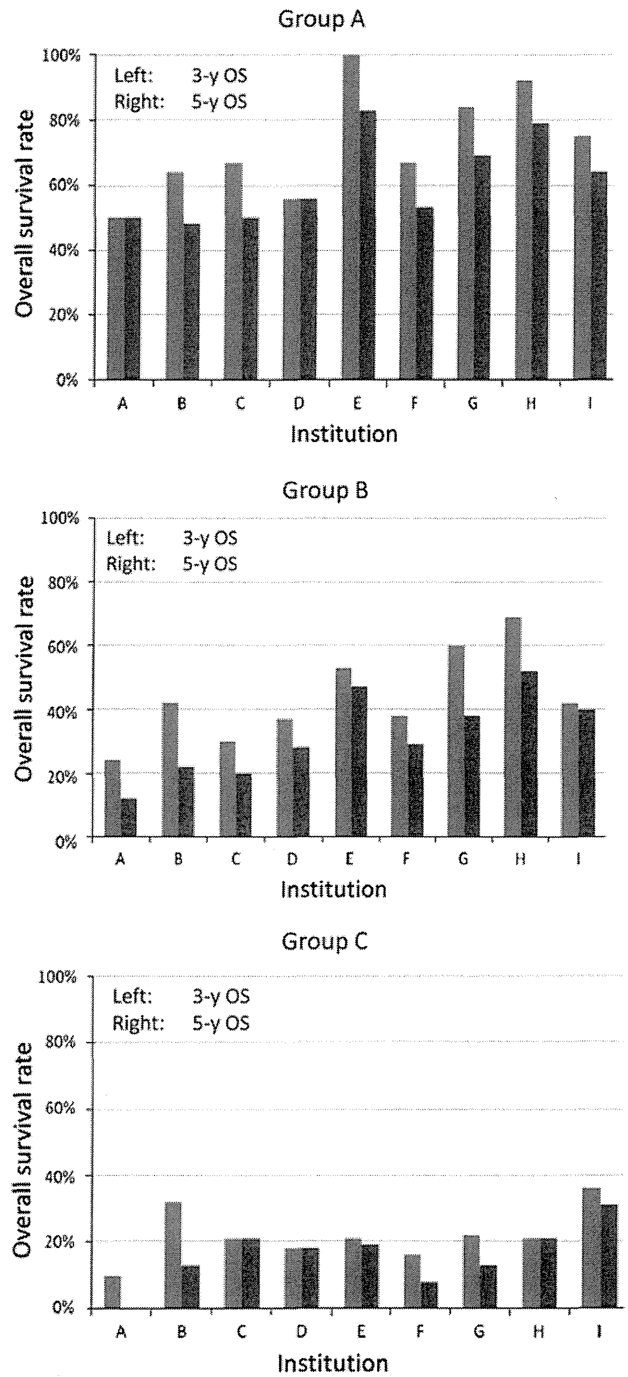


Fig. 1 The 3- and 5-year overall survival rates at each institution are shown for (**a**) group A, (**b**) group B, and (**c**) group C. The *left* and *right* columns are the 3- and 5-year overall survival rates of each institution, respectively

institution was analyzed for groups A, B, and C (Fig. 2). The correlation coefficient (r) and its 95% confidence interval for groups A, B, and C were 0.50 (−0.2455 to 0.8740), 0.70 (0.0602 to 0.9303), and 0.70 (0.0670 to 0.9312), respectively. A significant correlation between the number of patients treated per year and the 5-year overall

Table 3 The median and range of overall survival (OS) rates for patients with esophageal cancer treated between 1999 and 2003 at the 9 institutions

	3 years OS	5 years OS
Group A	67% (50–100%)	56% (48–83%)
Group B	42% (24–69%)	29% (12–52%)
Group C	21% (10–36%)	18% (0–31%)

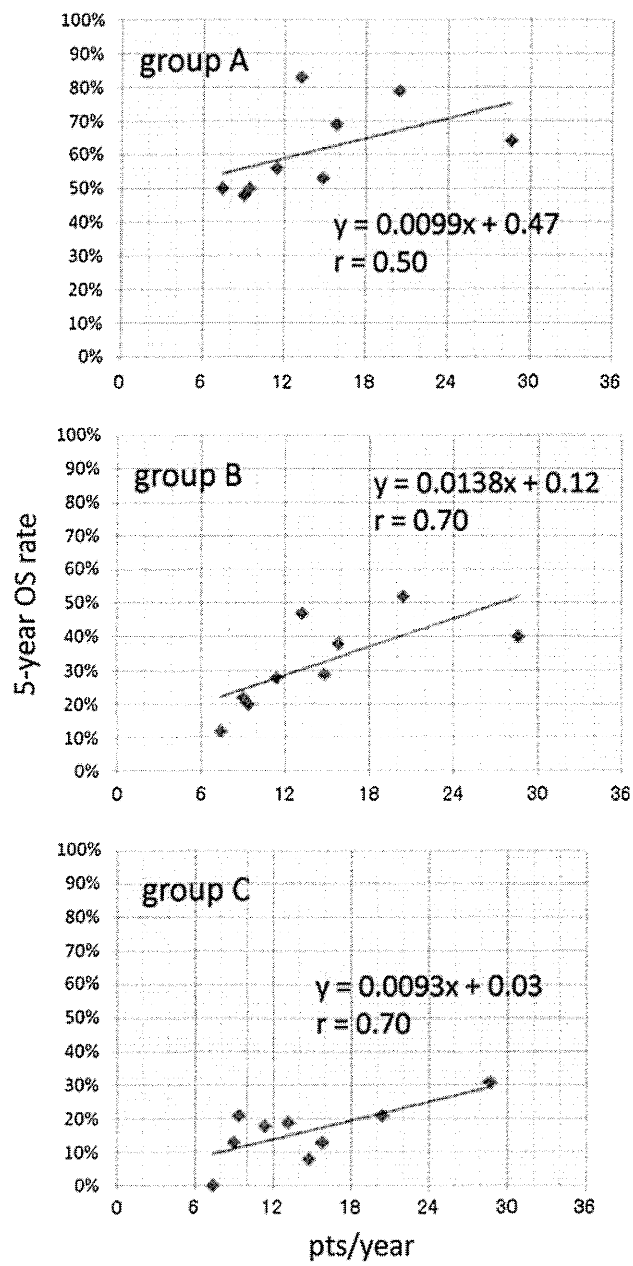


Fig. 2 Correlations between the number of patients treated per year (x-axis) and the 5-year overall survival rates of each institution (y-axis) for groups A, B, and C are plotted. The linear regression lines and correlation coefficients (r) for each group are shown

Table 4 Number of patients with serious late toxicities associated with CRT or RT

CTCAE version 3.0	Grade 3–4	Grade 5
Cardiac ischemia	1	3
Pericardial effusion	14	1
Pleural effusion	7	1
Radiation pneumonitis	4	2
Dysphagia	9	0
Hemorrhage, esophageal varices	1	0

survival rates was noted for groups B and C (both $p < 0.05$).

Based on the clinical charts of all patients, late toxicities of grade 3 or more (CTCAE version 3.0) were collected. The median and range of grade 3 or higher late toxicity rate for each institution were 11% (0–18%). Table 4 shows the number of patients with late toxicities of grade 3 or higher. Pericardial effusion and pleural effusion are most common late toxicities associated with CRT, followed by dysphagia and radiation pneumonitis. Although seven (1%) treatment-related deaths (grade 5) were reported, the deaths from cardiac ischemia may be coincidental.

Discussion

The present questionnaire-based survey revealed both clinical practice of care and outcomes for esophageal cancer treated by definitive RT or CRT in nine academic and major institutions between 1999 and 2003. The changes in clinical practice of RT for esophageal cancer in Japan have been well reported by the Japanese Patterns of Care Study (JPCS) [16, 17]. Based on the Comprehensive Registry of Esophageal Cancer in Japan for 2002, a total of 4,281 cases were registered from 222 institutions in Japan [24]. For cStage I–IIA (T1-3N0M0), the 5-year overall survival rates with concurrent CRT or RT alone were 52.0 and 32.5%, respectively. For cStage IIB–IVB, the 5-year overall survival rate with concurrent CRT was 14.9% [24]. However, no comparison of clinical outcomes of definitive RT or CRT at various institutions for esophageal cancer has been reported in Japan.

The JPCS between 1999 and 2001 revealed that CRT had become a common treatment for T2–4 esophageal tumors, although 72% of T1 tumors were treated by RT alone [16]. Therefore, clinical data for both RT alone and CRT were collected for stage I esophageal cancer (group A), although only data on CRT were collected for groups B and C. In the present analysis, 56% of the patients in group A were treated by RT alone and 44% were treated by CRT. Although the CRT rate for T1 tumors was higher than that in the JPCS between 1999 and 2001, more than half of T1 tumors were still treated by RT alone in Japanese academic and major institutions between 1999 and 2003. Following RT alone or CRT, 60 patients (36%) in group A were treated with IBT. The preference for IBT was heavily dependent on the institutional policy [9–12, 25].

For all institutions, medians of total RT dose for CRT ranged from 60 to 66 Gy. Although a total dose of 50.4 Gy combined with FP is the standard regimen for esophageal cancer in the USA, no institutions in this survey used a total dose of 50.4 Gy for definitive CRT. The type of chemotherapy differed significantly among the institutions. In Japan, low-dose protracted infusion chemotherapy combined with full-dose RT of 60–66 Gy used to be a popular regimen for locally advanced esophageal squamous cell carcinomas [5, 7, 16, 20, 22]. In the present analysis, full-dose FP was used most frequently (42.5%), followed by low-dose FP (36.8%) (Table 2). During this period, two clinical trials comparing full-dose FP and low-dose FP were performed at several institutions [18, 19]. In both trials, protracted low-dose FP with RT provided no advantage over standard short-term full-dose FP with RT for esophageal cancer. Low-dose FP will therefore decline in clinical practice in Japan.

The 5-year survival rates for stage I esophageal cancer exceeded 50% at most institutions, with a median 5-year survival rate of 56%. This survival rate seems excellent, as more than half of the patients were treated with RT alone. Thus, RT alone seems a definitive and effective treatment for elderly and complicated patients with superficial esophageal cancer.

One of the most notable findings in the present study was a significant disparity in overall survival rates among the institutions for patients with stage II–IVA disease treated definitively by CRT. The biggest difference in the 5-year overall survival rate was noted for group B. The highest 5-year overall survival rate of 52% was achieved at Tenri Hospital. At the hospital, definitive CRT was performed for responders to neoadjuvant CRT of 44 Gy/40 fractions, and surgery was performed for non-responders [9, 21]. This patient selection approach may be linked to the excellent survival rate. On the other hand, neither salvage surgery nor cancer board meetings were done for esophageal cancer at two hospitals showing poor 5-year survival rates of 12 and 22% for resectable esophageal cancer (Table 1). Thus, the disparity in overall survival rates may be related to the clinical practice at each institution.

A significant correlation between the number of patients treated per year and the 5-year overall survival rates was noted for groups B and C (both $p < 0.05$) (Fig. 2). A similar volume–outcome relation was demonstrated between the number of esophagectomy operations performed per year and the operative mortality [26]. In terms of esophagectomy for cancer, a hospital with less than five esophagectomy operations per year was classified as a low-volume hospital with high operative mortality [26]. As the present series included only medium- and high-volume hospitals for CRT, survival rates by CRT at low-volume hospitals may be much lower than this series.

High rates of serious late toxicities, especially of the heart and pleura, associated with CRT have been reported [4, 27]. In this analysis, the median grade 3 or higher late toxicity rate of each institution was 11%. This late toxicity rate was considered acceptable, although it may have been underestimated due to the retrospective nature of the analysis.

In conclusion, the 5-year survival rates for stage I esophageal cancer were excellent, even with RT alone, at most institutions. However, for patients with stage II–IVA tumors treated definitively by CRT, a significant disparity in overall survival was noted among the institutions.

Acknowledgments This study was partially supported by a Grant-in-Aid for Scientific Research (21249066) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and a Grant-in-Aid from the Japanese Radiation Oncology Study Group (JROSG).

Conflict of interest None declared.

References

1. Al-Sarraf M, Herskovic A, Martz K et al (1997) Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol 15:277–284
2. Cooper JS, Guo MD, Herskovic A et al (1999) Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 281:1623–1627
3. Smith TJ, Ryan LM, Douglass HO Jr et al (1998) Combined chemoradiotherapy vs. radiotherapy alone for early stage squamous cell carcinoma of the esophagus: a study of the Eastern Cooperative Oncology Group. Int J Radiat Oncol Biol Phys 42:269–276
4. Minsky BD, Pajak TF, Ginsberg RJ et al (2002) INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 20:1167–1174
5. Nishimura Y, Suzuki M, Nakamatsu K et al (2002) Prospective trial of concurrent chemoradiotherapy with protracted infusion of 5-fluorouracil and cisplatin for T4 esophageal cancer with or without fistula. Int J Radiat Oncol Biol Phys 53:134–139
6. Ohtsu A, Boku N, Muro K et al (1999) Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. J Clin Oncol 17:2915–2921
7. Sakai K, Inakoshi H, Sueyama H et al (1995) Concurrent radiotherapy and chemotherapy with protracted continuous infusion of 5-fluorouracil in inoperable esophageal squamous cell carcinoma. Int J Radiat Oncol Biol Phys 31:921–927
8. Hironaka S, Ohtsu A, Boku N et al (2003) Nonrandomized comparison between definitive chemoradiotherapy and radical surgery in patients with T(2–3)N(any) M(0) squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys 57:425–433
9. Murakami M, Kuroda Y, Nakajima T et al (1999) Comparison between chemoradiation protocol intended for organ preservation and conventional surgery for clinical T1–T2 esophageal carcinoma. Int J Radiat Oncol Biol Phys 45:277–284
10. Ariga H, Nemoto K, Miyazaki S et al (2009) Prospective comparison of surgery alone and chemoradiotherapy with selective surgery in resectable squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys 75:348–356
11. Nishimura Y, Okuno Y, Ono K et al (1999) External-beam radiation therapy with or without high-dose-rate intraluminal brachytherapy for superficial esophageal cancer. Cancer 86:220–228
12. Sai H, Mitsumori M, Araki N et al (2005) Long-term results of definitive radiotherapy for stage I esophageal cancer. Int J Radiat Oncol Biol Phys 62:1339–1344
13. Nemoto K, Matsumoto Y, Yamakawa M et al (2000) Treatment of superficial esophageal cancer by external radiation therapy alone: results of a multi-institutional experience. Int J Radiat Oncol Biol Phys 46:921–925
14. Nemoto K, Yamada S, Hareyama M et al (2001) Radiation therapy for superficial esophageal cancer: a comparison of radiotherapy methods. Int J Radiat Oncol Biol Phys 50:639–644
15. Kato H, Sato A, Fukuda H et al (2009) A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan Clinical Oncology Group Study (JCOG9708). Jpn J Clin Oncol 39:638–643
16. Murakami Y, Kenjo M, Uno T et al (2007) Results of the 1999–2001 Japanese patterns of care study for patients receiving definitive radiation therapy without surgery for esophageal cancer. Jpn J Clin Oncol 37:493–500
17. Kenjo M, Uno T, Murakami Y et al (2009) Radiation therapy for esophageal cancer in Japan: results of the Patterns of Care Study 1999–2001. Int J Radiat Oncol Biol Phys 75:357–363
18. Nishimura Y, Mitsumori M, Hiraoka M et al (2009) A randomized phase II study of cisplatin/5-FU concurrent chemoradiotherapy for esophageal cancer: short-term infusion versus protracted infusion chemotherapy (KROSG0101/JROSG021). Radiother Oncol 92:260–265
19. Sakayauchi T, Nemoto K, Ishioka C et al (2009) Comparison of cisplatin and 5-fluorouracil chemotherapy protocols combined with concurrent radiotherapy for esophageal cancer. Jpn J Radiol 27:131–137
20. Sai H, Mitsumori M, Yamauchi C et al (2004) Concurrent chemoradiotherapy for esophageal cancer: comparison between intermittent standard-dose cisplatin with 5-fluorouracil and daily low-dose cisplatin with continuous infusion of 5-fluorouracil. Int J Clin Oncol 9:149–153
21. Yamada K, Murakami M, Okamoto Y et al (2006) Treatment results of chemoradiotherapy for clinical stage I (T1N0M0) esophageal cancer. Int J Radiat Oncol Biol Phys 64:1106–1111
22. Sasamoto R, Sakai K, Inakoshi H et al (2007) Long-term results of chemoradiotherapy for locally advanced esophageal cancer, using daily low-dose 5-fluorouracil and *cis*-diammine-dichloroplatinum (CDDP). Int J Clin Oncol 12:25–30
23. Nemoto K, Matsushita H, Ogawa Y et al (2003) Radiation therapy combined with *cis*-diammine-glycolatoplatinum (Nedaplatin) and 5-fluorouracil for untreated and recurrent esophageal cancer. Am J Clin Oncol 26:46–49
24. Ozawa S, Tachimori Y, Baba H et al (2010) Comprehensive registry of esophageal cancer in Japan, 2002. Esophagus 7:7–22

25. Akagi Y, Hirokawa Y, Kagemoto M et al (1999) Optimum fractionation for high-dose-rate endoesophageal brachytherapy following external irradiation of early stage esophageal cancer. Int J Radiat Oncol Biol Phys 43:525–530
26. Fujita H, Ozawa S, Kuwano H et al (2010) Esophagectomy for cancer: clinical concerns support centralization operations within the larger hospitals. Dis Esophagus 23:145–152
27. Ishikura S, Nihei K, Ohtsu A et al (2003) Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 21:2697–2702

J. Radiat. Res., 53, 138–144 (2012)

Evaluation of Parotid Gland Function using Equivalent Cross-relaxation Rate Imaging Applied Magnetization Transfer Effect

Hidetoshi SHIMIZU[1*], Shigeru MATSUSHIMA[2], Yasutomi KINOSADA[3], Hiroki MIYAMURA[2], Natsuo TOMITA[1], Takashi KUBOTA[1], Hikaru OSAKI[1], Masashi NAKAYAMA[1], Manabu YOSHIMOTO[1] and Takeshi KODAIRA[1]

Radiotherapy/Function/ECRI/Scintigraphy/Parotid gland.

Safe imaging modalities are needed for evaluating parotid gland function. The aim of this study was to validate the utility of a magnetic resonance imaging (MRI) tool, equivalent cross-relaxation rate imaging (ECRI), as a measurement of parotid gland function after chemoradiotherapy. Subjects comprised 18 patients with head-neck cancer who underwent ECRI and salivary gland scintigraphy. First, we calculated ECR values (signal intensity on ECRI), maximum uptake rate (MUR) and washout rate (WOR) from salivary gland scintigraphy data at the parotid glands. Second, we investigated correlations between ECR values and each parameter of MUR (uptake function) and WOR (secretory function) obtained by salivary gland scintigraphy at the parotid gland. Next, we investigated each dose-response for ECR, MUR and WOR at the parotid gland. A correlation was detected between ECR values and MUR in both the pre- ($r = -0.55$, $p < 0.01$) and post-treatment ($r = -0.50$, $p < 0.05$) groups. A significant post-treatment correlation was detected between the percentage change in ECR values at 3–5 months after chemoradiotherapy and median dose to the parotid gland (Pearson correlation, $r = -0.62$, $p < 0.05$). However, no correlations were detected between median dose to the parotid gland and either MUR or WOR. ECRI is a new imaging tool for evaluating the uptake function of the parotid gland after chemoradiotherapy.

INTRODUCTION

Radiotherapy for head and neck cancers must be performed with care, as various high-risk organs are situated in the surrounding area. Decreasing side effects in these organs is thus problematic. The parotid gland shows high radiosensitivity and inclusion within the irradiation field during radiotherapy for head and neck cancer causes depression of parotid gland function. Evaluation of parotid gland function after radiotherapy has been performed using salivary gland scintigraphy.[1–3] This modality can evaluate parotid gland function by observing the movement of radionuclide ($^{99m}TcO_4^-$) that accumulates in the parotid gland. However, the use of radionuclides obviously means that radiation exposure for human bodies is unavoidable,[4] making this technique unsuitable for regular evaluation of parotid gland depression caused by radiotherapy.

Magnetic resonance imaging (MRI) uses magnetism and electromagnetic waves, representing a noninvasive modality with no exposure to radiation. The apparent diffusion coefficient (ADC) obtained by diffusion-weighted imaging has been reported as a parameter for evaluating parotid function.[5–7] However, ADC shows a low correlation coefficient with the function parameter obtained by salivary gland scintigraphy.[7]

We selected equivalent cross-relaxation rate imaging (ECRI) applied magnetization transfer effect using MRI.[8–12] ECRI can detect minute changes in organization and molecular structure, offering information reflecting interactions with water molecules and biomacromolecules.[8]

The aim of the present study was to validate the utility of ECRI for evaluating parotid gland function after chemoradiotherapy. ECRI provides difference information for parts irradiated with a single saturation pulse. ECRI can obtain cell-density-weighted images and fiber-density-weighted images by irradiating a saturation pulse close to or far from the center frequency of water, respectively.[10,12] The acinar

*Corresponding author: Phone: +81-52-762-6111,
Fax: +81-52-752-8390,
E-mail: hishimizu@aichi-co.jp
[1]Department of Therapeutic Radiation Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan; [2]Department of Diagnostic and Interventional Radiology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan; [3]Department of Biomedical Informatics, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 501-1193, Japan.
doi:10.1269/jrr.11059

cell composing the parotid gland plays a big role to the uptake of saliva. Therefore, we irradiated with a saturation pulse at 7 ppm downfield from the center frequency of water to obtain cell-density-weighted images in this research. We first investigated correlations between ECR values (signal intensity on ECRI) at the parotid gland and parameters (uptake function and secretory function) as obtained by salivary gland scintigraphy. We then investigated each dose-response for ECR and salivary gland scintigraphy parameters in the parotid gland.

MATERIALS AND METHODS

Patients

Subjects comprised 18 patients with head and neck cancer. Table 1 shows patient characteristics. Disease was staged according to the American Joint Committee on Cancer 1997 clinical staging.[13] All patients received an explanation about the purpose and methods of this research and issues related to the protection of privacy, and informed consent to participate in the study was obtained prior to enrolment. MRI and salivary gland scintigraphy were performed in 6 patients before chemoradiotherapy, 6 patients after chemoradiotherapy and 6 patients both before and after chemoradiotherapy. As a result, 24 series of data were obtained for 48 parotid glands.

Chemoradiotherapy

All patients were immobilized in a cast, and computed tomography (CT) with 2.5 mm slice thickness was taken for treatment planning. Scans included the target area, regional lymph nodes, and the parotid glands. Target objects and normal structures including both parotid glands were contoured on a Pinnacle workstation (Hitachi Medical Corporation, Tokyo, Japan). Computed tomography (CT) images with the contour objects were transferred to a specific treatment planning system (Tomoprovider; TomoTherapy, Madison, WI).

Table 1. Patient characteristics

N	18
Male/female	15/3
Median age (range)	53 (16–74)
Tumor site	
Nasopharynx	16
Oropharynx	2
Stage	
I	1 (6%)
II	2 (11%)
III	8 (44%)
IV	7 (39%)

A dose of 66–70 Gy was prescribed to the primary tumor. Most patients were treated using a fractionation scheme with 2 Gy administered 5 times/week. One patient received 1.8 Gy per fraction. Dose constraints for parotid glands were mean dose < 30 Gy, median < 23 Gy and whole parotid gland volume with < 20 Gy > 20 mm^3. Other planning parameters comprised: primary collimator width, 2.5 cm; pitch, 0.3; and modulation factor, 3.0–4.0.

Radiotherapy was performed using a Hi-ART System (TomoTherapy), which is specifically designed for intensity-modulated radiotherapy (IMRT). All patients received daily megavoltage CT (MVCT) acquisitions for setup verification.[14,15]

Chemotherapy was planned for 16 patients, with only 2 patient undergoing radiotherapy alone, as medical condition was considered insufficient for systemic chemotherapy. Three courses of chemotherapy comprising continuous intravenous administration of 5-fluorouracil at 800 $mg/m^2/24$ h for 5 days (Days 1–5) and nedaplatin (NDP) at 130 $mg/m^2/6$ h for 1 day (Day 6) were administered approximately every 4 weeks in the alternating setting. The details of contents of chemoradiotherapy have been reported in other articles.[16]

Imaging techniques

Salivary gland scintigraphy was performed before initial treatment and then 3–5 months after completion of chemoradiotherapy. Salivary gland scintigraphy was performed with the gamma camera from a MillenniumVG system (GE Yokokawa Medical System, Milwaukee, WI). The only restriction before the examination was a dietary restriction. Dynamic imaging was obtained in a 64 × 64 pixel matrix at 15 s per frame for 45 min immediately after intravenous injection of 370 MBq of $^{99m}TcO_4^-$. Lemon juice (0.5 ml) was dripped into the oral cavity in 1800 s after intravenous injection as a taste stimulus. The energy window was ±10% around the 140 keV photopeak of ^{99m}Tc.

MRI was scheduled before initial treatment and then 3–5 months after completion of chemoradiotherapy. A 1.5-T system (Signa; GE Yokokawa Medical System) was used. Sequences comprised 3-dimensional spoiled gradient recalled acquisition in the steady state (3DSPGR) and saturation-transfer-prepared 3DSPGR (ST-3DSPGR). Single saturation transfer pulse (3.26 μT) frequency was employed at the frequency of 7 ppm downfield from the center frequency of water. Scans included the whole parotid gland. A neurovascular coil was used. Conditions were: repetition time, 40 ms; echo time, 6.9 ms; flip angle, 30°; bandwidth, 15.63 kHz; field of view, 24 cm; slice thickness, 5 mm; overlap locations, 0; locations per slab, 16; acquisition matrix, 512 × 126; and reconstructed matrix size, 512 × 512 (zerofill interoperation process). The stimulation of the parotid gland by for example lemon juice was not performed as in the scintigraphy protocol during MRI.

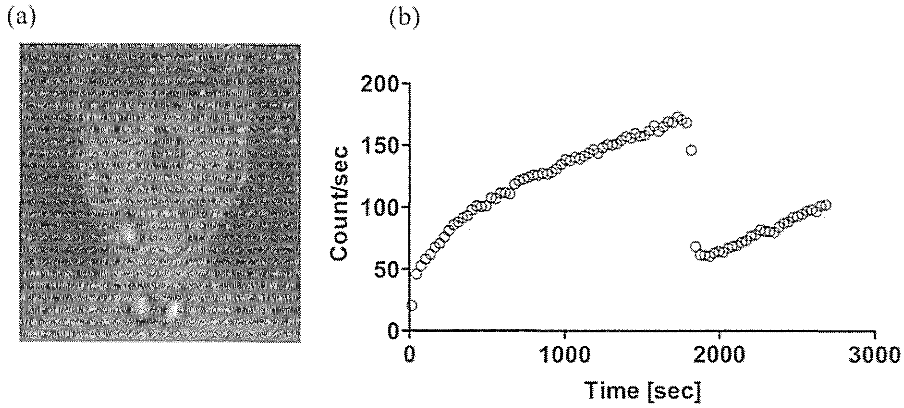


Fig. 1. (**a**) Planar image taken by salivary gland scintigraphy. ROIs were located for bilateral parotid glands and a frontal sinus. The count for the frontal sinus was used as the background level. (**b**) Representative time-activity curve (TAC) on a parotid gland. TAC on the parotid gland was created by subtracting background from the count for the gland.

Data analysis

Regions of interest (ROIs) were located for bilateral parotid glands and a frontal sinus on the planar image obtained by salivary gland scintigraphy (Fig. 1a), using the count for the frontal sinus as the background signal. A time-activity curve (TAC) for the parotid gland was created by subtracting the background from the count for the parotid gland (Fig. 1b). Maximum uptake rate (MUR) was calculated for bilateral parotid glands according to Equation 1.

$$MUR = (1 - C_{vpp} / C_{max}) \times 100\ [\%] \quad (1)$$

where C_{vpp} is the count on TAC at 60 s after administration of $^{99m}TcO_4^-$ (reflecting blood flow, capillary permeability and secretion rate in the parotid gland) and C_{max} is the maximum count on the TAC (reflecting capacities of blood vessel lumens and intercellular spaces in the parotid gland). MUR was used as the parameter indicating uptake function.

Washout rate (WOR) was calculated for bilateral parotid glands according to Equation 2.

$$WOR = (1 - C_{min} / C_{max}) \times 100\ [\%] \quad (2)$$

where C_{min} is the minimum counts after taste stimulation. WOR thus shows the secretion of $^{99m}TcO_4^-$ per capacities of blood vessel lumens and intercellular spaces in the parotid gland. WOR was used as the parameter indicating secretory function.

ECRI was obtained using Equation 3.

$$ECR = (M_0 / Ms - 1) \times 100\ [\%] \quad (3)$$

where Ms and M_0 represent signal intensities in 3DSPGR and ST-3DSPGR images, respectively. A ROI was located for the parotid gland on ECRI, and ECR at the parotid gland was measured.

We investigated correlations between ECR and both MUR and WOR at the parotid gland before and after chemoradiotherapy. Next, we investigated simple linear correlations between percentage changes in ECR, MUR and WOR at 3–5 months after chemoradiotherapy and median dose to the parotid gland.

Table 2. Changes in parameters

(a)

	Pre treatment series group (No. of parotid glands = 24)		Post treatment series group (No. of parotid glands = 24)
MUR	74.7 ± 10.8	***	59.7 ± 8.1
WOR	61.0 ± 9.6	***	21.0 ± 16.5

(b)

ECR values	30.0 ± 19.9	***	53.3 ± 22.5

Student's t test *** $p < 0.001$

Statistical analysis

R2.5.1 statistical software (www.r-project.org/) was used to perform all analyses. Student's t test was used to compare differences in patient groups. Pearson's correlation was used to evaluate correlations between ECR and MUR and between ECR and WOR at the parotid gland, and between percentage changes in ECR, MUR and WOR at 3–5 months after chemoradiotherapy and median dose to the parotid gland. The level of significance was set at 5%, and all p values were based on two-tailed tests.

RESULTS

Findings from salivary gland scintigraphy

Planar images taken by salivary gland scintigraphy were obtained in all cases without any acquisition failure. MUR and WOR could be obtained from all parotid glands on planar images. Table 2a shows changes in MUR and WOR

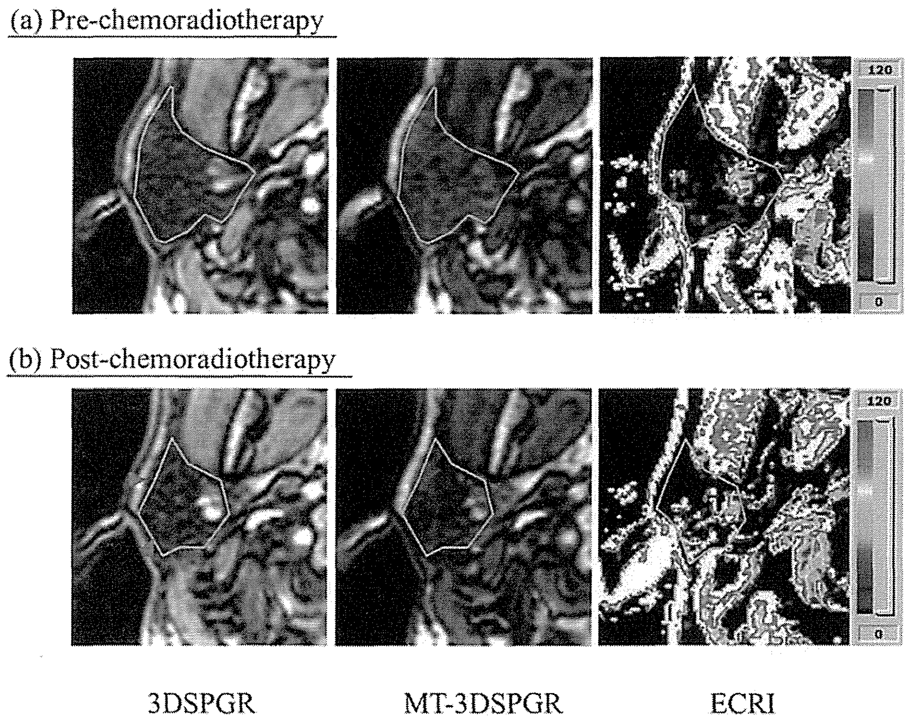


Fig. 2. Examples of 3DSPGR, MT-3DSPGR and ECR before (**a**) and after (**b**) chemoradiotherapy. Right parotid glands (areas surrounded by the yellow line) are shown in the axial plane. Volume reduction (indicated by arrowhead) was detected after chemoradiotherapy. ECRI was obtained using Equation 3.

between pre- and post-treatment groups. MUR was lower in the post-treatment group than in the pre-treatment group (Student's t test, $p < 0.001$). WOR was also lower in the post-treatment group than in the pre-treatment group (Student's t test, $p < 0.001$). Losses of uptake and secretory function in the parotid gland were thus confirmed by salivary gland scintigraphy.

Findings from ECRI

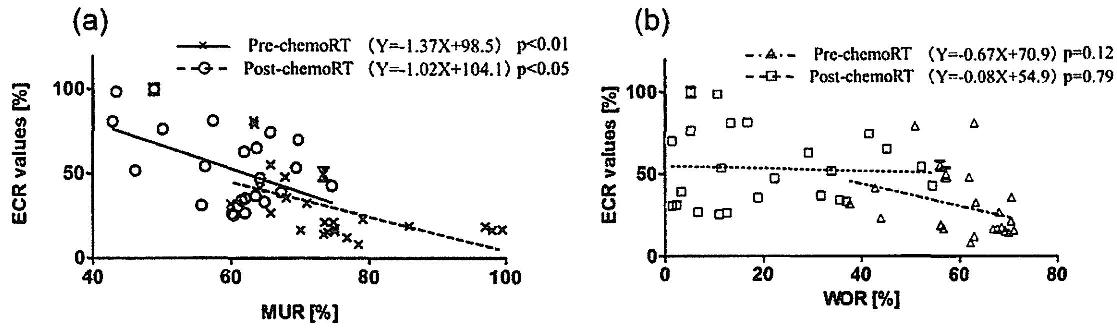
Both 3DSPGR and MT-3DSPGR images were obtained in all cases without any acquisition failure. ECR images were obtained using Equation 3. Figure 2 shows examples of 3DSPGR, MT-3DSPGR and ECR images before and after chemoradiotherapy. A clear reduction in parotid gland size after chemoradiotherapy was detected in this representative case (Fig. 2, arrowhead). ECR images were expressed in a graded color diagram of ECR values ranging from 0 to 120, with red indicating areas of high ECR, black showing areas of low ECR, and white representing areas with ECR > 120. Mean ECR values at parotid glands (± standard deviation) were 14.2 ± 0.72% and 34.3 ± 0.70% before and after chemoradiotherapy, respectively (Fig. 2). ECR values were higher in the post-treatment group than in the pre-treatment group (Table 2b; Student's t test, $p < 0.001$).

Correlations between ECR value and salivary gland scintigraphy parameters

To determine whether ECR values can be used to evaluate parotid gland function, we investigated correlations between ECR value and salivary gland scintigraphy parameters at the parotid gland. The correlation coefficient between ECR and MUR was –0.55 in the pre-treatment group (Pearson correlation, $p < 0.01$) and –0.50 in the post-treatment group (Pearson correlation, $p < 0.05$) (Fig. 3a). The correlation coefficients between ECR and WOR were –0.32 in the pre-treatment group (Pearson correlation, $p = 0.12$) and –0.06 in the post-treatment group (Pearson correlation, $p = 0.79$) (Fig. 3b).

Dose response

The 6 patients who underwent salivary gland scintigraphy and MRI both before and after chemoradiotherapy received a median dose of 19.8–26.5 Gy to the parotid glands (Table 3). The doses (several cGy per a MVCT acquisition) from the MVCT imaging were not contained in the median dose. Figure 4 shows the correlation between percentage change in parameters and median dose to the parotid gland. A significant correlation was identified between percentage change in ECR value at 3–5 months after chemoradiotherapy and median dose to the parotid gland (Pearson correlation, $r = -0.62$, $p < 0.05$). The correlation between percentage change



Abbreviation: chemoRT = chemoradiotherapy

Fig. 3. Relationships between ECR value and salivary gland scintigraphy parameters. (a) MUR; (b) WOR.

Table 3. Median dose to parotid glands [Gy]

Patient No.	Right	Left
1	26.5	24.5
2	22.3	21.8
3	26.0	24.7
4	19.8	20.3
5	22.7	21.2
6	20.1	20.5

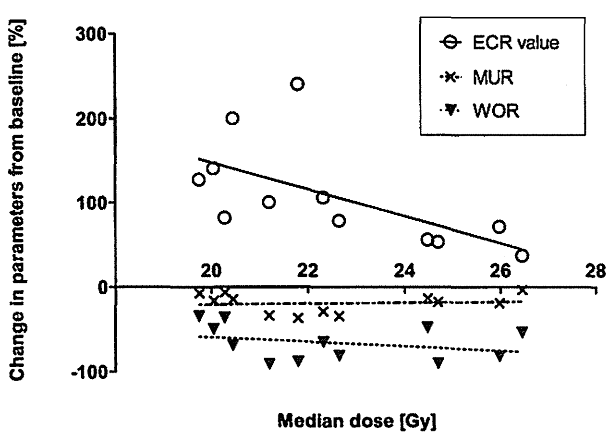


Fig. 4. Correlations between percentage change in parameters from baseline and median dose to parotid glands.

in MUR at 3–5 months after chemoradiotherapy and median dose to the parotid gland was not significant (Pearson correlation, r = 0.11, p = 0.74). The correlation between percentage change in WOR at 3–5 months after chemoradiotherapy and median dose to the parotid gland was also not significant (Pearson correlation, r = –0.31, p = 0.33).

DISCUSSION

Matsushima *et al.* previously reported ECRI as a potentially useful method for evaluating the efficacy of sentinel lymph node biopsy[9,10] and for cellular density imaging of axillary lymph nodes.[11] Yuen *et al.* reported ECRI as a feasible imaging technique for demonstrating breast cancer.[12] ECRI can thus detect minute changes in molecular and organizational structure.[8]

The present study represents the first trial of evaluating parotid gland function after chemoradiotherapy using ECRI. Parotid gland evaluation by MRI has been reported using ADC, which detects the motion of water molecules and microcirculatory blood flow.[5–7] Theony *et al.* reported that ADC value decreased immediately after taste stimulation, then increased until static state.[5] Dirix *et al.* reported that ADC value decreased significantly after irradiation.[6] Likewise, Lin *et al.* reported that ADC value decreased significantly after irradiation, and correlated with parameters obtained by salivary scintigraphy (uptake rate; r = 0.36, $p < 0.01$, MUR; r = 0.33, $p < 0.01$).[7] In our results, correlation coefficients between ECR and MUR were –0.55 ($p < 0.01$) in the pre-treatment group and –0.50 ($p < 0.05$) in the post-treatment group. The correlation coefficient between ECR and MUR was higher than that between ADC and MUR in past studies.[7] The reason why ECR correlated with MUR before chemoradiotherapy is as follows. When capacities of blood vessel lumens and intercellular spaces are large, C_{vpp} / C_{max} is low, and MUR (defined as $1 - C_{vpp} / C_{max}$) is high. Conversely, cell densities are relatively decreased, and the ECR (expressing cell density) is thus low. ECR thus showed a negative correlation with MUR. Moreover, ECR showed a correlation with MUR in the post-treatment group for the following reasons. Animal experiments have identified shrinkage of irradiated parotid glands.[17] Likewise, the parotid gland after chemoradiotherapy shrank in the present study (Fig. 2). ECR shows a high value due to the rise in cell density, while MUR was low due to decreased free water and the narrowness of the free water division, with shrinkage of gland tissues. ECR therefore shows a negative correlation with MUR in the post-treatment group. This relationship suggests that ECR value can be used to evaluate uptake function of the parotid gland after chemoradiotherapy without exposure to radiation. In addition, as ECRI can provide a 2-dimensional color map (Fig. 2), areas of weak uptake function in the parotid gland can be identified visually. The details of mechanism for the uptake of saliva are unknown. Therefore, the visualization of uptake function may contribute for the clarification of the loss part of uptake function of saliva. The correlation coefficients between ECR and WOR were –0.32 in the pre-treatment group (Pearson correlation, $p = 0.12$) and –0.06 in the post-treatment group (Pearson correlation, $p = 0.79$) (Fig. 3b). However, as the stimulation of the parotid gland by for example lemon juice was not performed as in the scintigraphy protocol during MRI, both exams could not be compared.

On salivary scintigraphy, dose-response with parotid gland function has been studied by other investigators,[1–3,18–20] Roesink *et al.* found a significant correlation between salivary excretion factor (defined as the percentage of activity in the parotid gland that disappeared within 15 min following administration of carbachol) and mean radiation dose to the parotid glands.[3] However, in our research, WOR did not show a linear correlation with radiation dose to the parotid glands (Fig. 4). This lack of correlation may be due to low number of patients and differences in dose ranges applied in this study. Moreover, the difference between median and mean doses might be involved. On the other hand, calculations of secretory functions (such as salivary excretion factor and WOR) and uptake functions (such as MUR) have been widely recognized for salivary scintigraphy. However, dose-response for uptake function has not been reported. In our research, the percentage change in MUR at 3–5 months after chemoradiotherapy did not show a linear correlation with median radiation dose to the parotid gland (Pearson correlation, $r = 0.11$, $p = 0.74$). Conversely, the percentage change in ECR values at 3–5 months after chemoradiotherapy showed a linear correlation with median radiation dose to the parotid gland (Pearson correlation, $r = -0.62$, $p < 0.05$). ECR thus showed a linear correlation with median radiation dose to parotid glands in the range of 19.8–26.5 Gy. The reason why ECR correlates with median radiation dose to the parotid gland can be described as follows from the perspective of cell density. In this research, cell-density-weighted images were obtained by irradiating the saturation pulse at a frequency 7 ppm downfield from the center frequency of water. Matsushima *et al.* reported that ECR correlated with cell density in clinical situations.[11] In addition, the number of acinar cells is known to be decreased in irradiated salivary gland.[21–27] Li *et al.* reported that the number of acinar cells in irradiated parotid glands was decreased at 16 weeks after radiotherapy.[27] This duration after radiotherapy is similar to that used in our research. Loss of acinar cells is markedly increased with increasing dose to the parotid gland.[26,27] The percentage change in ECR values at 3–5 months after chemoradiotherapy thus shows a clear inverse correlation with median radiation dose to the parotid gland. This suggests that ECR value can be used to predict uptake function of the parotid gland after chemoradiotherapy.

In conclusion, we verified that ECRI is useful for evaluating parotid gland function after chemoradiotherapy. ECRI allowed visual evaluation of uptake function in the parotid gland without exposure to radiation.

ACKNOWLEDGEMENTS

We are indebted to Masataka Murakami at National Institute for Physiological Sciences and Seiichi Era at Gifu University Graduate School of Medicine for many helpful discussions in the course of this investigation.

REFERENCES

1. Munter MW, *et al* (2007) Changes in salivary gland function after radiotherapy of head and neck tumors measured by quantitative pertechnetate scintigraphy: comparison of intensity-modulated radiotherapy and conventional radiation therapy with and without Amifostine. Int J Radiat Oncol Biol Phys **67**(3): 651–659.
2. Bussels B, *et al* (2004) Dose-response relationships within the parotid gland after radiotherapy for head and neck cancer. Radiother Oncol **73**(3): 297–306.
3. Roesink JM, *et al* (2004) Scintigraphic assessment of early and late parotid gland function after radiotherapy for head-and-neck cancer: a prospective study of dose-volume response relationships. Int J Radiat Oncol Biol Phys **58**(5): 1451–1460.
4. ICRP Publication 53 (1987) Radiation dose to patients from radiopharmaceuticals.
5. Thoeny HC, *et al* (2005) Gustatory stimulation changes the apparent diffusion coefficient of salivary glands: initial experience. Radiology **235**(2): 629–634.
6. Dirix P, *et al* (2008) Diffusion-weighted magnetic resonance imaging to evaluate major salivary gland function before and after radiotherapy. Int J Radiat Oncol Biol Phys **71**(5): 1365–1371.
7. Zhang L, *et al* (2001) Yoshimura R, Shibuya H. Functional evaluation with intravoxel incoherent motion echo-planar MRI in irradiated salivary glands: a correlative study with salivary gland scintigraphy. J Magn Reson Imaging **14**(3): 223–229.
8. Sogami M, *et al* (2001) Basic studies on the equivalent cross-relaxation rate imaging (equivalent CRI)--phantom studies. NMR Biomed **14**(6): 367–375.
9. Matsushima S, *et al* (2005) Equivalent cross-relaxation rate imaging for sentinel lymph node biopsy in breast carcinoma. Magn Reson Med **54**(5): 1300–1304.
10. Matsushima S, *et al* (2003) Equivalent cross relaxation rate image for decreasing a false negative case of sentinel lymph node biopsy. Magn Reson Imaging **21**(9): 1045–1047.
11. Mastsushima S, *et al* (2008) Equivalent cross-relaxation rate imaging of axillary lymph nodes in breast cancer. J Magn Reson Imaging **27**(6): 1278–1283.
12. Yuen S, *et al* (2004) Equivalent cross-relaxation rate imaging of breast cancer. J Magn Reson Imaging **20**(1): 56–65.
13. Fleming ID, Cooper JS and Henson DE (1997) AJCC cancer staging manual. 5th ed. Philadelphia: J. B. Lippincott.

14. Forrest LJ, *et al* (2004) The utility of megavoltage computed tomography images from a helical tomotherapy system for setup verification purposes. Int J Radiat Oncol Biol Phys **60**(5): 1639–1644.
15. Langen KM, *et al* (2005). Initial experience with megavoltage (MV) CT guidance for daily prostate alignments. Int J Radiat Oncol Biol Phys **62**(5): 1517–1524.
16. Fuwa N, *et al* (2002) Phase I study of combination chemotherapy with 5-fluorouracil (5-FU) and nedaplatin (NDP): adverse effects and eecommended dose of NDP administered after 5-FU. Am J Clin Oncol **25**(6): 565–569.
17. Vasquez Osorio EM, *et al* (2008) Local anatomic changes in parotid and submandibular glands during radiotherapy for oropharynx cancer and correlation with dose, studied in detail with nonrigid registration. Int J Radiat Oncol Biol Phys **70**(3): 875–882.
18. van Acker F, *et al* (2001) The utility of SPECT in determining the relationship between radiation dose and salivary gland dysfunction after radiotherapy. Nucl Med Commun **22**(2): 225–231.
19. Tenhunen M, *et al* (2008) Scintigraphy in prediction of the salivary gland function after gland-sparing intensity modulated radiation therapy for head and neck cancer. Radiother Oncol **87**(2): 260–267.
20. Maes A, *et al* (2002) Preservation of parotid function with uncomplicated conformal radiotherapy. Radiother Oncol **63**(2): 203–211.
21. Price RE, *et al* (1995) Effects of continuous hyperfractionated accelerated and conventionally fractionated radiotherapy on the parotid and submandibular salivary glands of rhesus monkeys. Radiother Oncol **34**(1): 39–46.
22. Coppes RP, Vissink A and Konings AW (2002) Comparison of radiosensitivity of rat parotid and submandibular glands after different radiation schedules. Radiother Oncol **63**(3): 321–328.
23. Urek MM, *et al* (2005) Early and late effects of X-irradiation on submandibular gland: a morphological study in mice. Arch Med Res **36**(4): 339–343.
24. Cooper JS, *et al* (1995) Late effects of radiation therapy in the head and neck region. Int J Radiat Oncol Biol Phys **31**(5): 1141–1164.
25. Konings AW, Coppes RP and Vissink A (2005) On the mechanism of salivary gland radiosensitivity. Int J Radiat Oncol Biol Phys **62**(4): 1187–1194.
26. Muhvic-Urek M, *et al* (2006) Imbalance between apoptosis and proliferation causes late radiation damage of salivary gland in mouse. Physiol Res **55**(1): 89–95.
27. Li J, *et al* (2005) Structural and functional characteristics of irradiation damage to parotid glands in the miniature pig. Int J Radiat Oncol Biol Phys **62**(5): 1510–1516.

Received on April 11, 2011
Revision received on October 4, 2011
Accepted on October 5, 2011

Journal of Radiation Research, 2012, 53, 906–915
doi: 10.1093/jrr/rrs052 Advance Access Publication 22 July 2012

Treatment outcomes of definitive chemoradiotherapy for patients with hypopharyngeal cancer

Rie NAKAHARA[1,2,*], Takeshi KODAIRA[1], Kazuhisa FURUTANI[1], Hiroyuki TACHIBANA[1], Natsuo TOMITA[1], Haruo INOKUCHI[1], Nobutaka MIZOGUCHI[1], Yoko GOTO[1], Yoshiyuki ITO[2] and Shinji NAGANAWA[2]

[1]Department of Radiation Oncology, Aichi Cancer Center Hospital, Aichi, Japan
[2]Department of Radiology, Nagoya University Graduate School of Medicine, Aichi, Japan
*Corresponding author. Department of Radiology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Aichi, Japan; Tel: +81-52-744-2327; Fax: +81-52-744-2335; Email: rie-naka@med.nagoya-u.ac.jp

(Received 6 March 2012; revised 28 May 2012; accepted 13 June 2012)

We analyzed the efficacy of definitive chemoradiotherapy (CRT) for patients with hypopharyngeal cancer (HPC). Subjects comprised 97 patients who were treated with definitive CRT from 1990 to 2006. Sixty-one patients (62.9%) with resectable disease who aimed to preserve the larynx received induction chemotherapy (ICT), whereas 36 patients (37.1%) with resectable disease who refused an operation or who had unresectable disease received primary alternating CRT or concurrent CRT (non-ICT). The median dose to the primary lesion was 66 Gy. The median follow-up time was 77 months. The 5-year rates of overall survival (OS), progression-free survival (PFS), local control (LC), and laryngeal preservation were 68.7%, 57.5%, 79.1%, and 70.3%, respectively. The T-stage was a significant prognostic factor in terms of OS, PFS and LC in both univariate and multivariate analyses. The 5-year rates of PFS were 45.4% for the ICT group and 81.9% for the non-ICT group. The difference between these groups was significant with univariate analysis ($P = 0.006$). Acute toxicity of Grade 3 to 4 was observed in 34 patients (35.1%). Grade 3 dysphagia occurred in 20 patients (20.6%). Twenty-nine (29.8%) of 44 patients with second primary cancer had esophageal cancer. Seventeen of 29 patients had manageable superficial esophageal cancer. The clinical efficacy of definitive CRT for HPC is thought to be promising in terms of not only organ preservation but also disease control. Second primary cancer may have a clinical impact on the outcome for HPC patients, and special care should be taken when screening at follow-up.

Keywords: hypopharyngeal cancer; chemoradiotherapy; survival; laryngeal preservation; local control

INTRODUCTION

Hypopharyngeal cancer (HPC) is usually diagnosed at an advanced stage and treated using multidisciplinary modalities. Chemoradiotherapy (CRT) is currently considered the standard treatment for unresectable head and neck cancer. It is also thought to be a treatment option for patients with resectable locally advanced lesions. Therefore, the number of patients treated with CRT, especially for organ preservation, is increasing. Several types of chemotherapy regimens have been reported to have positive outcomes, and concurrent CRT (CCRT) has become a standard treatment for patients with the aim of preserving the larynx [1, 2]. However, CCRT is reported to be accompanied by markedly increased toxicity compared to radiation alone, and patients who receive CCRT followed by salvage surgery sometimes have serious and intractable complications [3].

Induction chemotherapy (ICT) is often used in clinical practice for patients with advanced HPC and plays a considerable role in organ preservation and reduction of distant metastases [4]. To reduce treatment toxicities and avoid the risk of salvage surgery, we used ICT for patients with resectable tumors with the aim of optimally selecting candidates for larynx preservation.

CCRT regimens with cisplatin (CDDP) and 5-fluorouracil (5-FU) have been used in patients with advanced head and neck cancer. However, severe acute mucositis has been reported with these regimens [2]. For patients treated with definitive radiotherapy, we have used alternating CRT to reduce acute mucositis during treatment by avoiding concomitant administration of 5-FU without sacrificing the intensity of the chemotherapy.

To evaluate its clinical efficacy, we retrospectively reviewed the clinical results of HPC patients treated with definitive CRT at Aichi Cancer Center Hospital with relatively long follow-up.

MATERIALS AND METHODS

Patient and tumor characteristics

Ninety-seven patients with non-metastatic squamous cell HPC were treated with definitive CRT at Aichi Cancer Center Hospital between 1990 and 2006. The characteristics of the 97 patients are summarized in Table 1. The enrollment criteria were as follows: previously untreated and histologically confirmed squamous cell cancer without distant metastasis. Patients who received radiotherapy alone were excluded from this study. The treatment content of this cohort was as follows: patients with resectable disease and an aim to preserve the larynx received ICT followed by CCRT. Patients who did not want an operation or patients with unresectable disease received alternating CRT or CCRT. Tumors were staged according to the American Joint Committee on Cancer Staging, 5th version [5].

The pre-treatment evaluation consisted of a physical examination, laryngoscopy, biopsy of the primary site, chest radiography, computed tomography (CT) of the cervix and chest, and magnetic resonance imaging (MRI) of the primary site and neck disease. 18-fluorodeoxyglucose-positron emission tomography (18F-FDG PET) or PET/CT was also used after 2001.

Total parenteral nutrition or nasogastric (NG) tube feeding was performed on 39 patients (40%) due to inadequate oral

Table 1. Patient characteristics and treatment contents

Characteristics		All	ICT	non-ICT
Sex	Male	92	59	33
	Female	5	2	3
Age (years)	Median	65	64	66
	Range	36–86	36–80	43–86
Subsite	Postcricoid region	16	7	9
	Pyriform sinus	72	51	21
	Posterior wall	9	3	6
T	1	11	8	3
	2	43	20	23
	3	35	26	9
	4	8	7	1
N	0	33	16	17
	1	16	8	8
	2a	7	6	1
	2b	17	13	4
	2c	17	11	6
	3	7	7	0
Stage	I	5	2	3
	II	19	6	13
	III	22	13	9
	IVA	43	33	10
	IVB	8	7	1
Radiotherapydose (Gy)	Median	66.6	66.6	66.6
	Range	30.6–76.9	30.6–76.9	36–76
IMRT		6	6	0

intake during treatment. In this study a planned gastrostomy was not intended during treatment.

A planned neck dissection was performed in 21 patients (21.6%) who had highly advanced nodal disease (N2b, N2c, or N3) or residual neck disease after CRT. After 2001 the indication of a planned neck dissection was decided by 18F-FDG PET or PET/CT taken within three months after completion of CRT.

Radiotherapy

Ninety-one patients were treated with 3D conformal radiotherapy, and six patients were treated with intensity-modulated radiotherapy (IMRT) using helical tomotherapy. Six patients who were treated with IMRT received ICT. External beam radiotherapy was administered five times a week at a dose of 1.8–2.0 Gy in once-daily fractions using 6-MV photon beams. Treatment planning was made by an X-ray simulator or radiation planning system for 3D conformal radiotherapy.

Patients having conventional radiotherapy were initially treated with opposed lateral fields to the primary and upper neck areas matched to the anterior fields for the lower neck and supraclavicular regions up to 36–40 Gy. The primary lesion and involved neck nodes were further boosted to 66–70 Gy with oblique parallel opposed fields or a dynamic conformal method in order to spare the spinal cord. The gross tumor volume (GTV) was defined as the total volume of the primary lesion and the involved lymph nodes. The GTV was determined by a laryngoscopy, CT, MRI and 18F-FDG PET scan. A positive lymph node was defined as >10 mm in the short axis on CT/MRI or positive 18F-FDG PET findings. The clinical target volume (CTV) was defined as the GTV plus a 10-mm margin to cover microscopic disease. The planning target volume (PTV) was defined as the CTV plus 5-mm margins in every direction. The CTV prophylactic was designed to include the lymph nodes at Levels II–V, the retropharyngeal node and the subclavicular lymph node. The PTV prophylactic was defined as the CTV prophylactic plus 5-mm margins. The initial field included the PTV prophylactic.

Patients receiving IMRT were defined the same as patients receiving conventional radiotherapy. All patients treated with IMRT underwent treatment planning using simultaneous integrated boost methods. A planned delivery dose at D95 was calculated at the PTV/PTV prophylactic for 70 Gy/54 Gy in 35 fractions. Among the patients in this cohort, the median dose to the primary site was 66 Gy (range 30.6–76.9 Gy) and that for the involved lymph node was 63 Gy (range 30–78 Gy).

Chemotherapy

Patients were allocated to receive the ICT or non-ICT protocol (Fig. 1). Patients with resectable disease who aimed to preserve the larynx received ICT, and those who acquired a sufficient response were added to the radiotherapy or CRT protocols. Patients with resectable disease who refused an operation or who had unresectable disease underwent the non-ICT protocol. Of 97 patients, 80 (82%) underwent multi-agent chemotherapy consisting of CDDP and 5-FU (FP) or nedaplatin and 5-FU (FN). Chemotherapy consisted of continuous infusion of 5-FU at a dose of 600 mg/m^2/24 h for five days (Days 1–5). CDDP was given at a dose of 80 mg/m^2/24 h for two days (Days 6 and 7), or nedaplatin was given at a dose of 130 mg/m^2/6 h for one day (Day 6). ICT was used in 61 patients (63%). In the ICT protocol, two courses of FP were administered to 52 patients. Patients who achieved a complete response (CR) with ICT were treated with radiotherapy only, whereas patients who achieved a partial response (PR) received CCRT, which consisted of weekly or triweekly

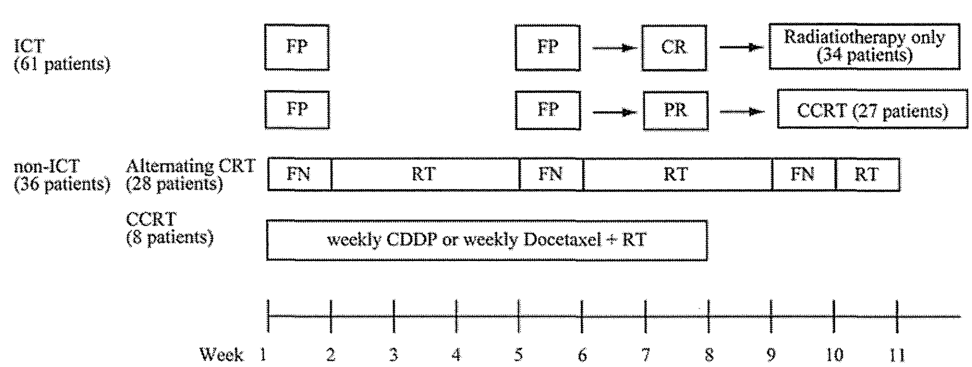


Fig. 1. Treatment scheme of the induction chemotherapy (ICT) group and the non-ICT group. ICT was used in 61 patients (63%). In the ICT protocol, two courses of 5-FU and CDDP (FP) were administered to 52 patients. Patients who achieved a complete response with ICT were treated with radiotherapy only, whereas patients who acquired a partial response received concurrent chemoradiotherapy (CCRT). Non-ICT was used in 36 patients (37%), 28 of whom were administered alternating chemoradiotherapy (CRT) consisting of three cycles of 5-FU and nedaplatin (FN) or 5-FU and CDDP (FP). Another eight patients received CCRT consisting of weekly CDDP or weekly docetaxel.

CDDP. Non-ICT was used in 36 patients (37%), 28 of whom were administered alternating CRT consisting of three cycles of FN or FP. Another eight patients received CCRT consisting of weekly CDDP or weekly docetaxel.

Follow-up

Patients were followed up monthly during the first six months and then every 3–6 months thereafter. Follow-up examinations included a physical examination, laryngoscopy, and a CT or MRI of the neck. 18F-FDG PET or PET/CT was also performed at least annually during follow-ups after 2001. An upper gastrointestinal endoscopy was performed once a year to detect double cancer after the end of CRT. Acute and late toxicity were scored according to the Common Terminology Criteria of Adverse Events, version 3.0 [6].

Statistical analysis

The survival period was calculated from the start of treatment to the date of death or the last follow-up. Progression-free survival (PFS) was defined as the time until an event of disease progression or death of any cause. Local control (LC) was defined as the time until an event of local disease progression or a residual tumor. Laryngeal preservation time was defined as the time until laryngectomy for any reason, except for partial excision. The rates of overall survival (OS), PFS, LC and laryngeal preservation were calculated using the Kaplan-Meier method. The difference between the two groups was tested with the log-rank test. Multivariate analyses were performed using Cox's proportion hazards model. A probability value of <0.05 was defined as significant.

RESULTS

Treatment outcomes

Ninety-four patients (96.9%) completed their scheduled CRT. The median duration of the overall time of ICT-plus-CRT or radiotherapy only was 104 days, and that of alternating CRT was 63 days. At the primary site, 88 patients (90.7%) achieved a CR, 7 (7.2%) had a PR, one (1.0%) had a mild response (MR), and one (1.0%) had progressive disease (PD) after completion of radiotherapy. As for neck disease, 75 patients (79.8%) achieved CR, 17 (17.5%) had PR, one (1.0%) had MR, one (1.0%) had no change, and two (2.0%) had PD. The median follow-up time of this cohort was 77.7 months (range 31.1–175 months). At the last follow-up, 58 (59.8%) of the 97 patients were alive, and 39 (40.2%) had died, of whom 25 (25.7%) patients died from HPC, five patients died from double cancer (two from esophageal cancer, one from lung cancer, one from stomach cancer and one from colon cancer), and nine patients died from other causes (pneumonia in four patients, aspiration asphyxia in one patient and unknown in four patients). Thirty-nine patients (41.2%) were alive without disease and 19 (19.6%) were alive with recurrent disease. The 5-year rates of OS, PFS, LC and laryngeal preservation rates for all patients were 68.7%, 57.5%, 79.1% and 70.3%, respectively. Figure 2 shows the OS curve for all patients and groups. The 5-year rate of OS of groups divided by Stage was 76.9% for Stage I–II and 51.5% for Stage III–IV. The 5-year rate of PFS was 72.3% for Stage I–II and 41.1% for Stage III–IV. The 5-year laryngeal preservation rates of both groups by stage were 85.4% for Stage I–II and 73.2% for Stage III–IV. The LC rate of groups divided by T-stage was 90.0% for T1, 90.1% for T2, 58.5% for T3, and 50.0% for T4 (Fig. 3). In the subgroup analysis, PFS rates at five years were 45.4% in the ICT group and 81.9% in the non-ICT group (Fig. 4); the difference in the PFS rate between these groups was statistically significant ($P = 0.006$).

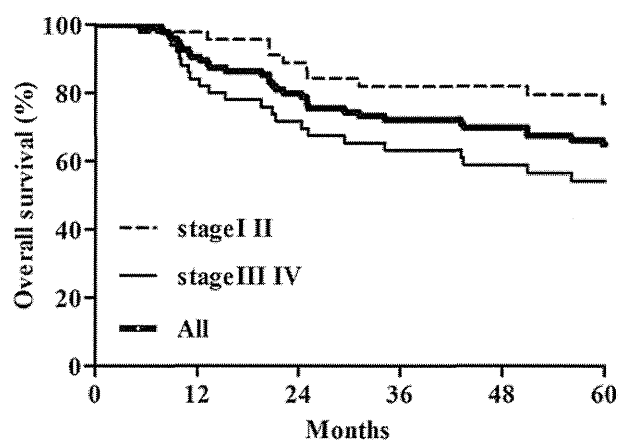


Fig. 2. Overall survival curves of all patients and groups divided by stage.

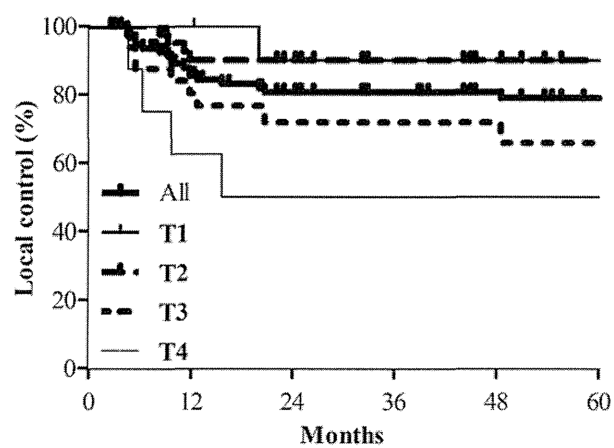


Fig. 3. Local control curves of all patients and groups divided by T-stage.

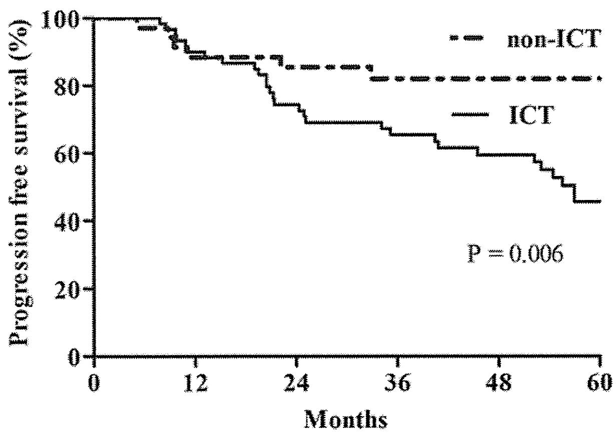


Fig. 4. Progression-free survival of groups using induction chemotherapy (ICT) and non-ICT. The difference between the two groups was statistically significant ($P = 0.006$).

Table 2. Second primary cancer

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

Patterns of treatment failure

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

Second primary cancer

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

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

Univariate and multivariate analysis

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

Treatment toxicities

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

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

DISCUSSION

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

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

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

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

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

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

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

Table 5. Incidence of moderate to severe toxicity

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

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

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

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

Table 6. Results of the treatment outcome for hypopharyngeal cancer

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

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

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

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

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

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

REFERENCES

1. Pignon JP, Bourhis J, Domenge C *et al.* Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet* 2000; **355**:949–55.
2. Adelstein DJ, Li Y, Adams GL *et al.* An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol* 2003;**21**:92–8.
3. Taki S, Homma A, Oridate N *et al.* Salvage surgery for local recurrence after chemoradiotherapy or radiotherapy in hypopharyngeal cancer patients. *Eur Arch Otorhinolaryngol* 2010;**267**:1765–9.
4. Lefebvre JL, Chevalier D, Luboinski B *et al.* Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. *J Natl Cancer Inst* 1996;**88**:890–9.
5. American Joint Committee on Cancer: AJCC Cancer Staging Manual. ed Fifth. Philadelphia: Lippincott Williams and Wilkins; 1997.
6. Cancer Therapy Evaluation Program. Common terminology criteria for adverse events version 3.0 (CTCAE). Bethesda: