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ORIGINAL ARTICLE

Efficacy and toxicity of concurrent chemoradiotherapy in patients with advanced oropharyngeal squamous cell carcinoma

Makiko Mori · Mamoru Tsukuda · Hideki Matsuda · Choichi Horiuchi · Takahide Taguchi · Masahiro Takahashi · Goshi Nishimura · Masanori Komatsu · Tatsuo Niho · Naoko Sakuma · Asako Miyakoshi · Yasuhiro Isono · Sayaka Iwahana

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Abstract
Purpose The aim of this study was to evaluate the feasibility and toxicity of concurrent chemoradiotherapy (CCRT) with docetaxel, cisplatin (CDDP) and 5-fluorouracil (5-FU) (TPF regimen) or with CDDP, 5-FU, methotrexate and leucovorin (PFML regimen) in previously untreated patients with advanced oropharyngeal squamous cell carcinoma (SCC).
Methods Fifty-six eligible patients with stage III or IV oropharyngeal SCC were treated with CCRT. Forty-four patients were men and 12 were women, and the average age of the patients was 58.8 years (range, 37–72 years). In the TPF group, patients received CCRT with the TPF regimen [docetaxel (50 mg/m^2, day 1), CDDP (60 mg/m^2, day 4) and a continuous 5-FU infusion (600 mg/m^2/day, days 1–5)]. In the PFML group, patients received CCRT with the PFML regimen [CDDP (60 mg/m^2, day 4), a continuous 5-FU infusion (600 mg/m^2/day, days 1–5), methotrexate (30 mg/m^2, day 1) and leucovorin (10 mg/m^2/day, days 1–5)]. The total radiation dose was between 66.6 and 70.2 Gy.
Results The overall 5-year survival rate was 64.6% in all patients, 68.6% in the resectable group and 47.4% in the unresectable group. The 5-year disease-specific survival rate was 72.2% in all patients, 78.1% in the resectable group and 47.7% in the unresectable group. Regarding clinical stage, the 5-year disease-specific survival rates were 91% in stage III, 72% in stage IVa and 44% in stage IVb.
Conclusion CCRT with TPF or PFML regimen for advanced oropharyngeal SCC is tolerable and effective, especially in patients with resectable disease.

Keywords Concurrent chemoradiotherapy · Oropharynx · Squamous cell carcinoma · TPF · PFML

M. Mori (✉) · M. Tsukuda · H. Matsuda · C. Horiuchi · T. Taguchi · M. Takahashi · G. Nishimura · M. Komatsu · T. Niho · N. Sakuma · A. Miyakoshi · Y. Isono · S. Iwahana
Department of Otolaryngology, and Head and Neck Surgery, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-Ku, Yokohama 236-0004, Japan
e-mail: watamaki@yokohama-cu.ac.jp

Introduction

After the usefulness of concurrent chemoradiotherapy (CCRT) for head and neck squamous cell carcinoma (HNSCC) was reported in 1998 [1, 2], combined treatment modalities, e.g. definitive surgery followed by CCRT, CCRT followed by salvage surgery and neoadjuvant (induction) chemotherapy (NAC) plus definitive RT or definitive surgery [3], have been used for advanced HNSCC patients to obtain a better survival rate [4–8]. The oropharynx is critical for speech and swallowing functions. The management of patients with advanced oropharyngeal carcinoma remains extremely controversial in terms of organ preservation. CCRT has replaced surgery as the preferred treatment method for treating advanced oropharyngeal SCC [9–12]. Since 1999 till now, we have mainly performed CCRT with the two regimens PFML (cisplatin, 5-fluorouracil, methotrexate and leucovorin) or TPF (docetaxel, cisplatin and 5-fluorouracil) for advanced HNSCC [13–17]. We evaluated the efficacy and toxicity of CCRT for stage III and IV oropharyngeal SCC regarding organ preservation.

Patients and methods

Patient population

We included patients with untreated histologically confirmed SCC of the oropharynx, stage III or IV disease according to the 1997 staging system of the Union Internationale Contre le Cancer. Both resectable and unresectable cases were enrolled. Unresectable cases were defined as patients with prevertebral muscle invasion, common or internal carotid artery invasion (i.e. those with positive results from the artery occlusion test), or bulky metastasis in the retropharyngeal lymph nodes. The patients were between 20 and 75 years of age and met the following criteria: an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; no prior radiotherapy or chemotherapy; adequate bone marrow function, defined as a neutrophil count of >1,500 cells/mm^3 and platelet count of >100,000/mm^3; adequate liver function, defined as AST, ALT and alkaline phosphatase levels below 2.5 times the upper limit of normal and a 24-hour creatinine clearance rate >65 mL/min. Patients with significant cardiovascular and cerebral disorders were ineligible. All patients provided written informed consent prior to enrolment. This study was approved by the Institutional Review Board of our institution.

Before treatment began, histopathological examinations of the primary site, fibrescopy of the head and neck lesion, gastrointestinal fibrescopy, ultrasonography of the neck and abdomen, head and neck computed tomography (CT), head and neck magnetic resonance imaging (MRI) and whole-body fluoro-2-deoxy-D-glucose- positron emission tomography (FDG-PET) were performed to determine the diagnosis and the initial stage of cancer. Patients with distant metastases or tumours in other anatomical sites were not enrolled in the present study.

Treatment schedule

CCRT with the two regimens TPF [13, 14] or PFML [15–17] was performed. The TPF regimen consisted of a combination of three agents: docetaxel (50 mg/m^2, day 1), cisplatin (60 mg/m^2, day 4) and 5-fluorouracil (5-FU; 600 mg/m^2, days 1–5). The PFML regimen consisted of a combination of four agents: cisplatin (60 mg/m^2, day 4), 5-FU (600 mg/m^2, days 1–5), methotrexate (MTX; 30 mg/m^2, day 1) and leucovorin (LV; 20 mg/m^2 days 1–5).Two cycles of each regimen were administered every four weeks during RT. The conventional radiotherapy was administered 5 days per week as a single daily fraction of 1.8 or 2.0 Gy using 6MV X-ray linear accelerators. The field size included the primary tumour and regional (cervical) metastasis. After a total dose of 40 Gy with the first course of each regimen, all patients were clinically re-evaluated. Patients with a 50% or greater decrease (responders) in the product of two perpendicular diameters of primary and neck tumour continued CCRT and completed CCRT with a total dose of 66.6–70.2 Gy. Definitive surgery was recommended for non-responders and patients with recurrent disease who had resectable tumours.

Response assessment

The clinical response of each patient was assessed 6–8 weeks after the end of CCRT on the basis of the combined findings of CT scanning, MRI, ultrasonography and FDG-PET. A complete response (CR) was defined as the disappearance of all clinical evidence of disease. A partial response (PR) was defined as a 50% or greater decrease in the product of two perpendicular diameters of the primary and regional tumours. The patients in whom the disease did not fulfil the criteria for both CR and PR were considered as having no change (NC) or progressive disease (PD) based on the standard definition established by WHO. The pathological response to the CCRT was confirmed by biopsy at the primary site in all patients. Patients with N1-3 lymph node disease underwent fine-needle aspiration cytology of the neck lymph nodes. Patients with less than CR of the primary and neck tumour (evaluated by histopathological examinations) were considered for surgery 6–8 weeks after CCRT completion.

The overall survival (OS) rate and the disease-specific survival rate were calculated by the Kaplan–Meier method and were statistically analysed by the Wilcoxon test.

Toxicity assessment

Toxicity was assessed during the treatment according to the 2003 Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0).

Results

Patient population

Between January 1998 and March 2007, we enrolled 56 previously untreated patients with stage III or IV oropharyngeal SCC. Patient characteristics are shown in Table 1. Forty-four patients were men and 12 were women, and their average age was 58.8 years (range, 37–72 years). The PS (ECOG) of all patients was 0–1. Twelve patients had stage III disease, 35 patients had stage IVa disease and nine patients had stage IVb disease. Of the 56 patients, 36 had a tumour in the lateral wall, 13 in the tongue base, four in the soft palate and three in the posterior pharyngeal wall.

Table 1 Patient characteristics

Characteristics	No.	(%)
Age, years		
Mean (Range)	58.8 (37–72)	
Sex		
Male/female	44/12	
Subsite		
Lateral wall	36	(64.3)
Tongue base	13	(23.2)
Soft palate	4	(7.1)
Posterior pharyngeal wall	3	(5.4)
T stage		
T1	4	(7.1)
T2	19	(33.9)
T3	13	(23.2)
T4a	15	(26.8)
T4b	5	(8.9)
N stage		
N0	6	(10.7)
N1	12	(21.4)
N2a	0	(0)
N2b	23	(41.1)
N2c	10	(17.9)
UICC stage		
III	12	(21.4)
IVa	35	(62.5)
IVb	9	(16.1)
Resectability		
Resectable	45	(80.3)
Unresectable	11	(19.6)

Forty-five patients were considered to have resectable disease, and 11 patients were considered to have unresectable disease.

Toxicity

No deaths resulted from the treatments in this study. Forty-four of 56 patients (78%) received planned CCRT. In contrast, the second course was discontinued in 12 patients because of renal toxicity (six patients), chronic neutropenia (four patients), pneumonia (one patient) and diarrhoea (one patient). The degrees of toxicity are listed in Table 2. Grade 3 and 4 mucositis was observed in 27%, dermatitis in 23%, neutropenia in 23%, nausea and vomiting in 16%, anaemia in 9%, diarrhoea in 4% and thrombocytopenia in 2% of patients. During CCRT, 39 of the 56 patients (70%) had difficulty eating because of the pain caused by mucositis and required nutritional support with a gastric tube.

Table 2 Toxicity degrees

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Haematological				
Anaemia	14 (25%)	11 (20%)	5 (9%)	0
Neutropenia	8 (14%)	8 (14%)	12 (21%)	1 (2%)
Thrombocytopenia	15 (27%)	3 (5%)	1 (2%)	0
Non-haematological				
Diarrhoea	11 (20%)	4 (7%)	2 (4%)	0
Elevation of ALT, AST	13 (23%)	1 (2%)	0	0
Nausea/vomiting	5 (9%)	16 (29%)	9 (16%)	0
Renal (creatinine)	6 (11%)	3 (5%)	0	0
Related to radiation				
Dermatitis	1 (2%)	17 (30%)	13 (23%)	0
Mucositis	1 (2%)	15 (27%)	7 (13%)	8 (14%)

Treatment response

The treatment response rate and recurrence rate of patients with pathological CR are listed in Table 3. The overall response rate at the end of CCRT was 96% (54/56), the pathological CR rate was 82% (46/56) and the PR rate was 14% (8/56). After CCRT, one patient showed NC and one patient showed PD. At the primary site, the CR rate was 94% (53/56): T1 (100%), T2 (100%), T3 (85%), T4a (100%) and T4b (80%). Six patients had a primary recurrence (one in T2, one in T3 and four in T4a). Two of six patients received curative surgery. One patient had an unresectable neck lymph node, three patients with a primary site relapse refused surgery and 39 of 50 patients (78%) with node-positive cases had cytologically confirmed CR at the neck lymph nodes (N1 100%, N2b 78%, N2c 60%, N3 60%). Six patients had cervical lymph node recurrence. Two of six patients underwent neck dissection, one patient had unresectable disease and three patients refused surgery.

Eleven of 50 patients showed PR or NC at the neck lymph nodes after CCRT. Six of 11 patients underwent salvage surgery, three patients had distant metastases and two patients had unresectable disease.

Survival

The overall 5-year survival rate was 64.6% in all patients (Fig. 1), 68.6% in the resectable group and 47.4% in the unresectable group ($P = 0.139$) (Fig. 2). The 5-year disease-specific survival rate was 72.2% in all patients, 78.1% in the resectable group and 47.7% in the unresectable group ($P = 0.122$) (Fig. 3). The 5-year disease-specific survival rate was 91% in stage III, 72% in stage IVa and 44% in stage IVb disease (Fig. 4). The 5-year disease-specific survival rate was 75% in T1 patients, 81% in T2 patients,

Table 3 Treatment response according to T and N stage

Response	CR	PR	NC	PD	Recurrent cases in CR cases
All cases ($n = 56$)	46 (82%)	8 (14%)	1 (2%)	1 (2%)	
T stage					
T1 ($n = 4$)	4 (100%)				0
T2 ($n = 19$)	19 (100%)				1 (5%)
T3 ($n = 13$)	11 (85%)	1	1		1 (9%)
T4a ($n = 15$)	15 (100%)				4 (26%)
T4b ($n = 5$)	4 (80%)			1	0
Total ($n = 56$)	53 (94%)	1	1	1	6 (12%)
N stage					
N1 ($n = 12$)	12 (100%)				2 (16%)
N2b ($n = 23$)	18 (78%)	5			3 (19%)
N2c ($n = 10$)	6 (60%)	3		1	1 (14%)
N3 ($n = 5$)	3 (60%)	2			0
Total ($n = 50$)	39 (78%)	10		1	6 (15%)

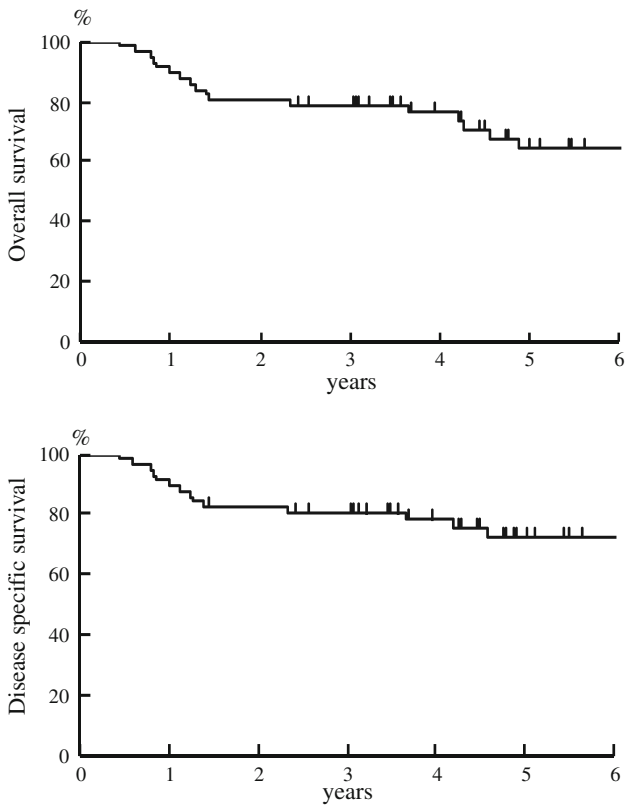

Fig. 1 The overall 5-year survival rate in all patients. The overall 5-year survival rate was 64.6%, and the 5-year disease-specific survival rate was 72.2% in all patients

77% in T3 patients, 67% in T4a patients and 40% in T4b patients. The 5-year disease-specific survival rate was 83% in N0 patients, 83% in N1 patients, 70% in N2b patients, 65% in N2c patients and 60% in N3 patients (Fig. 5).

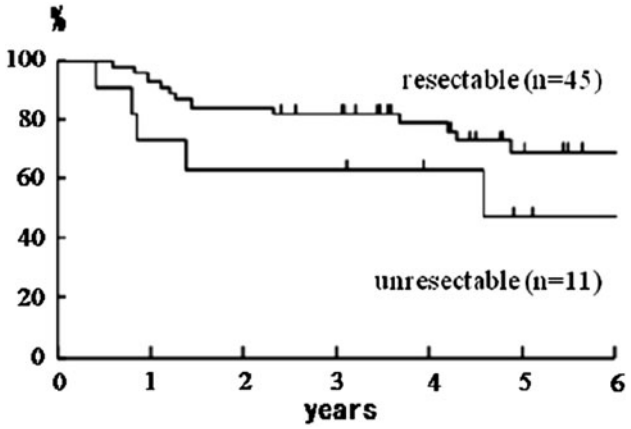

Fig. 2 The overall 5-year survival rate in the resectable group and the unresectable group. The overall 5-year survival rate was 68.6% in the resectable group and 47.7% in the unresectable group. There was no significant difference between the two groups ($P = 0.139$)

Discussion

Oropharyngeal carcinoma accounts for 8.4% of all head and neck carcinomas in Japan [18]. The most common sites for oropharyngeal carcinoma are the tonsillar regions (lateral wall) and tongue base, whereas carcinoma of the soft palate and posterior pharyngeal wall is less common [19]. At our institute, the incidence rate of oropharyngeal carcinoma is 65% in the lateral wall, 23% in the tongue base, 7% in the soft palate and 5% in the posterior pharyngeal wall.

CCRT has been increasingly used to treat patients with head and neck carcinoma over the past three decades [20, 21]. Since 2000, survival rates after CCRT have improved [22]. Since the emergence of the finding that

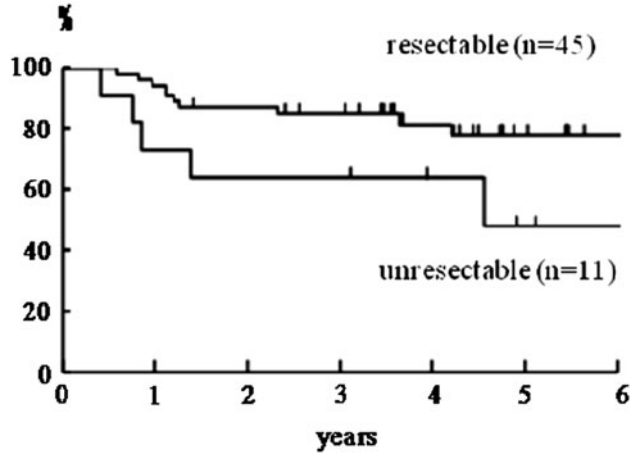

Fig. 3 The 5-year disease-specific survival rate in the resectable group and the unresectable group. The 5-year disease-specific survival rate was 78.1% in the resectable group and 47.7% in the unresectable group. There was no significant difference between the two groups ($P = 0.122$)

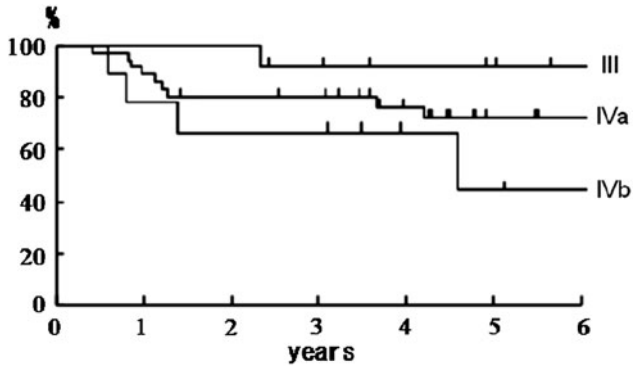

Fig. 4 The 5-year disease-specific survival rate in stage III and IV diseases. The 5-year disease-specific survival rate was 91% in stage III, 72% in stage IVa and 44% in stage IVb disease

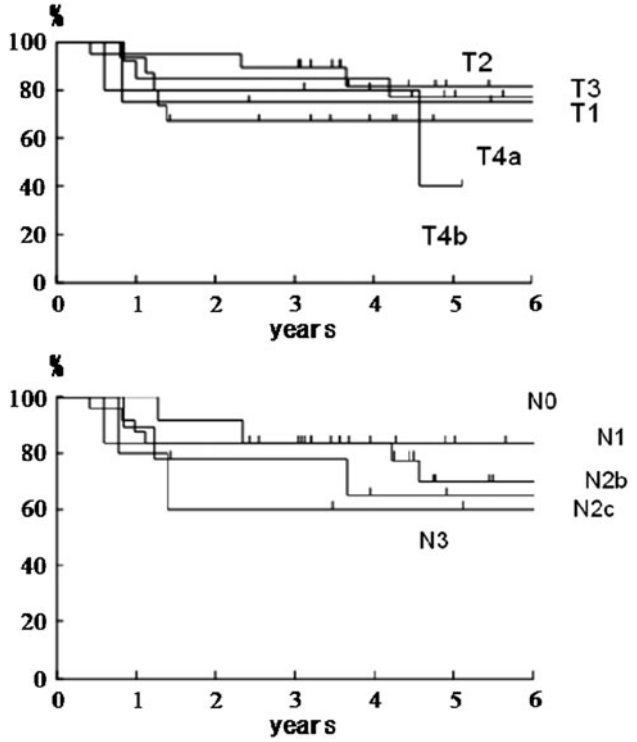

Fig. 5 The 5-year disease-specific survival rate in terms of T and N patients. The 5-year disease-specific survival rate was 75% in T1 patients, 81% in T2 patients, 77% in T3 patients, 67% in T4a patients and 40% in T4b patients. The 5-year disease-specific survival rate was 83% in N0 patients, 83% in N1 patients, 70% in N2b patients, 65% in N2c patients and 60% in N3 patients

radiation and concurrent platin-based chemotherapy is superior to radiotherapy alone, CCRT that includes platins has been considered an effective treatment modality, particularly for unresectable HNSCC.

There are a few studies in subsite of the oropharynx. Bensadoun et al. [23] compared the efficacy of combination chemotherapy (CDDP + 5-FU) plus concurrent twice-daily radiotherapy with that of twice-daily radiotherapy alone in 123 patients with unresectable oropharyngeal carcinoma. OS, disease-free survival (DFS) and specific survival were significantly better in the CCRT group than those in the radiotherapy-alone group (OS: 41% vs. 22%, DFS: 51% vs. 27%, specific survival: 54% vs. 31%). Two randomized, controlled trials limited to patients with oropharyngeal carcinoma have been conducted in France [24, 25]. These studies compared radiotherapy (70 Gy) + concomitant carboplatin + 5-FU with radiotherapy (70 Gy) alone in patients with stage III or IV disease. The results for 226 patients reported by GORTEC demonstrated a significantly greater improvement in 5-year OS rates (22% vs. 16%, $P = 0.05$) and DFS rates (27% vs. 15%, $P = 0.01$) in the CCRT group. Local–regional control was also significantly better in the CCRT group (48% vs. 25%, $P = 0.02$). These reports revealed better organ preservation in the CCRT group. However, the management of resectable patients with primary oropharyngeal carcinoma remains extremely controversial. For early-stage primary lesion (T1–2, N0) oropharyngeal carcinoma, GETTEC recommends surgical extirpation [26]. Insufficient randomized data are available to determine whether surgery or radiotherapy is more effective. The oropharynx is a good site for use of the organ preservation technique because of the potential compromise in speech or swallowing as a result of surgery. The Southwest Oncology Group treated 37 patients with advanced resectable base of tongue cancer with induction chemotherapy followed by definitive chemotherapy. The 3-year OS estimate was 67%, and the 3-year progression-free survival estimate was 62% [27]. In a meta-analysis of North American academic institutions that used surgery with or without radiotherapy or radiotherapy with or without neck dissection for patients with

SCC of the tonsillar region or the base of tongue, the rates of local control, rates of local–regional control and 5-year survival rates were similar between the two groups [28].

For the purpose of organ preservation, we have performed CCRT since 1999 in patients with resectable and unresectable advanced oropharyngeal SCC [29]. Our previous studies have clarified that CCRT with PFML regimen is safe and shows a high CR rate, resulting in good prognosis in patients with locally advanced HNSCC [15–17]. MTX and LV indicated the enhancement of 5-FU cytotoxicity. Recently, in addition to platinum-based chemotherapy, the use of multiagent NAC including docetaxel has showed a high CR rate and improved survival rates in patients with advanced HNSCC [35, 36]. We had compared NAC with TPF regimen followed by definitive RT and CCRT with TPF regimen. Both regimens were safe and tolerable. They showed almost similar pCR rate; however, CCRT group showed a significantly better OS rate than NAC group [13, 14]. In the present study, 44 of 56 patients (78%) received planned CCRT. Severe adverse events (e.g. grade 3 and 4) associated with CCRT included mucositis, dermatitis, neutropenia, nausea and vomiting. The second course of chemotherapy was discontinued in 12 patients because of one or more of the following reasons: renal toxicity, leukocytopenia, pneumonia, diarrhoea and ileus. Renal toxicity associated with CDDP administration is a major concern. To reduce and manage acute and late toxicities associated with CCRT, it is important to perform regular blood tests and urinalyses. Early nutritional support using a nasogastric tube or a gastric fistula sustains CCRT. Oral cavity care and pain control also help to sustain the planned CCRT [30].

At the primary site of cancer, the CR rate was 94%. In the remaining three patients, one patient with unresectable disease in the posterior pharyngeal wall (T3N2cM0) with bulky metastasis in the retropharyngeal lymph nodes showed NC after receiving planned CCRT with PFML regimen. One patient with resectable disease in the lateral wall (T4bN0M0) discontinued the planned second course of CCRT with PFML regimen because of severe renal toxicity and received definitive surgery instead. Another patient with resectable disease (T3N2bM0) showed NC after receiving planned CCRT with TPF regimen, but refused surgery. The results of our study clearly showed that CCRT of the primary site has a high CR rate in patients with T1 and T2 disease. In contrast, CCRT may not be effective in patients with T4 disease of the tongue base because four of six such patients experienced recurrence at the primary site after CCRT, and the tumours tended to be aggressive and deeply infiltrated the muscle. Two of six patients with disease at the tongue base, one with T2 disease and one with T4a disease, received salvage surgery after recurrence at the primary site. Recurrence at this site poses a great challenge because of lower survival rates, speech and swallowing difficulties associated with salvage surgery and longer hospital stay. Zafereo et al. [31] reviewed OS, functional outcomes and prognostic factors in patients who underwent salvage surgery for locally recurrent oropharyngeal SCC after initial radiotherapy. The 3-year OS rate in these patients was 48.7%. Age, DFS, recurrent tumour stage, recurrent neck disease and surgical margin status were the prognostic factors of OS and of the recurrence rate after salvage surgery. They reported that the patients for salvage surgery needed to be identified.

For patients with disease of the cervical lymph nodes, the CR rate was 78%. Two patients with unresectable (N3) disease showed NC after CCRT and subsequently died. The 5-year disease-specific survival rate was lower in patients with stage IVb disease. In contrast, six patients with resectable disease of the neck lymph nodes showed PR or NC after salvage surgery, and five of these six patients are still alive. Salvage surgery after CCRT was effective in patients with resectable cancer of the neck lymph nodes. Reddy et al. [32] reported excellent OS (100%) and DFS (93.8%) rates in 16 patients with stage III and IV oropharyngeal cancer with cervical nodal metastasis after initial neck dissection followed by radiotherapy with or without chemotherapy.

We have regularly used FDG-PET/CT for the early detection of recurrence in HNSCC patients. The usefulness of CT and MRI scans for HNSCC patients is sometimes limited because of tissue oedema, fibrosis, granulation, necrosis and scarring after definitive radiotherapy. Early detection of recurrent tumours at the locoregional site is critical to successful curative salvage surgery in patients with resectable disease.

In this series, we observed no postoperative complications of salvage surgery after CCRT. Both radiotherapy and chemotherapy adversely affect wound healing because they can result in wound infection, skin necrosis, fistula formation and adhesion [33, 34]. Thus, optimal care of wounds is necessary after CCRT.

The overall 5-year survival and 5-year disease-specific survival rates of our patients were 64.6% and 72.2%, respectively. The overall 5-year survival rate was 68.6% in patients with resectable disease and 47.7% in those with unresectable disease. The 5-year disease-specific survival rate was also better in patients with resectable disease than in those with unresectable disease. We conclude that CCRT is an effective treatment modality in terms of good outcome and function preservation for advanced oropharyngeal SCC, especially in patients with resectable disease.

Conflict of interest We have no conflict of interest.

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