tumors by definitive CRT [6].

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