Can Concurrent Chemoradiotherapy Replace Surgery and Postoperative Radiation for Locally Advanced Stage III/IV Tonsillar Squamous Cell Carcinoma?

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Abstract. *Aim: To compare surgery and postoperative radiotherapy (PORT) with the non-surgical combination of chemotherapy and radiation therapy (CCRT) for locally advanced squamous cell carcinoma (SCC) of the tonsil by measuring treatment outcomes and treatment-related complications. Patients and Methods: The records of 114 patients with non-metastatic stage III/IV tonsillar SCC treated between July, 1998 and December, 2010 were reviewed retrospectively. Among the 114 patients, 65 received PORT and 49 received CCRT. In the PORT group, treatment included wide surgical resection of the tumor with neck dissection and administration of PORT to the primary tumor bed with a median dose of 60 Gy. In the CCRT group, a median dose of 70 Gy was delivered to the gross tumor, and 46 patients received concurrent chemotherapy with i.v. cisplatin. The median follow-up time was 58 months in the PORT group and 44 months in the CCRT group. Results: There was no significant difference between PORT and CCRT in terms of 5-year locoregional recurrence-free survival (88.4% vs. 91.4%, p=0.68), distant metastasis-free survival (88.9% vs. 92.3%, p=0.60), disease-free survival (79.5% vs. 84.2%, p=0.63) or overall survival (78.9% vs. 88.9%, p=0.45). More CCRT patients than PORT patients experienced grade 3 (or higher) hematological toxicities and grade 2 pharyngitis during treatment. Chronic toxicity, manifested as swallowing difficulty, dry mouth and trismus, was similar between the two treatment groups. Conclusion: CCRT provides similar levels of local and distant control in patients with locally advanced tonsillar SCC as PORT, yet fails to show any superiority in preserving functions such as swallowing, saliva production, and mastication.*

The management of advanced squamous cell carcinoma of the head and neck (SCCHN) is a challenging clinical problem, with a dismal 5-year survival rate not exceeding 40%, despite the combination of surgery and postoperative radiotherapy (PORT) (1). In locally advanced or multi-nodal disease, SCCHN usually necessitates extensive surgery, requiring major tissue reconstruction and radiotherapy (RT), which can lead to dysfunction of speech or swallowing and cosmetic deformities, which are detrimental to quality of life (QOL) (1). For these reasons, primary RT with concurrent and/or induction chemotherapy is increasingly used to preserve organ function and improve survival in patients with advanced disease. Growing evidence suggests that the combination of chemotherapy and RT may be synergistic, improve locoregional control, eradicate micrometastases, and increase survival in patients with locally advanced SCCHN (2-4).

Oropharyngeal carcinoma is the most common type of head and neck malignancy. It is generally accepted that surgery or RT-alone are equally effective as single-modality treatment for early-stage disease (5); however, the management of advanced oropharyngeal carcinoma is still controversial (1, 6-8). Combined surgical resection and PORT is the standard treatment for locally advanced oropharyngeal cancer, whereas organ preservation using primary RT is an alternative to surgery in unresectable or medically inoperable patients. More recently, even though many oncologists have adopted concurrent chemoradiotherapy (CCRT) as a primary treatment modality to prevent the impairment of swallowing or speech, which leads to malnutrition and distress in social situations (9), there is clearly no consensus among clinicians

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Key Words: Tonsil cancer, surgery, radiotherapy, concurrent chemoradiotherapy.

Table I. *Patient and treatment characteristics.*

	No. of patients (%)		
	PORT (N=65)	CCRT (N=49)	*p*-Value
Median age (range), years	52 (32-77)	56 (37-70)	0.04
Gender			
Male	60 (92)	43 (88)	0.53
Female	5 (8)	6 (12)	
ECOG performance score			
0-1	65 (100)	49 (100)	-
Smoking	41 (63)	32 (65)	0.85
Tumor status			
T1	17 (26)	10 (20)	0.27
T2	31 (48)	20 (41)	
T3	6 (9)	3 (6)	
T4	11 (17)	16 (33)	
Nodal status			
N0	0 (0)	2 (4)	0.41
N1	7 (11)	6 (12)	
N2	57 (88)	40 (82)	
N3	1 (2)	1 (2)	
Overall staging			
Stage III	4 (6)	4 (8)	0.43
Stage IVA	59 (91)	41 (84)	
Stage IVB	2 (3)	4 (8)	
Median tumor size (range), cm	2.8 (0.6-5.5)	2.9 (0.5-5.2)	0.54
Histological differentiation			
Well	6 (9)	2 (4)	0.02
Moderately	41 (63)	25 (51)	
Poorly	17 (26)	14 (29)	
Unknown	1 (2)	8 (16)	
Neck dissection	65 (100)	2 (4)	< .01
Radiotherapy			
Median dose (range), Gy	60 (50-73)	70 (62-76)	<0.01
Median treatment duration, Days (range)	48 (31-73)	51 (41-65)	0.01
IMRT	34 (52)	22 (45)	0.46
Chemotherapy			
Concurrent	4 (6)	49 (100)	<0.01
Induction	14 (22)	38 (78)	<0.01
Median follow-up (range), months	58 (4-164)	44 (7-147)	0.16

PORT, Postoperative radiotherapy; CCRT, concurrent chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity-modulated radiotherapy.

regarding the optimal treatment approach for locally advanced oropharyngeal cancer.

Because of the controversy regarding whether the best therapeutic approach is surgical or non-surgical, this retrospective study was designed to compare outcomes and treatment-related complications after PORT or CCRT in patients with locally advanced squamous cell carcinoma (SCC) of the tonsillar region (including pillars and fossae).

Table II. *Tumor response at three months after the concurrent chemoradiotherapy.*

	N	%
Complete response	47	96
Partial response	0	0
Stable disease	0	0
Progressive disease	2	4
Total	49	100

Patients and Methods

The medical records of 114 patients treated with either PORT or CCRT for newly diagnosed, histologically proven stage III/IV tonsillar SCC between July, 1998 and December, 2010 were analyzed retrospectively. Patients with distant metastasis at initial diagnosis, those who had previous malignant disease, and those who were treated with palliative intent were excluded. All patients were staged using flexible endoscopy, computed tomography (CT) scanning and/or magnetic resonance imaging (MRI) of the head and neck region, and chest X-ray. The median follow-up times were 58 months and 44 months in the PORT and CCRT groups, respectively.

Patients. Table I shows that the demographic and clinical characteristics, including gender, ECOG performance score, smoking habits, stage, and tumor size, were comparable between the two treatment groups. The median age was significantly higher in the CCRT group (56 years for CCRT *vs*. 52 years for PORT; p=0.04). Tumors were restaged according to the 2009 American Joint Committee on Cancer TNM staging system (10). Overall, eight patients had stage III, 100 had stage IVA, and six had stage IVB disease.

Treatment. The treatment philosophy at our Institution has evolved over several decades. The prevailing option for advanced disease is PORT; however, in recent years, CCRT has emerged as an alternative modality depending on the extent of the disease, the medical condition of the patient, the clinician's experience, and the patient's preference. Sixty-five and 49 patients were treated with a PORT or CCRT regimen, respectively. RT was performed using 4-6 photons from a linear accelerator, and all patients were immobilized using a custom-made thermoplastic mask.

In the PORT group, surgery involved wide resection of the tumor, with neck dissection for unilateral or bilateral disease as needed. Neck dissection was performed in all patients, 64 of whom underwent modified radical neck dissection and one of whom underwent supraomohyoid neck dissection. RT was administered to the primary tumor bed with a median total dose of 60 Gy (range=50-73 Gy), and a single daily dose of 1.8-2.2 Gy per fraction. All patients received elective nodal irradiation at levels I-IV with a median dose of 50.4 Gy. Thirty-four patients received RT using intensity-modulated radiotherapy (IMRT). Fourteen patients underwent induction chemotherapy consisting mainly of cisplatin plus taxane/TS-1 before surgical resection, and four patients received three cycles of cisplatin concurrently with RT.

Table III. *Acute and chronic toxicities by treatment*.

	PORT				CCRT				
	Gr 0-1	Gr 2	Gr 3	Gr 4	Gr 0-1	Gr 2	Gr 3	Gr4	*p*-Value
Acute									
Dermatitis	39	24	2	-	26	22	1	-	0.67
Mucositis	13	40	12	-	9	25	15	-	0.31
Pharyngitis	16	48	1	-	3	44	2	-	0.03
Leucopenia	54	9	2	-	24	16	9	-	< .01
Neutropenia	60	3	1	1	27	14	8	-	< .01
Thrombocytopenia	64	1	-	-	45	4	-	-	0.16
Chronic									
Swallowing difficulty	53	12	-	-	45	4	-	-	0.17
Dry mouth	24	41	-	-	20	29	-	-	0.70
Trismus	65	-	-	-	48	1	-	-	0.43

PORT, Postoperative radiotherapy; CCRT, cconcurrent chemoradiotherapy.

In the CCRT group, 11 patients underwent tonsillectomy and the remainder underwent incisional or excisional biopsy for tissue diagnosis. External beam RT was performed with a median dose of 70 Gy (range=62-76 Gy) to the gross tumor with a single daily dose of 1.8-2.4 Gy per fraction and a median dose of 46 Gy delivered to elective nodal areas. Twenty-two patients received RT with IMRT. Forty-six patients completed at least two cycles of cisplatin concurrently with RT and 38 patients received platinum-based induction chemotherapy with the most common agents being cisplatin and TS-1 followed by cisplatin, 5-fluorouracil and docetaxel.

Response evaluation and follow-up. In the CCRT group, tumor response was evaluated 2-3 months after the completion of treatment by clinical examination of the head and neck, flexible endoscopy, and CT and/or MRI according to the World Health Organization criteria (11). Subsequently, patients were followed-up with physical examination and endoscopy every 3 months for the first 2 years and, thereafter, patients were usually seen every 6 months. Treatment-related toxicity was recorded using Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis. Patient characteristics and toxicities were compared between the two treatment groups using the χ^2 test or two-sample *t*-tests, as appropriate. Locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS) were assessed using the Kaplan-Meier method and compared using the log-rank test. Survival was measured from the date of surgery, or initiation of chemoradiotherapy, to the date of locoregional recurrence for LRFS, distant metastasis for DMFS, first failure for DFS, and death or last follow-up for OS. All deaths, regardless of cause, were recorded in the OS analysis. The Cox proportional hazard model was used to evaluate factors predicting survival by multivariate analysis. A *p*-value ≤0.05 was considered statistically significant. SPSS software version 18.0K (SPSS Institute, Chicago, IL, USA) was used for all statistical analyses.

Results

Clinical response. Response evaluation for all patients in the CCRT group was conducted 2-3 months after the completion of radiation. Forty-seven (96%) patients showed a complete response to treatment (Table II). Progressive disease was observed in two patients who refused salvage surgical resection.

Site of relapse and time-to-recurrence. Figure 1 shows the distribution of sites of first relapse. Nineteen patients presented with at least one component of relapse. Locoregional recurrence occurred in 10 patients (six PORT *vs*. four CCRT). Eight patients presented with distant metastasis, frequently in the lung or bone. One case of relapse in the PORT treatment group involved both locoregional and distant metastasis. All recurrences were observed within five years of treatment (median=12 months; range=3-48 months).

Survival. At the time of analysis, 19 patients (13 PORT *vs*. six CCRT) had died. The most common cause was locoregional recurrence (five PORT *vs*. three CCRT) followed by distant metastasis (two PORT *vs*. two CCRT). One patient in the PORT group died due to both locoregional recurrence and distant metastasis. Six patients died of other causes: four of other primary cancer, one of cardiac causes, and one of aspiration pneumonia after gastrostomy tube removal. The LRFS, DMFS, DFS and OS curves for the two treatment groups are shown in Figures 2 to 5. No significant difference was observed between the PORT and CCRT groups in terms of 5-year LRFS (88.4% *vs*. 91.4%, *p*=0.68), DMFS (88.9% *vs*. 92.3%, *p*=0.60), DFS (79.5% *vs*. 84.2%, *p*=0.63) or OS (78.9% *vs*. 88.9%, *p*=0.45).

Treatment toxicity. Table III shows the acute and chronic toxicity according to treatment. More CCRT patients experienced grade 3 (or higher) leucopenia (two PORT *vs*. nine CCRT, *p*=0.01) and neutropenia (two PORT *vs*. eight CCRT, *p*=0.02) during treatment. Pharyngitis greater than grade 2 occurred in 49 (75%) patients in the PORT group and 46 (94%)

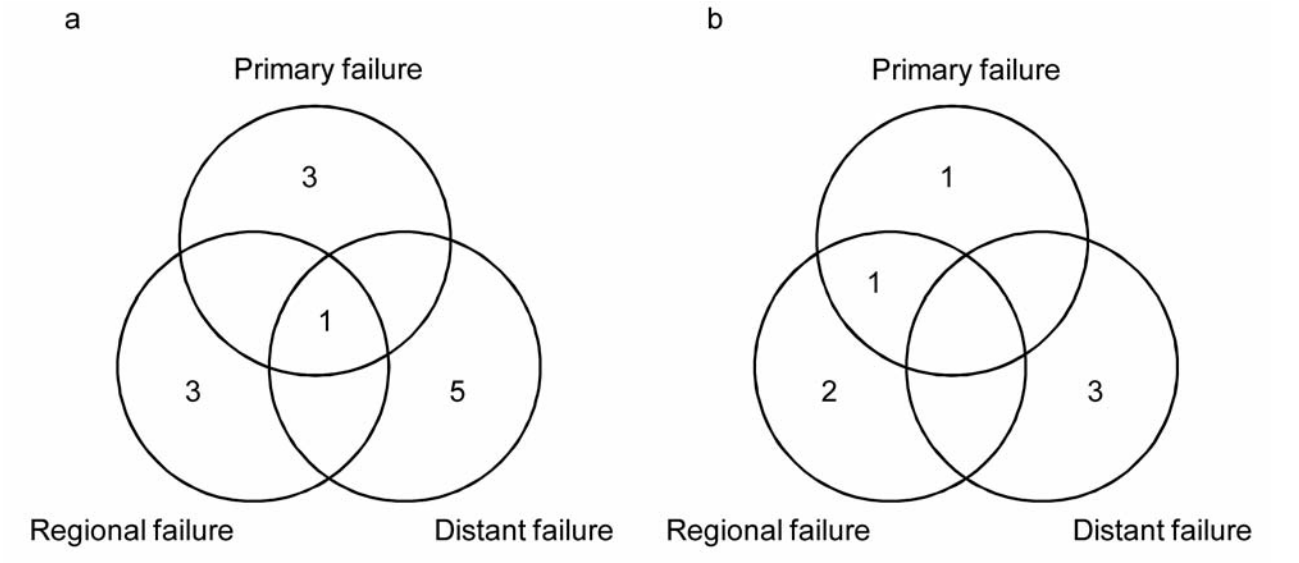

Figure 1. *Site of first relapse in patients treated with: surgery and postoperative radiotherapy (a), concurrent chemoradiotherapy (b).*

patients in the CCRT group (p=0.01). In the CCRT group, acute complications due to concurrent chemotherapy were almost resolved after completing treatment. No difference in the rate of pharyngitis above grade 3 (one PORT *vs*. two CCRT, p=0.58) was observed between the two groups. No patient experienced severe acute complications requiring surgical intervention or hospitalization in either group. Chronic toxicity involving swallowing difficulty, dry mouth, and trismus was similar between the PORT and CCRT groups. No patient had a gastrostomy tube for more than six months after completion of treatment in either group.

Discussion

In this study, we compared the treatment outcomes in patients treated with PORT after surgery and CCRT for locally advanced stage SCC of the tonsillar region. Although the management of stage III-IV tonsillar carcinoma remains controversial, surgery and PORT is the standard treatment modality (12). However, there has been no definitive randomized study on this subject. In our hospital, surgery and PORT was initially considered in patients with locally advanced tonsillar carcinoma and RT with or without chemotherapy was considered in cases that were medically inoperable, surgically unresectable, or for those who refused surgery. On the basis of treatment policy, patients undergoing surgery and PORT had a more favorable prognosis than patients with CCRT.

In the results of this study, the survival of patients with locally advanced tonsillar SCC treated with CCRT was excellent and did not differ significantly from that of patients treated with PORT after surgery. More CCRT patients experienced treatment-related toxicity, including hematological complications and pharyngitis during treatment. However, these complications required neither surgical intervention nor hospitalization. The present study has several limitations, including its retrospective design, comparing non-randomized patients, and differences in age and histological differentiation between the two treatment groups. Additionally, no information is presented regarding the prescribed radiation dose, which was variable between the treatment groups. Despite these limitations, this report is one of relatively few comparing clinical outcome and toxicity between PORT and CCRT in patients with locally advanced SCC of the tonsillar region. Additionally, the number of patients in the present study is relatively large compared with those in previous reports. Most studies have compared the efficacy of surgery and RT for locally advanced tonsillar cancer, except for a small randomized study by Kramer *et al*. (13), which had a retrospective design and reviewed patients treated before the era of concurrent chemotherapy.

Tonsillar carcinoma exhibits radiosensitivity and the high-dose RT has been an effective treatment modality for patients with squamous cell carcinoma of the tonsillar region. Mendenhall *et al*. (12) updated their experience with definitive RT-alone and compared the outcome with that of postoperative RT reported in the literature. They concluded that RT-alone did not compromise survival, and was associated with a lower rate of severe complications. The treatment outcomes of RT for tonsillar carcinoma were satisfactory because the prognosis of tonsillar carcinoma was

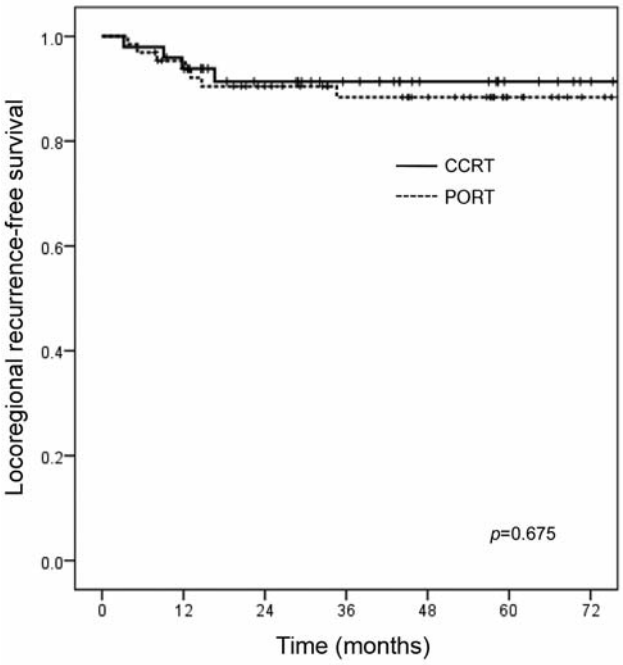

Figure 2. *Locoregional recurrence-free survival rate estimated by Kaplan–Meier method in tonsillar carcinoma by treatment (postoperative radiotherapy vs. concurrent chemoradiotherapy).*

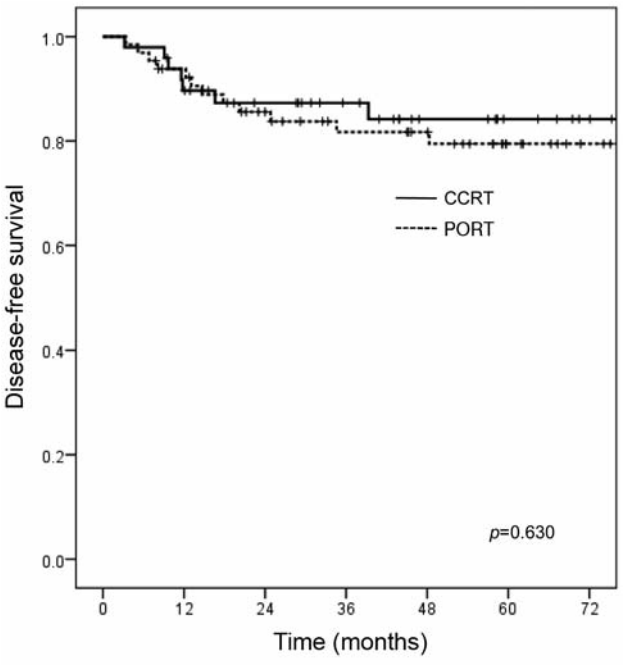

Figure 4. *Disease-free survival rate estimated by Kaplan–Meier method in tonsillar carcinoma by treatment (postoperative radiotherapy vs. concurrent chemoradiotherapy).*

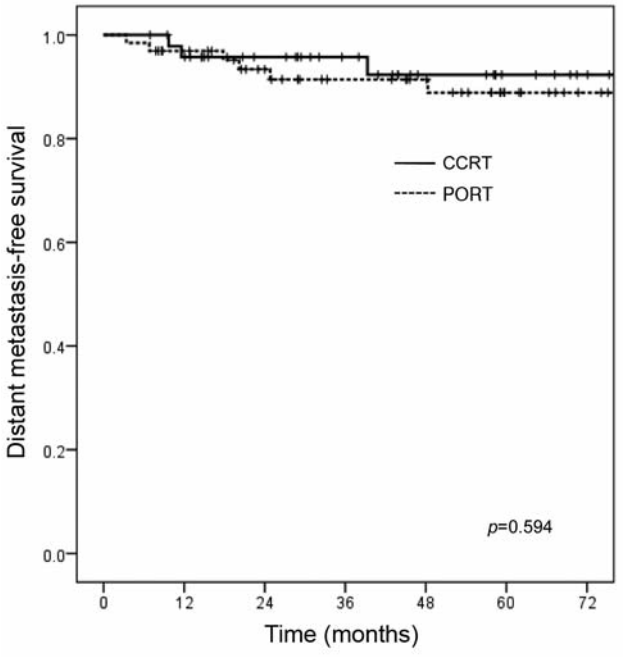

Figure 3. *Distant metastasis-free survival rate estimated by Kaplan–Meier method in tonsillar carcinoma by treatment (postoperative radiotherapy vs. concurrent chemoradiotherapy).*

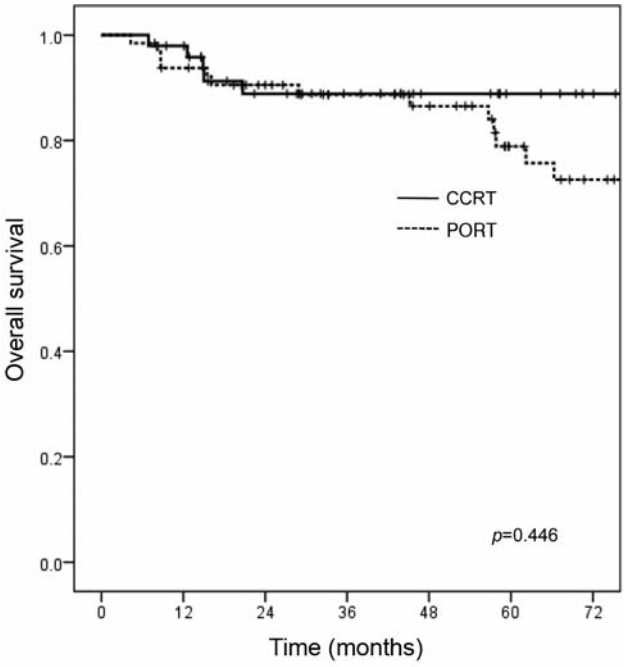

Figure 5. *Overall survival rate estimated by Kaplan–Meier method in tonsillar carcinoma by treatment (postoperative radiotherapy vs. concurrent chemoradiotherapy).*

good. Charbonneau *et al*. (14) also reported that local control and survival after definitive RT were similar to those for postoperative RT published in the literature. Parsons *et al*. (1) presented a pooled analysis of treatment results from over 6,000 patients with oropharyngeal cancer. They found marked similarities in locoregional control and survival between the two treatment modalities, and a greater incidence of severe or fatal complications in the surgical treatment group. In contrast, there are several reports, including these of Perez *et al*. (15) Poulsen *et al*. (16) and Hicks *et al*. (5) reporting that surgery with or without PORT offered better tumor control than definitive RT for patients with locally advanced disease.

Since CCRT was introduced, and gained widespread acceptance for the treatment of locally advanced SCCHN (2-4,17,18), it has become another mainstay of primary treatment, like primary surgery, for advanced oropharyngeal cancer. However, no prospective study directly comparing CCRT with surgical treatment has been reported. There are a few retrospective studies (19,20) on this subject, and the results of retrospective studies at single institutions can provide useful clinical information. Chung *et al*. (19) compared survival and QOL of 42 patients with early T- and advanced N-stage tonsillar SCC treated with PORT or CCRT: no significant difference was observed in 2-year OS (PORT 91.7% *vs*. CCRT 100%, p=0.18) or global health status (PORT 80.7±18.2 *vs*. CCRT 66.1±27.2, p=0.06). Boscolo-Rizzo *et al*. (20) compared CCRT and PORT in 57 patients with stage III/IV oropharyngeal cancer and reported improved long-term QOL in patients treated with CCRT, but no difference in survival.

The rate of treatment-related complications for surgery and PORT patients was similar to that for CCRT patients. Although the complication rate was similar by treatment methods (21), the patterns of complications depended on the type of treatment methods. However, a limitation of this study is the lack of detailed analysis for patterns of treatment-related complications. Open surgical resection will cause deformities of the face and neck; CCRT has advantages in this respect. According to Lee *et al*., intensity- modulated radiotherapy showed excellent locoregional control and low rates of xerostomia (22) and the primary treatment modality did not affect treatment outcome.

In conclusion, the combination of primary RT and chemotherapy in patients with locally advanced tonsillar SCC provides similar local control to that provided by surgery and PORT. However, it showed no superiority in terms of function preservation (swallowing, saliva production, mastication). Considering the lack of prospective trials reporting outcomes after PORT *vs*. CCRT, future randomized controlled trials are needed to clarify the advantage of organ preservation with CCRT.

Conflicts of Interest

No potential conflicts of interest exist. None of the Authors have any external funding or grants to disclose.

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