Clinical Outcomes of Hypopharyngeal Cancer Receiving Definitive Radiotherapy with Concurrent Chemotherapy

MASAKUNI SAKAGUCHI¹, TOSHIYA MAEBAYASHI¹, TAKUYA AIZAWA¹,
NAOYA ISHIBASHI¹ and TSUTOMU SAITO²

¹Department of Radiology, Nihon University School of Medicine, Tokyo, Japan;

²Sonodakai Radiation Oncology Clinic, Tokyo, Japan

Abstract. Aim: To evaluate clinical outcomes of concurrent chemoradiotherapy (CCRT) in patients with hypopharyngeal cancer (HPC). Patients and Methods: This retrospective study included 80 patients (75 males) aged 48 to 78 years (median=66 years) with a histological diagnosis of HPC. The 5-fluorouracil and cisplatin (FP) regimen was used until 2007 and then switched to the docetaxel, cisplatin, and 5-fluorouracil (TPF) regimen. Radiotherapy was administered to a total dose of 60 to 72 Gy (median=66 Gy). Results: The 5-year overall survival and disease-free survival rates were 49.3% and 60.7%, respectively. Improved disease-free survival was associated with lower N-stage (hazard ratio=0.249; 95% confidence interval=0.096-0.643; $p=0.041$). Conclusion: There were no significant differences in overall and disease-free survival between patients receiving CCRT with the TPF regimen and those who received FP for a long period of treatment but did not finish two courses.

Hypopharyngeal cancer (HPC) is usually diagnosed at an advanced stage (1). The prognosis for patients with squamous cell carcinoma (SCC) of the hypopharynx is among the worst types of head and neck carcinomas despite improvements in treatment (2). Locally advanced SCC of the hypopharynx is generally treated with surgery, with or without postoperative radiotherapy (RT). However, organ-preserving strategies that use induction chemotherapy and concurrent chemoradiotherapy (CCRT) have become a treatment option for patients with HPC who refuse or are unfit for surgery. Systematic reviews that included meta-analysis have revealed that CCRT has a

significant benefit on the survival rate in patients with SCC of the head and neck, compared to RT alone (3, 4). In a phase III trial in which induction chemotherapy with 5-fluorouracil and cisplatin (FP) followed by RT was compared with CCRT with cisplatin alone in selected patients with T3N0 pyriform sinus carcinoma (1), the CCRT group had a significantly higher rate of laryngeal preservation at 2 years than the induction chemotherapy group. A phase II trial showed that the 3-year survival rate in patients with squamous cell carcinoma of the head and neck who received CCRT with docetaxel, cisplatin, and 5-fluorouracil (TPF) was higher than that in patients who received modified FP, although the overall and complete response rates were similar in the two groups (5). However, severe toxicity was reported with use of CCRT. Adelstein *et al.* (6) reported that survival among patients treated with CCRT combined with FP was not significantly different from that among patients treated with CCRT with cisplatin alone, although toxicity was greater and compliance with the treatment regimen was lower among patients in the former group. Although RT doses to the pharyngeal constrictors has been demonstrated to be associated with swallowing outcomes, such structures cannot be spared, even when advanced irradiation techniques, such as intensity-modulated RT, are employed (7, 8). It is important to balance adverse events with treatment effects. We conducted a retrospective review of our experience treating HPC with CCRT to evaluate factors affecting patient survival and tolerability of CCRT.

Patients and Methods

Patients. This retrospective study included 80 patients (75 males) aged 48 to 78 years (median=66 years) with a histological diagnosis of SCC of the hypopharynx who underwent three-dimensional conformal RT (3D-CRT) and concurrent chemotherapy between January 2002 and 2011. All patients were treated at the Nihon University Itabashi Hospital.

Staging investigations. Staging was performed using findings of contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and fiberoptic. Whole-body CT was performed to

Correspondence to: Masakuni Sakaguchi, Department of Radiology, Nihon University School of Medicine, 30-1, Oyaguchi Kami-cho, Itabashi-ku, Tokyo, 173-8610, Japan. Tel: +81 339728111 ext.2554, Fax: +81 339582454, e-mail: sakaguchi.masakuni@nihon-u.ac.jp

Key Words: Concurrent chemoradiotherapy, hypopharyngeal cancer, radiotherapy.

exclude distant metastases. Gastrointestinal fiberoscopy was performed to exclude double cancer. Positron-emission tomography was performed when gastrointestinal fiberoscopy was not performed for various reasons. Staging, therapeutic effect, and presence or absence of recurrence was determined by radiologists, radiotherapists, and otorhinolaryngologists.

Radiation therapy. Recent improvements in RT techniques have led to the widespread popularity of intensity-modulated RT for reducing damage to normal tissues. However, this method requires greater precision and accuracy than 3D-CRT. Intensity-modulated RT was not used because our Institution had no established policy for use of this treatment modality in patients with cancer of the head and neck until 2011. When intensity-modulated RT is not available, it is reasonable to perform 3D-CRT.

The treatment plan was performed with enhanced CT. Scans were assessed in 5-mm sections. The gross tumor volume is the volume of the area occupied by the tumor as measured by imaging and fiberoscope. The clinical target volume (CTV) was defined as gross tumor volume plus 0.5 cm and bilateral lymph node area $\pm$ subclavicular area. The internal target volume was the CTV plus the tumor margin for any organ movement. The internal target volume included a 0.5-cm 'set up' margin to establish the planning target volume (PTV). The radiation field was defined as the PTV plus a 5-mm leaf margin. Using a 4-MV X-ray beam, right-left opposed portals irradiation and use field in field methods was administered. Each beam was created using PTV along the path of the beam with a margin.

The Clarkson algorithm was used to calculate the irradiation dose. The minimum and maximum doses according to the PTV were 95% and 107%, respectively. RT was delivered 5 days a week using a single daily fraction of 2.0 Gy. None of the patients was administered accelerated hyperfractionated RT. After a total dose of 40 Gy, all patients were evaluated clinically by CT, MRI, or both. Patients with decrease in the primary and neck tumors (responders) continued CCRT and completed RT for a total dose of 60-72 Gy (median=66 Gy). For nonresponders, definitive surgery was recommended, and these patients were excluded from the study. The elective bilateral lymph node area received a dose of 40 to 50 Gy.

Chemotherapy. We administered the basic FP regimen until 2007, and then the TPF regimen became the standard. Although there was no strict protocol, patients were required to meet the following criteria: <75 years of age, Eastern Cooperative Oncology Group performance status 0 or 1, white blood cell count $>4,000/\mu\text{l}$, neutrophil count $>2,000/\mu\text{l}$; platelet count $>100,000/\mu\text{l}$, and 24-h creatinine clearance >70 ml/min. Patients who did not meet these criteria received chemotherapy with docetaxel twice a week or two courses of cisplatin plus docetaxel. The TPF regimen was a combination of docetaxel (50 mg/m², day 1), cisplatin (50 mg/m², day 1), and 5-fluorouracil (600 mg/m² given over 24 h on days 1-5). The FP regimen was a combination of cisplatin (80 mg/m², day 1) and 5-fluorouracil (800 mg/m² given over 24 h on days 1-5). Two cycles of these regimens were given during RT. The first course of CCRT stopped at 40 Gy and the patients were then evaluated clinically. The second started when we confirmed that side-effects were cured. At any time when grade 2 or more toxicities (myelosuppression, mucositis, fever) were observed, CCRT was suspended for 7 to 10 days. Although there was no strict protocol,

retreatment required the following: neutrophil count $>2,000/\mu\text{l}$, platelet count $>100,000/\mu\text{l}$, hemoglobin >9.5 g/dl, and 24-h creatinine clearance >60 ml/min. If severe toxicity continued for more than 7 days or grade 3 toxicity occurred, the second round of chemotherapy was changed to docetaxel at 12 mg/m² twice weekly. Every effort was made to continue RT on schedule. Subcutaneous granulocyte colony-stimulating factor (G-CSF, at 150 mg/day) was injected if the neutrophil count was $1,000/\mu\text{l}$ by CCRT. If the patient was to maintain oral intake because of oral or pharyngeal pain induced by CCRT, a gastric tube was inserted to maintain the patient's nutritional condition.

Evaluation of initial clinical response and toxicity on follow-up. All patients were closely observed during CCRT. Follow-up response was assessed within 4 weeks from the date of completion of treatment by CT, MRI, fiberoscope, and routine blood examination. These scans were performed within 3 to 6 months after the first follow-up. The recommended follow-up protocol at our Institute includes investigation at 3-month intervals for the first 6 months and every 6 months thereafter. Several patients who received CCRT and changed hospitals were unable to visit our hospital. Therefore, we were unable to carry out strict follow-up for some patients. In these cases, information on the patient's condition was obtained from the family by telephone. The definitions of complete response, partial response, stable disease, and progressive disease were based on the standard definitions established by the World Health Organization (9). Responses were scored when the treatment was most effective. Local recurrence was defined as an increase in tumor size on MRI, CT, or fiberoscopy. The date of recurrence was determined as the first day when the local recurrence was observed. Adverse events were defined once per week during CCRT and 4 weeks after treatment according to the Common Terminology Criteria (CTC) for Adverse Events, version 4.0, with toxicity graded as mild (CTC grade 1), moderate (CTC grade 2), severe (CTC grade 3), or life-threatening (CTC grade 4) (10).

Statistical analysis. The overall survival and disease-specific survival after CCRT were calculated by the Kaplan-Meier method based on the interval between the last day of treatment and the date of death or the most recent follow-up as of 2011. Data from patients who reached the end of the following period without sustaining an event were censored. Local tumor control was calculated based on the interval from the first day of treatment until local relapse. Data for patients who died with no evidence of recurrence were censored. Univariate survival comparisons were performed using the log-rank test. The analyzed prognostic factors for disease-specific survival were age (≤ 70 vs. >70 years), T-stage ($\leq T3$ vs. $T4$), N-stage ($N0-1$ vs. $N2-3$), radiation dose (≤ 66 vs. >66 Gy), and type of chemotherapy (TPF vs. FP). Independent variables that showed a statistically significant association on univariate analysis were included in the multivariate analysis. A value of $p < 0.05$ indicated statistical significance. All calculations and survival displays were conducted using SPSS 15.0 J statistical software (SSPS, Chicago, IL, USA).

Patient consent. The present study was a retrospective analysis of data on diagnosis and treatment. Written informed consent was obtained from all patients for inclusion of their data in the study. Patient records and information were anonymized and de-identified prior to analysis in this study. All procedures performed in the study

Table I. Baseline clinical characteristics of patients.

Characteristic	Value
Patients	80
Age, years	
Median (range)	66 (48-78)
<70	24
≥70	56
Gender, n	
Male	75
Female	5
PS, n	
0	12
1	68
Histology, n	
Squamous cell carcinoma	80
Other	0
Location, n	
Post cricoid	5
Pyriiform sinus	64
Posterior wall	11
T-Stage, n	
T1	7
T2	30
T3	17
T4a	22
T4b	4
N-Stage, n	
N0	26
N1	16
N2a	3
N2b	19
N2c	7
N3	9
Treatment strategy, n	
FP	40
TPF	25
Other*	15
Radiation dose, n	
≤66 Gy	53
>66 Gy	27

FP: Cisplatin plus 5-fluorouracil; TPF: cisplatin plus 5-fluorouracil plus docetaxel. *Cisplatin plus docetaxel, docetaxel alone.

were in accordance with the ethical standards of the institutional and national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

Patient characteristics. Baseline patient characteristics are listed in Table I. More than 80% of patients had stage III or IV progressive disease.

Toxicity. Table II shows the toxicities observed in the study population. No treatment-related deaths occurred. Neutropenia was the most common adverse event, with

Table II. The number of patients who had severe complications (grade 3 or more) according to therapy.

	TPF	FP or other
Hematological		
Neutropenia	12	14
Anemia	2	1
Thrombocytopenia	0	0
Non-hematological		
Dermatitis	10	7
Mucositis	12	9
Dysphagia	12	9
Renal dysfunction	1	1
Liver dysfunction	0	0

FP: Cisplatin plus 5-fluorouracil; TPF: cisplatin plus 5-fluorouracil plus docetaxel; other: cisplatin plus docetaxel, docetaxel alone.

grade 3 or more in 26 patients (32.5%). Acute mucositis and dysphagia were the second most common adverse reactions, with grade 3 or more in 21 patients (26.3%). Six patients who had grade 3 dysphagia caused by acute mucositis required tube feeding during CCRT. Two patients underwent percutaneous endoscopy gastrostomy (PEG) after CCRT because of recurrence, one patient was permanently dependent on PEG due to dysphagia. Patients on the TPF regimen had more serious adverse events than those on the FP regimen.

Treatment compliance. Among patients treated with TPF or FP, 50 patients (76.9%) completed the scheduled two courses of chemotherapy. Seven and eight patients, respectively, discontinued the second course of FP and TPF. The most common causes of discontinuation of two course of chemotherapy were myelosuppression (five patients each for TPF and FP) and renal dysfunction (one patient each for TPF and FP). Among patients who received only one course of TPF, six received a docetaxel regimen, and one did not receive an additional second course of chemotherapy. Among patients who received only one course of FP, eight received a docetaxel regimen. The overall treatment time was 49 to 115 days (median of 59 days for TPF and 58 for FP). The successful completion rate of TPF was 68%, compared with 82.5% for FP.

Response. The overall response rate for primary tumors was 100% (complete response in 61 patients and partial response in 19 patients). Among patients with lymph node involvement, the lymph node response was 98.8% (complete response or partial response in 79 patients and stable disease in one patient). The 5-year local tumor control rate was 67.2% (Figure 1).

Figure 1. Patients had 5-year local control rate of 67.2%.

Figure 2. Overall survival in patients with hypopharyngeal cancer treated with concurrent chemoradiotherapy. The 5-year overall survival rate was 49.3%.

Table III. Second primary cancer (synchronous and metachronous).

Site	Number of patients
Esophagus	16
Stomach	6
Colon	5
Pancreas	1
Kidney	1
Lung	1
Breast	1
Melanoma	1

Second primary cancer. A second primary cancer developed in 32 out of the 80 patients (40%) (Table III). The most common site was the esophagus (16 patients), followed by the stomach (six patients). Both synchronous and metachronous double cancers were observed. Among the 16 patients with esophageal cancer, 10 were treated before CCRT with HPC and six patients were diagnosed during or after treatment for HPC. Of these six patients, one underwent a curative operation after CCRT. One patient had superficial esophageal cancer and underwent endoscopic mucosal resection after CCRT. One patient received TS-1 (tegafur/gimeracil/oteracil) plus RT for esophageal cancer. One patient had no treatment and only underwent follow-up. One patient had a subarachnoid hemorrhage before treatment for esophageal cancer. The treatment history for one patient is unknown. Other double cancers were treated before CCRT.

Survival. The median duration of follow-up was 37 months (range=1-157 months). Twenty-eight patients died during follow-up. The cause of death was primary disease or related

Figure 3. Disease-free survival in patients with hypopharyngeal cancer with concurrent chemoradiotherapy. The 5-year overall survival rate was 60.7%.

to primary disease in 21 patients, double cancer in six patients, and other disease in one patient. The 5-year overall survival and disease-free survival rates were 49.3% and 60.7%, respectively (Figures 2 and 3). Data on disease-free survival and prognostic factors identified on univariate and multivariate analyses are given in Table IV. Improved disease-free survival was associated with lower N-stage (hazard ratio=0.249; 95% confidence interval=0.096-0.643; $p=0.041$) on both univariate and multivariate analysis. Patients with a long overall treatment time had a tendency toward a reduced survival rate, but no significant differences according to treatment were observed. Among 20 patients with persistent or relapsed primary cancer after CCRT, 13 underwent surgery. Among 22 patients with neck lymph node relapse after CCRT, 11 underwent neck dissection. Two patients who underwent salvage surgery died, and 18 patients

Table IV. Correlates of disease-specific survival in univariate and multivariate analyses.

Variable	Univariate	Multivariate		
	p-Value	HR	95% CI	p-Value
Age: ≤70 vs. >70 years	0.755	0.804	0.354-1.827	0.603
T-Stage: T1-3 vs. T4	0.027	1.375	0.597-3.167	0.454
N-Stage: N0-1 vs. N2-3	0.002	0.249	0.096-0.643	0.041
Chemotherapy: TPF vs. FP or other	0.549	1.713	0.475-6.182	0.571
Radiation dose: ≤66 Gy vs. >66 Gy	0.388	1.104	0.438-2.780	0.833

HR: Hazard ratio; CI: confidence interval; FP: cisplatin plus 5-fluorouracil; TPF: cisplatin plus 5-fluorouracil plus docetaxel; other: cisplatin plus docetaxel, docetaxel alone.

were alive with no evidence of disease at the latest follow-up. Four patients who were alive with disease received adjuvant chemotherapy or palliative support care.

Discussion

The treatment for HPC is complex and considers tumor stage, age, performance status, and individual preference. CCRT is the standard treatment for those who refuse surgery or have unresectable head and neck cancer. The number of patients treated with CCRT, especially for organ preservation, is increasing. However, few reports of the definitive outcomes of CCRT for HPC have been published (11, 12). Some studies have reported the efficacy of induction chemotherapy for HPC (13, 14). Induction chemotherapy was often performed for advanced disease and plays a role in organ preservation and avoidance of the risk of salvage surgery (15). However, in several clinical studies, local tumor control and overall survival rates of patients receiving induction chemotherapy were not superior to those of patients receiving CCRT (16). Tai *et al.* reported the outcomes of induction chemotherapy followed by CCRT in 42 patients with stage III or IV HPC. The 3-year overall survival, disease-free survival, and local tumor control rates were 35.3%, 33.1%, and 54.8%, respectively (12). In a trial comparing induction chemotherapy with either TPF or FP followed by RT or CRT in patients with stage III or IV SCC of the larynx and the hypopharynx (17), the estimated 3-year survival for patients with HPC receiving TPF was 49%. The estimated 3-year laryngectomy-free survival was 52% in patients with advanced SCC of the larynx and the hypopharynx treated with induction TPF followed by RT or chemoradiotherapy. Our study found 5-year overall survival and disease-free survival rates of 49.3% and 60.7%, respectively. These results were superior to those in previous

reports of induction chemotherapy. We administered CCRT with the FP regimen with RT until 2007, and thereafter we administered the TPF regimen with RT.

The rationale for CCRT is that specific chemotherapeutic agents have radio-sensitizing properties and reduce tumor cells within the radiation field in addition to their own antitumor effect (18, 19). In a previous report, the complete response rates after CCRT for SCC of the head and neck were 90% in the TPF group and 77% in the modified FP group (5). Taguchi *et al.* reported that patients treated with the high-dose TPF regimen (consisting of docetaxel at 50 mg/m² on day 1, cisplatin at 60 mg/m² on day 4, and 5-fluorouracil at 600 mg/m² given over 24 hours on days 1-5) or the modified FP regimen (consisting of cisplatin at 60 mg/m² on day 4 and 5-fluorouracil at 600 mg/m² given over 24 hours on days 1-5) had a better survival rate than FP (20). However, the superiority of TPF compared with modified FP was unclear. In the present study with multivariate analysis, the chemotherapeutic regimen had no significant effect on overall survival or disease-free survival. The successful completion rate of TPF was 68% compared with 82.5% for FP. The most common causes of discontinuation of chemotherapy were myelosuppression and renal dysfunction. The patients who had severe side-effects chose docetaxel as the second course of chemotherapy. It is assumed that the treatment result was not better than FP if two courses of TPF were not completed. It is thought that a strong regimen with its own antitumor effects is necessary for CCRT in patients with advanced SCC of the hypopharynx. However, strict supportive care is mandatory, since adverse events occur frequently with the high-dose regimens. Hematological side-effects and renal and liver dysfunction due to chemotherapy cannot be avoided and are hard to manage. However, dysphagia and dystrophia due to mucositis can be managed by pain control and PEG or the insertion of a feeding tube. Lambert *et al.* reported that 6% of patients with advanced laryngeal cancer and HPC receiving platinum-based CCRT were still dependent on PEG for adequate food intake for a mean duration of 43 months after radiotherapy (21). Mekhail *et al.* reported that 91 out of 158 patients treated with definitive CCRT or RT required feeding tube placement at some time during treatment (22). Tsao *et al.* reported that among patients with stage III and IV head and neck cancer, feeding tubes were in place in 76.9%, 72.5%, 56%, and 42.9% of patients at 6 weeks, 3 months, 6 months, and 12 months, respectively, after CCRT (23). In our study, there was no patient who had undergone PEG before CCRT. Two patients underwent PEG after CCRT because of recurrence, one underwent PEG because of toxicity. Six patients (7.5%) were dependent on a feeding tube during CCRT because of grade 3 dysphagia as acute toxicity. When dysphagia and dystrophia due to mucositis were aggravated, we stopped CCRT, but a feeding tube was required in only six patients. Patients who had grade 2 mucositis refused

feeding-tube insertion because it felt like an alien substance and did not restart treatment after dysphagia disappeared. Therefore, our mean overall treatment time was 59 days, a relatively long period. There was no significant effect of CCRT regimen on treatment results, but treatment results tended to be better if the treatment period was short. It is important to make the treatment period as short as possible by appropriately using a feeding tube when pain and dysphagia occur. Stopping CCRT due to pain and dysphagia should be avoided.

In a systematic review that addressed the prognostic significance of neck node volume in head and neck cancer, patients were treated with CCRT or RT alone, and increased nodal volume had a negative effect on survival in most studies (24). In a previous study in which CCRT was the first treatment in patients with stage III or IV HPC (25), possible prognostic factors that affected the local control rate, including pathology, nodal number and volume, and T stage above 3, had a significant correlation with treatment outcome. In the present study, the T and N stages were significant negative prognostic factors according to univariate analysis, and patients with higher N stage had a significantly lower disease-specific survival rate according to multivariate analysis, as in a previous report (20).

Six patients in our study died from double cancer, and overall survival was worsened. Patients with HPC, especially esophageal cancer, are well known for having synchronous and metachronous malignancies. Kohmura *et al.* reported that 18% of patients with HPC had esophageal cancer, which occurred in less than 3 years after HPC in all metachronous cases (26). They reported that most HPCs were at an advanced stage, but all of the esophageal cancers were at an early stage and were superficial. Morimoto *et al.* reported that 41% of patients with HPC had esophageal cancer, and the 5-year overall survival rates for patients with esophageal cancer were 83% for stage 0, 47% for stage I, and 0% for stages IIA-IVB (27). In our study, 16 patients had esophageal cancer, which were simultaneous with HPC in six. Four patients were treated by minimally-invasive treatment and had no recurrence. We perform gastrointestinal fiberoptic examinations for patients after treatment for HPC. Early detection of esophageal cancer enables successful minimally invasive treatment such as endoscopic mucosal resection or endoscopic submucosal dissection. To improve the clinical efficacy of HPC treatment, early detection of metachronous malignancies is essential. We believe that it is also necessary to perform periodic endoscopic examination of patients with HPC after treatment.

Our study had several limitations, most of which were related to the retrospective design. Overall treatment time was variable and chemotherapy, except FP and TPF, had no strict protocol. Fifteen patients (18.8%) who received chemotherapy other than FP and TPF were included in this study. Treatment strategy for recurrent tumors was also

controversy. These facts can lead to bias in interpreting data for survival, for which the results of multivariate analysis were unclear. This limitation may be addressed in the future by maintaining consistency chemotherapy protocols and overall treatment time by treatment of adverse events appropriately.

Conclusion

The retrospective nature of this study within a single center does not detract from the value of these preliminary findings. Patients who received TPF and FP in CCRT had good overall survival and disease-specific survival, and adverse events were manageable. Even with the chemotherapy regimen, patients with advanced nodal diseases, especially N2 or higher, had low disease-free survival. There were no significant differences in overall and disease-free survival between patients receiving CCRT with the TPF regimen and those who received FP during a long period of treatment but did not finish two courses.

Competing Interests

The Authors have no financial disclosures.

Conflicts of Interest

The Authors declare no conflicts of interest in regard to this study.

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Received December 18, 2016

Revised January 26, 2017

Accepted January 27, 2017