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Treatment outcomes of definitive chemoradiotherapy for patients with hypopharyngeal cancer

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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

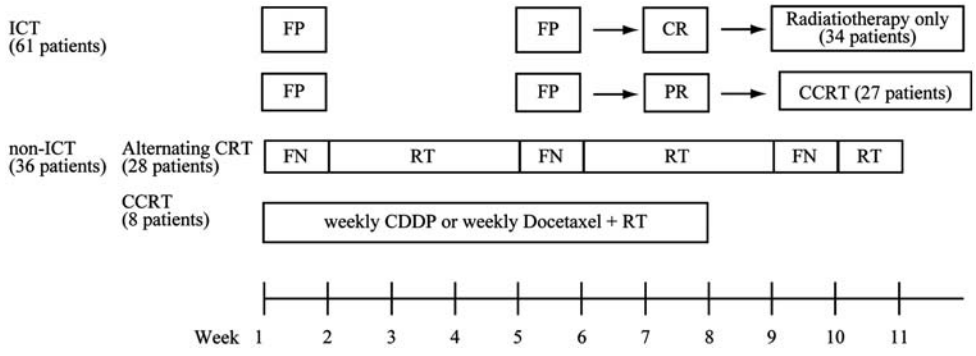

Fig. 1. Treatment scheme of the induction chemotherapy (ICT) group and the non-ICT group. ICT was used in 61 patients (63%). In the ICT protocol, two courses of 5-FU and CDDP (FP) were administered to 52 patients. Patients who achieved a complete response with ICT were treated with radiotherapy only,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

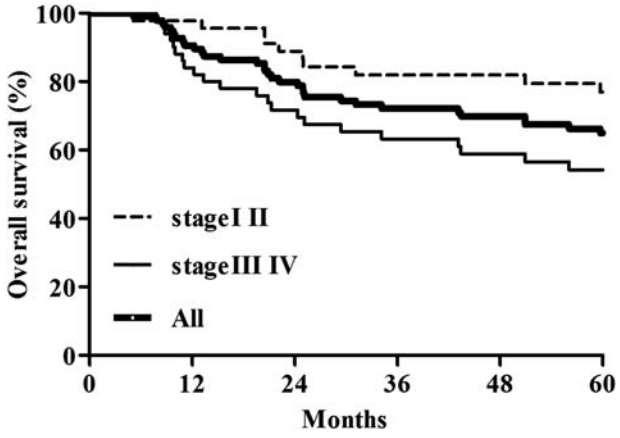

Fig. 2. Overall survival curves of all patients and groups divided by stage.

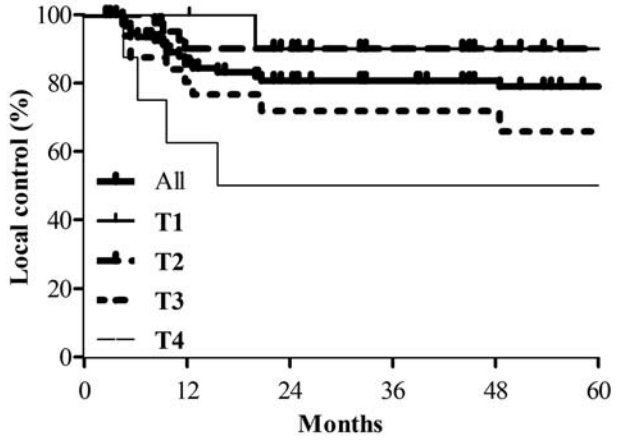

Fig. 3. Local control curves of all patients and groups divided by T-stage.

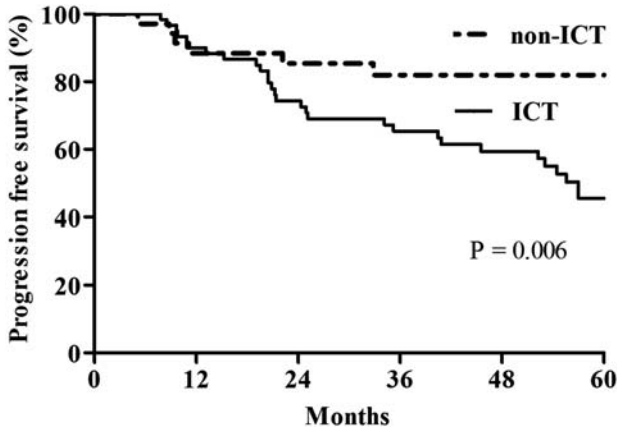

Fig. 4. Progression-free survival of groups using induction chemotherapy (ICT) and non-ICT. The difference between the two groups was statistically significant ($P = 0.006$).

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.

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