3 or higher leukopenia, neutropenia, thrombocytopenia and anemia occurred in 37, 22, 11 and 18 patients, respectively. Grade 3 or higher mucositis and dermatitis developed in 20 and 18 patients, respectively.

Late toxicities are listed in Table 6. Three Grade 3 osteomyelitis of the mandible occurred in this series. One patient died because of late toxicity due to lethal mucosal bleeding. The patient diagnosed as cT3N1M0 with histology of Type I received 80 Gy to the primary site including additional SRT boosts of 10 Gy due to an insufficient response at the planned 70 Gy. The patient developed active mucosal bleeding in the nasopharynx, and died five years later. We experienced no Grade 3 or higher late toxicity of brain necrosis, visual disturbance or swallowing disturbance.

DISCUSSION

A randomized control trial showed survival advantages of concurrent chemoradiotherapy over radiation alone, thus it is believed to be the standard treatment for locally advanced NPC. In the IGS, Stage III–IVB patients with NPC were randomized to CRT or RT, and the combined CRT group was treated with radiation and concurrent triweekly CDDP followed by three adjuvant cycles of FP [1]. The 3-year rate of OAS of the RT-only group was significantly lower than that of the CRT group (46% vs 76%; $P < 0.001$), and the same results were noted for the 3-year rate of PFS (24% vs 69%; $P < 0.001$). However, some problems with the results from the IGS were identified. Firstly, results of the RT arm in the IGS seem to be unacceptably bad because the reported 3-year rates of OAS for the same stages were over 70%. One of the reasons for this discrepancy is that the rate of WHO type I histology in the IGS series (24%) is larger than that of endemic regions, which is believed to have adversely impacted on clinical results. Secondly, the compliance of chemotherapy was insufficient in the IGS. The completion rates of planned chemotherapy of concurrent and adjuvant series were reported as 63% and 55%, respectively. In order to confirm this result, the IGS should be extrapolated in endemic regions [4]. In Hong Kong, the NPC-9901 trial on patients with T1-4N2-3M0 disease was designed to confirm the therapeutic ratio achieved by the IGS regimen. Regarding the compliance of chemotherapy, 65% of patients completed all six cycles, and 79% had five cycles. The CRT arm achieved significantly higher failure-free survival (72% vs 62% at 3 years, $P = 0.027$), mostly as a result of improvements in locoregional control. However, DMFS did not improve significantly (76% vs 73%, $P = 0.47$) and OAS was identical (78% vs 78%, $P = 0.97$). In other RCTs reported by Lin and Chen, the CRT arm significantly improved PFS and OAS [2, 3].

There is also evidence by meta-analysis dealing with eight randomized trials of 1753 patients regarding locally advanced NPC. In this analysis, the pooled hazard ratio of death for adding chemotherapy was 0.82 (95% confidence interval, 0.71–0.94; $P = 0.006$), corresponding to an absolute survival benefit of 6% at 5 years (56% vs 62%). A

Table 4. Compliance of chemotherapy

	n	median (range)
Total cycles given		
1	2	
2	7	
≥3	87	
Total dose given		
Cisplatin (mg/m^2)		300 (150–340)
Nedaplatin (mg/m^2)		375 (80–400)
5-fluorouracil (mg/m^2)		12 000 (3050–12 000)

Table 5. Acute, severe and life-threatening toxicities due to chemoradiotherapy

Toxicity	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5	unknown	≥ Gr 3
Leukopenia	4	12	43	32	5	0	4	37
Granulocytopenia	18	27	28	17	5	0	5	22
Anemia	6	33	39	14	4	0	4	18
Thrombocytopenia	28	37	10	8	3	0	4	11
Liver dysfunction	71	20	5	1	0	0	1	1
Renal dysfunction	71	28	0	0	0	0	1	0
Vomiting	33	14	50	3	0	0	0	3
Mucositis	0	13	67	19	1	0	0	20
Dermatitis	0	37	45	17	1	0	0	18
Salivary gland changes	1	13	86	0	0	0	0	0

Table 6. Late, severe and life-threatening toxicities due to chemoradiotherapy

Toxicity	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5	≥ Gr 3
Swallowing dysfunction	95	4	1	0	0	0	0
Visual dysfunction	99	0	1	0	0	0	0
Hearing impairment	81	5	14	0	0	0	0
Osteomyelitis	96	0	1	3	0	0	3
Brain necrosis	99	1	0	0	0	0	0
Bleeding	99	1	0	0	0	1	1

significant interaction was observed between the timing of chemotherapy and overall survival ($P = 0.005$), with the highest benefit resulting from concomitant chemotherapy [5]. However, increasing acute toxicities caused by administration of chemotherapy were also reported in this analysis. In the IGS, acute toxicities of ≥ Grade 3 were reported as 50% and 76% for RT and CRT arms, respectively. Similarly, in the NPC-9901 trial, toxicities of ≥ Grade 3 were observed as 53% and 84% for RT and CRT arms, respectively ($P < 0.01$). The 3-year actuarial rate of late toxicity was slightly higher in the CRT arm than in that of the RT arm, although it was not significant (28% vs 13%, $P = 0.24$).

In our institute, we adopted alternating CRT for NPC from 1987. In a previous report, 32 patients with NPC received alternating CRT, and the 5-year rates of OAS and PFS were 75% and 63%, respectively. A Phase II study of alternating chemoradiotherapy for patients with NPC was performed in four medical institutions including our institution from 1997 and reported promising results with high compliance (91%), of which the 2-year OAS and PFS rates were 94% and 83%, respectively [10]. In the present study with longer follow-up and a larger cohort, the 5-year rates of OAS and PFS were 78.1% and 68.3%, respectively. We think these data are comparable with previous series. In addition, we believe that acute and late complication rates were sufficiently low according to longer follow-up with 65.9 months.

We believe alternating chemoradiotherapy has several advantages in CRT for NPC. Because the radiation field has to be large, severe mucositis and dermatitis sometimes develops and leads to a treatment break. In addition, late complications, such as disturbances in swallowing or hearing sometimes become significant problems. Alternating chemoradiotherapy has the potential benefit in reducing acute toxicities. As for reported data of the NPC-9901 trial, acute mucositis and skin reactions over Grade 3 were observed in 62% and 20% patients in the CRT arm, respectively. In the present study, acute mucositis or dermatitis of ≥ Grade 3 developed in 20% and 18%, respectively. By alternating chemotherapy and radiotherapy, we could also use intensive multi-agent chemotherapy regimens such as FP or FN without increasing acute and late complications. Although our data is a retrospective analysis in a single institute, the 5-year rate of OAS in the present study (78.1%) was more promising than that of the IGS trial (67%). Regarding the compliance of chemotherapy, over 90% patients in the present study could receive three courses of chemotherapy and 70% of our cohort had completed planned full doses. As a result the total dose of chemotherapy in patients who received a reduced dose was still about 80% of the planned dose. Our data is thought to be more encouraging than that of the IGS, in which only 55% patients completed the planned chemotherapy. Failure patterns in CRT for NPC patients are thought to be both loco-regional, but also in distant sites. In the present study, DMFS at 5-years was 87.8%, which was higher than that of the reported series. The 3-year DMFS rate of the NPC-9901 study was reported as 76%. We believe that it was caused by the advantages of intensive chemotherapy in the present study. An unexpected RT break was needed in 14 patients (14%), of which only 2 patients needed RT breaks longer than one week.

The argument against alternating CRT is that planned RT interruptions may lead to sacrifices in treatment efficacy. In many studies, it is well known that prolongation of overall treatment time negatively influences clinical outcomes. *In vitro*, accelerated repopulation occurred 28 days after the start of RT; thus, prolongation of treatment time led to the development of radiation resistance. In the present study, OTT was not significantly related to clinical outcome. One of the reasons is that the high compliance of the present study would have helped avoid essential prolongation of OTT in our cohort.

In the present series, WHO type I histopathology was a significantly unfavorable factor of both OAS and PFS. The incidence of WHO type I histology in Western countries is very different from East Asian countries. In the IGS series conducted in North America, the rate of WHO type I histology was 22%, which was higher than the rates in studies

conducted in endemic regions. WHO type I histopathology, keratinizing squamous cell carcinoma, was reported to be much less related to EBV infection than non-keratinizing carcinoma. It was also reported to be less sensitive to RT [11]. However, there are not so many reports regarding clinical results. One of the reasons is that the proportion of type I histopathology is very low in endemic regions. In Japan, the proportion of type I histopathology is about 20%, which was similar to North America. Kawashima *et al.* reported a Japanese multi-institutional survey of 333 NPC patients, in which the proportion of type I histopathology was 19% [12]. In that series, type I histopathology proved to be a significantly worse prognostic factor of OAS and PFS on both UVA and MVA. In the present study, the population of type I histopathology was 8%; however, these eight patients had remarkably poor prognosis. Six of the eight patients developed treatment failure. In our series, WHO type I histopathology was a significantly worse factor of both OAS (3-year rates; 50.5% vs 89.3%; $P < 0.0001$) and LRPFS (3-year rates; 21.4% vs 84.5%, $P < 0.0001$). The majority of failure patterns of these patients were in loco-regional sites. In order to improve treatment outcomes of these patients, dose escalation without increasing adverse events is believed to be promising. In recent years, intensity-modulated radiation therapy (IMRT) is widely used for head and neck cancer because of its dose conformity ability for PTV, reducing doses to normal tissue. RTOG 0225, a multi-institutional Phase II trial was conducted to test the feasibility of IMRT with or without chemotherapy for NPC. A 90% LRPF rate was reported as well as an acceptably low incidence of Grade 3 adverse events without xerostomia of Grade 4 [13]. In our institution, we started IMRT for NPC patients using Helical Tomotherapy until June 2006, and we have reported our preliminary clinical results [14]. In the future, dose escalation for patients with type I histopathology using IMRT will be helpful for improving clinical results.

The 5-year rates of PFS and LRPFS of patients with T4 were significantly inferior to those with T1–3, even though there was no significant difference in the 5-year rates of DMFS between these two groups. Because of the proximity of tumors to critical structures such as the brain-stem, spinal cord, optic pathway and temporal lobes, the radiation fields and dose coverages for primary tumors are often compromised. Preliminary results of radiation dose escalation for patients with T3–T4 NPC show good local control (2-year rate of locoregional control; 95.7%) and survival (2-year rate of OAS; 92.1%) [15]. For these patients, dose escalation using IMRT is also promising improved clinical results.

The 5-year rates of OAS and DMFS of patients with N3 were significantly inferior to those with N0–2 in the present series. On the other hand, N3 showed no apparent correlation with worsening LRPF. From this result, patients with N3 are expected to have a higher incidence of distant metastasis. Thus, a more effective regimen of chemotherapy should be considered to overcome limitations. In fact, TAX 324, a randomized Phase III trial, has shown the distinct survival advantages of multi-agent intensive chemotherapy including docetaxel and FP over PF for locally advanced head and neck cancer [16].

We believe that the present results for alternating chemoradiotherapy are promising compared to previously reported series of concurrent chemoradiotherapy. However, several subgroups with some risk factors proved to have insufficient outcomes. In order to refine clinical results without increasing adverse events, there is room for modification especially in patients with high-risk factors. Dose escalation using IMRT for type I histopathology and/or T4 disease and more intensive modifications of chemotherapy for N3 disease should be considered in future.

REFERENCES

1. Al-Sarraf M, LeBlanc M, Giri PG *et al.* Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol* 1998;**16**:1310–7.
2. Lin JC, Jan JS, Hsu CY *et al.* Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. *J Clin Oncol* 2003;**21**:631–7.
3. Chen Y, Liu MZ, Liang SB *et al.* Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of China. *Int J Radiat Oncol Biol Phys* 2008;**71**:1356–64.
4. Lee AW, Lau WH, Tung SY *et al.* Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. *J Clin Oncol* 2005;**23**:6966–75.
5. Baujat B, Audry H, Bourhis J *et al.* Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. *Int J Radiat Oncol Biol Phys* 2006;**64**:47–56.
6. Greene FL, Page DL, Fleming ID *et al.* AJCC cancer staging handbook from the AJCC cancer staging manual. 6th ed. New York: Springer; 2002.
7. Fuwa N, Ito Y, Kodaira T *et al.* Therapeutic results of alternating chemoradiotherapy for nasopharyngeal cancer using cisplatin and 5-fluorouracil: its usefulness and controversial points. *Jpn J Clin Oncol* 2001;**31**:589–95.
8. Cancer Therapy Evaluation Program. Common terminology criteria for adverse events version 3.0 (CTCAE). Bethesda: Chemoradiotherapy for hypopharyngeal cancer 9 National Cancer Institute, 2003. http://ctep.cancer.gov/forms/CTCAEv3.pdf.
9. Kaplan E, Meier P. Non-parametric estimation from incomplete observation. *J Am Stat Assoc* 1958;**53**:475–81.

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

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.

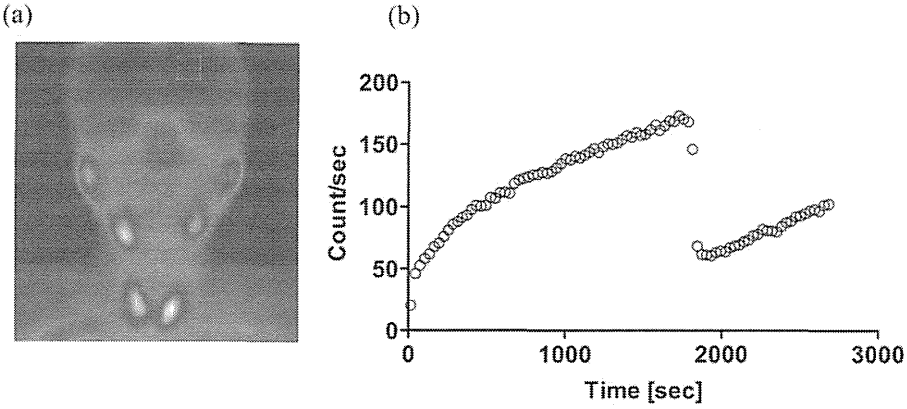

Fig. 1. (**a**) Planar image taken by salivary gland scintigraphy. ROIs were located for bilateral parotid glands and a frontal sinus. The count for the frontal sinus was used as the background level. (**b**) Representative time-activity curve (TAC) on a parotid gland. TAC on the parotid gland was created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

	Pre treatment series group (No. of parotid glands = 24)		Post treatment series group (No. of parotid glands = 24)
(a)			
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

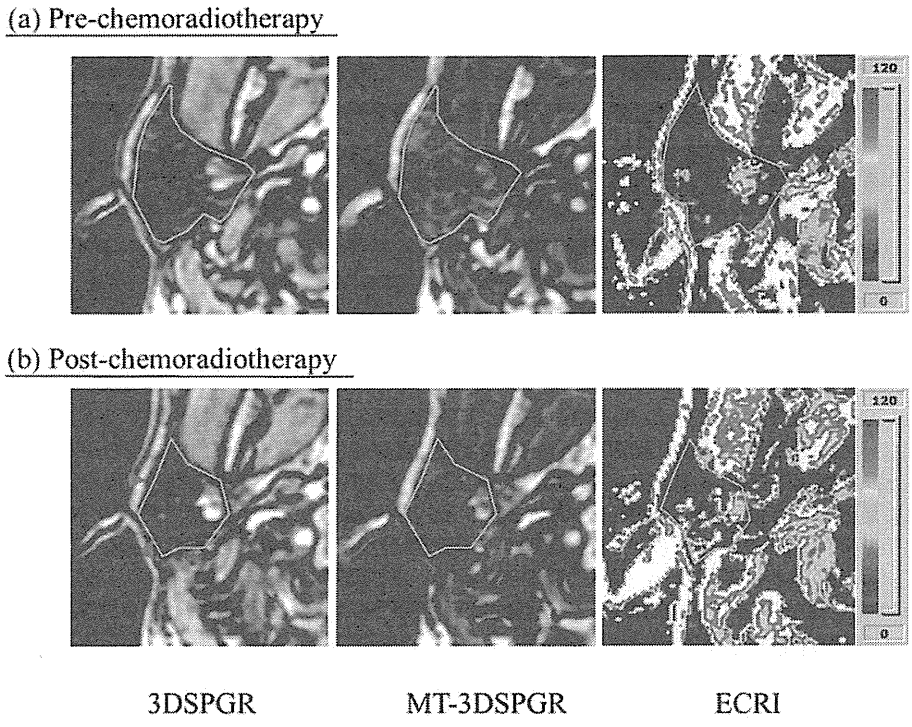

Fig. 2. Examples of 3DSPGR, MT-3DSPGR and ECR before (**a**) and after (**b**) chemoradiotherapy. Right parotid glands (areas surrounded by the yellow line) are shown in the axial plane. Volume reduction (indicated by arrowhead) was detected after chemoradiotherapy. ECRI was obtained using Equation 3.

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

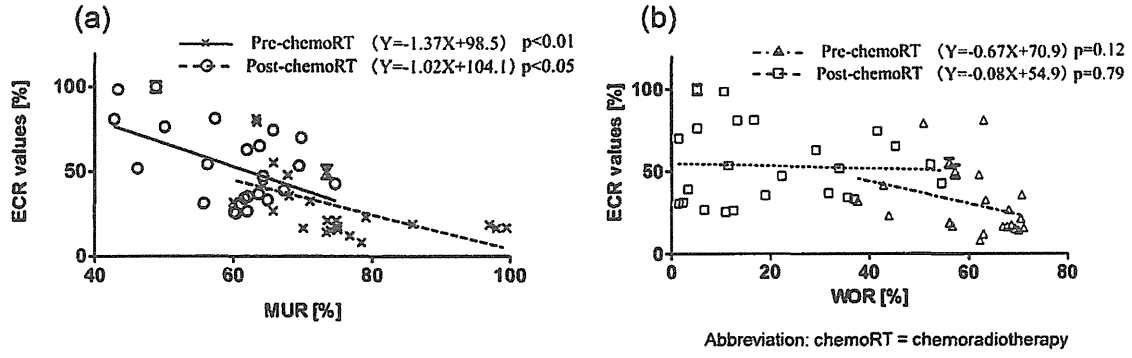

Fig. 3. Relationships between ECR value and salivary gland scintigraphy parameters. (a) MUR; (b) WOR.

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

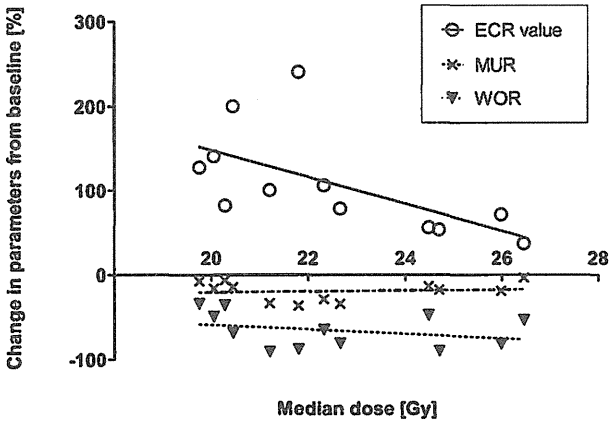

Fig. 4. Correlations between percentage change in parameters from baseline and median dose to parotid glands.

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

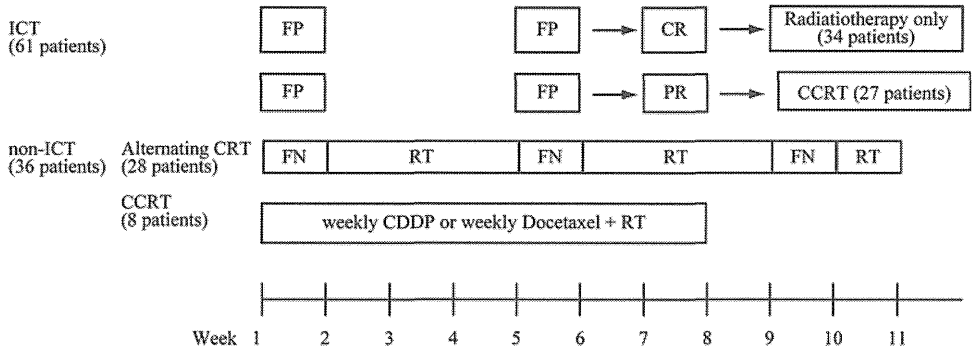

Fig. 1. Treatment scheme of the induction chemotherapy (ICT) group and the non-ICT group. ICT was used in 61 patients (63%). In the ICT protocol, two courses of 5-FU and CDDP (FP) were administered to 52 patients. Patients who achieved a complete response with ICT were treated with radiotherapy only, 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 ($P = 0.006$).

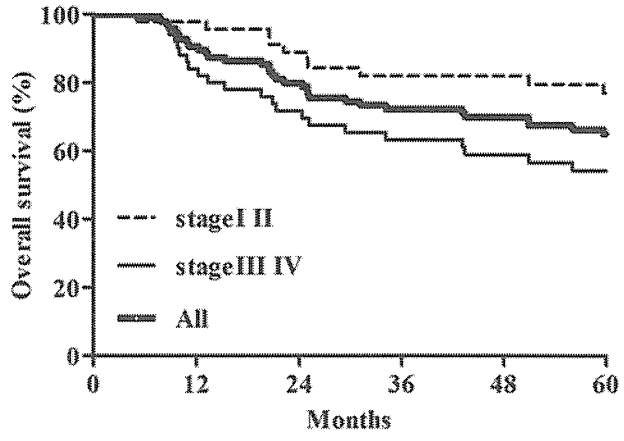

Fig. 2. Overall survival curves of all patients and groups divided by stage.

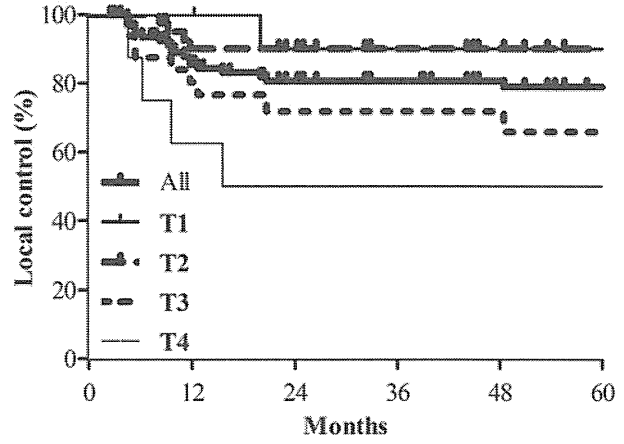

Fig. 3. Local control curves of all patients and groups divided by T-stage.

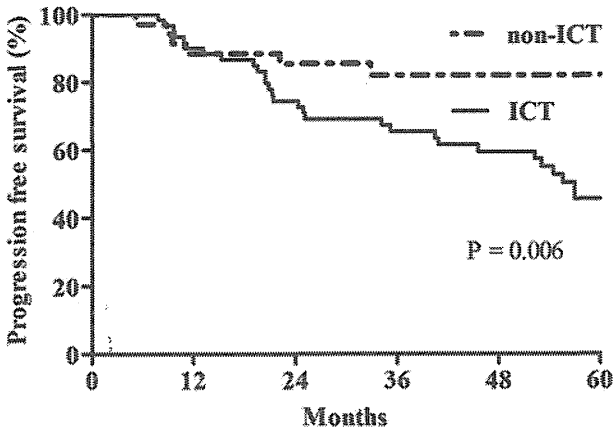

Fig. 4. Progression-free survival of groups using induction chemotherapy (ICT) and non-ICT. The difference between the two groups was statistically significant ($P = 0.006$).

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

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

Table 6. Results of the treatment outcome for hypopharyngeal cancer

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

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

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

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

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

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

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: