

Original Article

Treatment selection for tonsillar squamous cell carcinoma

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Abstract

Background: The optimal treatment for tonsillar squamous cell carcinoma (SCC) remains controversial. The purpose of this study was to evaluate long-term treatment outcomes of patients with tonsillar SCC, in order to aid in appropriate treatment selection.

Methods: We conducted a retrospective chart review of 105 patients with curatively treated tonsillar SCC between January 1996 and December 2005. Forty-three patients (41.0%) underwent primary surgery with or without adjuvant therapy (primary surgery group), and 62 patients (59.0%) were treated with radiotherapy/chemoradiotherapy (RT/CRT, organ preservation group). Twenty patients (19%) received tumor tonsillectomy before definitive RT/CRT and were grouped into the organ preservation group.

Results: No significant differences were observed between the primary surgery and organ preservation groups in terms of local control ($p = 0.212$), regional control ($p = 0.684$), distant metastasis ($p = 0.627$), 5-year disease-specific survival (DSS, $p = 0.774$), and overall survival rates (OS, $p = 0.667$). The rates of major complication ($p = 0.216$), long-term dependency on feeding tubes ($p = 0.876$), and tracheostomy ($p = 0.401$) were also similar. Advanced T classification (T3–4) was the only factor associated with significantly worse DSS ($p = 0.007$) and OS ($p = 0.012$). However, there was also no difference in final treatment outcomes in T3–4 patients regardless of whether they were treated with primary surgery or RT/CRT. In the organ preservation group, tumor tonsillectomy before RT/CRT did not improve local control ($p = 0.520$) or other treatment outcomes, including 5-year DSS ($p = 0.707$) and OS ($p = 0.745$).

Conclusion: Both primary surgery and RT/CRT organ preservation are effective treatments for tonsillar SCC. Single modality treatment, either surgery or RT/CRT, can typically be provided for stage I–II diseases. Although RT/CRT organ preservation is used more frequently for stage III–IV tonsillar SCC in recent years, primary surgery combined with adjuvant therapy still achieves equivalent outcomes. Multidisciplinary pretreatment counseling and the facilities and personnel available are therefore important for decision-making. In addition, if RT/CRT organ preservation is selected as the primary treatment, tumor tonsillectomy is not indicated.

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Keywords: organ preservation; squamous cell carcinoma; surgery; tonsil; tonsillectomy

1. Introduction

Tonsillar squamous cell carcinoma (SCC) is the most common type of oropharyngeal cancer and is relatively radio-sensitive.¹ Multiple treatment modalities are thus available,

including primary surgery with or without adjuvant therapy and radiotherapy/chemoradiotherapy (RT/CRT) organ preservation. Early tonsillar SCC can be effectively treated with either RT or surgery alone.² Many patients, however, present at advanced stages, and a combination of primary surgery and postoperative radiotherapy (PORT) is the traditional treatment of choice.^{3,4}

Over the past decade, however, there has been a paradigm shift toward RT/CRT organ preservation because surgical

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excision for advanced tonsillar SCC is technically demanding and frequently associated with post-treatment cosmetic and functional sequelae.^{5,6} The combination of chemotherapy with RT in organ preservation treatment has been demonstrated to improve the efficacy of RT alone for advanced oropharyngeal SCC, offering comparable treatment outcomes to primary surgery with PORT.^{7–9} However, high rates of acute grade 3–4 toxicities and late treatment sequelae can be observed under intense CRT treatment, including xerostomia, dysphagia, soft tissue fibrosis, and radionecrosis.¹⁰ So far, no randomized studies have compared the treatment outcomes of CRT and primary surgery for tonsillar SCC, and therefore, the optimal treatment selection remains unsettled.^{5,11}

Another controversial issue is the benefit of tumor tonsillectomy before RT/CRT organ preservation. Surgical excision of the primary tumor reduces tumor burden and can theoretically provide better local tumor control. Yildirim et al¹² demonstrated that gross primary tumor removal by tonsillectomies followed by RT achieved excellent treatment outcomes. However, no control group without tonsillectomy was available for comparison in their study, and the benefit of tumor tonsillectomy remains unclear.

The purpose of this study was to compare the treatment outcomes, major complication rates, and functional results of patients with tonsillar SCC treated with either primary surgery or RT/CRT organ preservation. Furthermore, we also investigated the role of tumor tonsillectomy before RT/CRT organ preservation.

2. Methods

2.1. Study population

Between January 1996 and December 2005, 105 patients with histologically confirmed tonsillar SCC were curatively treated at the Department of Otolaryngology, Taipei Veterans General Hospital, Taiwan. None of the patients had radiologic evidence of distant metastasis at presentation, and those with a previous history of cancer were excluded unless they had been disease free for at least 2 years.

Pretreatment evaluations included a physical examination, panendoscopy tumor mapping and biopsy, computed tomography (CT) or magnetic resonance imaging of the primary tumor and the neck, chest X-ray or chest CT, and routine laboratory studies. Treatment records were reviewed, and the patients were categorized into two groups: surgery with or without adjuvant therapy (primary surgery group) and RT/CRT (organ preservation group). After treatment completion, the patients entered a monthly follow-up program for the 1st year, and every 3 months thereafter. Patients were staged according to the 2002 criteria of the American Joint Committee on Cancer. This study was approved by the hospital's Institutional Review Board.

2.2. RT and CRT regimens

PORT was delivered at 2 Gy per fraction, 5 days per week, at a total dose of 60–66 Gy to the primary site and/or positive

neck levels and 50 Gy to the N0 neck levels. Patients in the organ preservation group received RT under the same RT schedule with a total dose of 70 Gy to the primary site and gross lymphadenopathy (≥ 1 cm), and 50 Gy to the N0 neck. Both sides of the neck were included in treatment portals and RT was administered with 6-MV X-rays from a linear accelerator. Most of the RT techniques used were initial 2D followed by 3D boost after 56 Gy. Ten patients received intensity-modulated RT, and accelerated fractionation was not used.

Cisplatin-based induction chemotherapy was given mainly to those patients with bulky T3–4 primary tumors and/or neck diseases. In primary concurrent chemoradiotherapy (CCRT) treatment, weekly cisplatin (20 mg/m²) and 5-fluorouracil (400 mg/m²) were delivered concurrently with the RT. In postoperative concurrent chemoradiotherapy (POCCRT) treatment, the chemotherapy regimen consisted of weekly cisplatin (30 mg/m²) and daily oral tegafur–uracil (250 mg/m²) concurrently with PORT.

2.3. Statistical analysis

Local and regional controls were defined as no evidence of disease at the primary site and the neck. Differences in the pretreatment and treatment variables between the two groups were determined using the Chi-square or Fisher exact test and *t* test. The rates of disease-specific survival (DSS) and overall survival (OS) were calculated using the Kaplan–Meier product limit method and compared by the logrank test. Follow-up times were defined as the duration between the date of treatment initiation and the events or last contact. DSS was defined as the time to death from cancer or treatment-related events. Functional results were evaluated by long-term dependency on feeding tubes for nutrition and tracheostomy for breathing. Major complications were defined as treatment-related events that necessitated a second operation, prolonged hospitalization, or were life-threatening. All analyses were performed using the Statistical Package for the Social Sciences software version 17.0 (SPSS Inc., Chicago, IL, USA). All tests were two sided, and results were considered significant at $p < 0.05$.

3. Results

3.1. Patient characteristics

The characteristics of the patients are summarized in Table 1. Of the 105 patients in our study, 40 (38.1%) had locally advanced T3–4 tumors and 71 (67.6%) had advanced stage III–IV disease at initial diagnosis. Forty-three patients (41.0%) were treated with primary surgery with or without adjuvant therapy, and 62 patients (59.0%) were treated with RT/CRT organ preservation. There were no differences between the two groups in terms of age, gender, T and N classifications, TNM stage, and histological differentiation. The treatment paradigm changed significantly at our institute before and after 2002. Only 35.3% of the patients underwent

Table 1
Patient characteristics by treatment group.

Variable	All patients (<i>n</i> = 105)	Organ preservation (<i>n</i> = 62) ^a	Primary surgery (<i>n</i> = 43)	<i>p</i>
	No. (%)	No. (%)	No. (%)	
Mean age (range) (y)	54.3 (30–83)	54.8 (30–83)	53.7 (34–81)	0.670
Gender				
Male	89 (84.8)	52 (83.9)	37 (86.0)	—
Female	16 (15.2)	10 (16.1)	6 (14.0)	—
T classification				
T1–2	65 (61.9)	39 (62.9)	26 (60.5)	—
T3–4	40 (38.1)	23 (37.1)	17 (39.5)	—
N classification				
N0–1	53 (50.5)	28 (45.2)	25 (58.1)	—
N2–3	52 (49.5)	34 (54.8)	18 (41.9)	—
Stage				
I–II	34 (32.4)	17 (27.4)	17 (39.5)	—
III–IV	71 (67.6)	45 (72.6)	26 (60.5)	—
Histological grade				
WD-MD	46 (43.8)	22 (35.5)	24 (55.8)	—
PD	20 (19.0)	11 (17.7)	9 (20.9)	—
Unknown	39 (37.1)	29 (46.8)	10 (23.3)	—

MD = moderately differentiated; PD = poorly differentiated; WD = well differentiated.

^a Patients undergoing tumor tonsillectomy followed by radiotherapy/chemoradiotherapy were grouped into the organ preservation group.

RT/CRT organ preservation treatment before 2002, in contrast to 81.5% of the patients after 2002 ($p < 0.001$).

Of the 43 patients in the primary surgery group, mandibular surgery to approach the primary tumor was performed in 39 patients (90.7%), including mandibulotomy in 20 patients (46.5%) and marginal or segmental mandibulectomy in 19 patients (44.2%). Reconstructive surgeries were required to repair oropharyngeal defects in 35 patients (81.4%). Eighteen patients (41.9%) were treated with surgery alone, while 20 (46.5%) and 5 (11.6%) patients received adjuvant PORT and POCRT, respectively, mainly due to the presence of adverse pathologic features.

Of the 62 patients in the organ preservation group, 23 (37.1%) received RT alone, 18 (29.0%) received CCRT, and 21 (33.9%) received induction chemotherapy with CCRT. Twenty patients (32.3%) received a tumor tonsillectomy before definitive RT/CRT treatment. Seven patients received neck dissection for advanced N2–3 presentation before definitive RT/CRT. Eight patients received planned neck dissection for residual neck mass after completion of RT/CRT, and one (12.5%) of them tested positive for SCC.

3.2. Oncologic results

The median follow-up times of the surviving patients were 108.2 and 82.7 months for the primary surgery and organ preservation groups, respectively. Treatment details and outcomes are summarized in Table 2. Neck dissection was primarily performed on patients in the primary surgery group, while chemotherapy was used with significantly greater frequency in the organ preservation group ($p < 0.001$). In addition, patients in the organ preservation group received significantly higher doses of radiation compared with those in the primary surgery group ($p < 0.001$). However, disease

control was equivalent between the two groups. There were no significant differences in local control ($p = 0.212$), regional control ($p = 0.684$), and distant metastasis ($p = 0.627$). The 5-year DSS rates were 68.9% and 72.8% ($p = 0.744$), and the 5-year OS rates were 62.9% and 64.9% ($p = 0.667$) in the primary surgery group and organ preservation group, respectively (Fig. 1A and B). Taken together, all oncologic results were similar regardless of whether the patients were treated with primary surgery or RT/CRT organ preservation.

Table 2
Treatment and outcomes by treatment group.

	Organ preservation (%) (<i>n</i> = 62)	Primary surgery (%) (<i>n</i> = 43)	<i>p</i>
Neck dissection			
Yes	24.2	88.4	<0.001
No	75.8	11.6	
Chemotherapy			
Yes	62.9	11.6	<0.001
No	37.1	88.4	
Mean RT dose (range) (Gy)	67.4 (52–76)	61.2 (56–66)	<0.001
Median follow-up (range) ^a (mo)	82.7 (6–170)	108.2 (8–146)	0.282
Disease control			
Local control	79.0	88.4	0.212
Regional control	88.7	86.0	0.684
Distant metastasis	12.9	16.3	0.627
5-year survival			
Disease-specific survival	72.8	68.9	0.774
Overall survival	64.9	62.9	0.667
Functional results			
Feeding tube dependent	12.9	14.0	0.876
Tracheostomy dependent	6.6	2.3	0.401
Major complications	17.7	27.9	0.216

RT = radiotherapy.

^a For surviving patients.

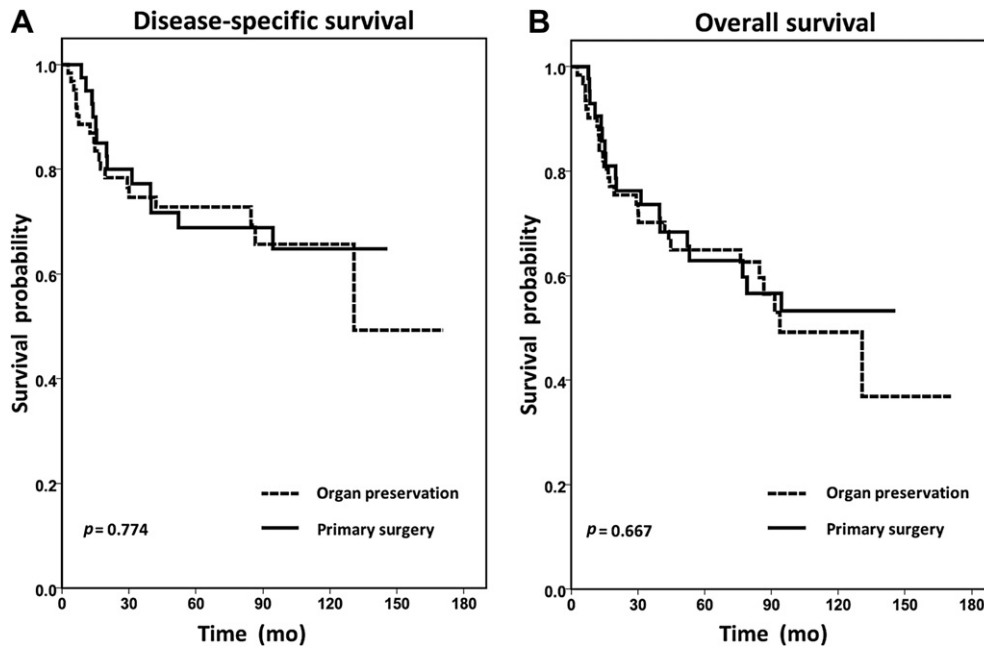


Fig. 1. (A) Disease-specific survival and (B) overall survival rates in the treatment group of 105 patients with tonsillar squamous cell carcinoma.

3.3. Functional results and major complications

Functional results were determined by the dependence on feeding tubes and tracheostomy at least 6 months after completion of treatment. As shown in Table 2, feeding tube dependency was observed in 14.0% and 12.9% ($p = 0.876$), and tracheostomy dependency was observed in 2.3% and 6.6% ($p = 0.401$) of patients in the primary surgery group and the organ preservation group, respectively. The only factor predicting feeding tube dependency and tracheostomy dependency was advanced T3–4 classifications ($p = 0.001$ and 0.006 , respectively). Major complications occurred in 12 patients (27.9%) in the primary surgery group and 11 patients (17.7%) in the organ preservation group ($p = 0.216$). Mandibular osteoradionecrosis was the most common type of major complication in both treatment groups (Table 3). Flap failure, severe wound infection, and pneumonia occurred mostly in the primary surgery group, while pharyngeal bleeding, renal failure, and gastrointestinal bleeding were only observed in the organ preservation group.

Table 3
Major complications by treatment group.

	Organ preservation, no. (%)	Primary surgery, no. (%)
Mandibular ORN	6 (9.6)	6 (14.0)
Flap failure	0 (0)	3 (7.0)
Severe wound infection	1 (1.6)	2 (4.7)
Pneumonia	0 (0)	1 (2.3)
Pharyngeal bleeding	2 (3.2)	0 (0)
Renal failure	1 (1.6)	0 (0)
GI bleeding	1 (1.6)	0 (0)
Total	11 (17.7)	12 (27.9)

GI = gastrointestinal; ORN = osteoradionecrosis.

3.4. Treatment results of locally advanced tumors

Advanced T classification (T3–4) was the only significant predictor of worse DSS ($p = 0.007$) and OS ($p = 0.012$) in this study. Consequently, further analysis was carried out on this poorly performing subgroup (Table 4). Although T3–4 patients treated with primary surgery demonstrated a trend toward better local control (88.2% vs. 69.6%, $p = 0.256$) and higher distant metastasis rates (41.2% vs. 17.4%, $p = 0.153$), neither were statistically significant. There were no significant differences in the 5-year DSS rate ($p = 0.638$), and the 5-year OS rate ($p = 0.921$) between those treated with primary surgery and RT/CRT organ preservation. Functional outcomes

Table 4
Disease control, survival, and functional results in the patients with T3–4 tumors by treatment group.

	Organ preservation (%) ($n = 23$)	Primary surgery (%) ($n = 17$)	p
N2–3	65.2	64.7	0.973
Chemotherapy	87.0	17.6	<0.001
Mean RT dose (range) (Gy)	69.7 (60–76)	61.6 (59–66)	<0.001
Disease control			
Local control	69.6	88.2	0.256
Regional control	82.6	88.2	0.978
Distant metastasis	17.4	41.2	0.153
5-year survival			
Disease-specific survival	62.8	46.3	0.638
Overall survival	51.5	46.3	0.921
Functional results			
Feeding tube dependent	21.7	35.3	0.477
Tracheostomy dependent	18.2	5.9	0.363
Major complications	17.4	35.3	0.274

RT = radiotherapy.

by feeding tube ($p = 0.477$), tracheostomy dependency ($p = 0.363$), and major complication rates ($p = 0.274$) were also similar between the two groups.

3.5. Role of tonsillectomy in organ preservation treatment

Twenty (32.3%) of the 62 patients in the organ preservation group underwent tumor tonsillectomy before RT/CRT treatment. Nineteen (95%) of the 20 patients had early T1–2 tumors, and 12 (60%) had N0–1 classification at initial diagnosis (Table 5). Significantly fewer patients received chemotherapy (20.0% vs. 83.3%, $p < 0.001$), and the RT dose was also significantly lower in those patients undergoing tumor tonsillectomy ($p < 0.001$). According to the surgical records, tumor tonsillectomy with a confident surgical margin was achieved in three (15%) cases. The final reports of pathological studies revealed that surgical margin was adequate in only one (5%) patient, close or positive in 10 (50%), and uncertain in nine (45%). After long-term follow-up, the local control rate was not significantly improved with tumor tonsillectomy (85% vs. 76.2%, $p = 0.520$). There were no significant improvements in regional and distant controls, and 5-year DSS and OS rates (Fig. 2A and B) among those with or without tumor tonsillectomy. The differences in functional outcomes and major complications were also not significant (Table 5).

4. Discussion

Tonsillar SCC usually responds well to CRT, and there has been widespread interest in performing such organ preservation treatment in recent years.^{6,13} Chen et al¹³ analyzed the primary treatment modalities of oropharyngeal SCC in the United States from 1985 to 2001, and found that the use of cancer-directed surgery remained stable, whereas CRT was

increasingly prevalent and RT alone significantly decreased. The optimal treatment for tonsillar SCC remains controversial as no randomized studies have compared primary surgery and RT/CRT organ preservation. At our institute, the treatment paradigm for tonsillar SCC changed dramatically after 2002. The proportion of patients treated with primary surgery decreased significantly from 64.7% to 18.5% after 2002, while those treated with RT/CRT organ preservation increased significantly from 35.3% to 81.5% ($p < 0.001$). Thus, matched patient samples in T or N classification were available for this retrospective study, providing a reliable comparison with low selection bias between the two groups (Table 1). Our results show that primary surgery can achieve equivalent results as organ preservation treatment for tonsillar SCC (Table 2). This indicates that primary surgery with or without adjuvant therapy remains a treatment choice for tonsillar SCC.

It is generally accepted that early T1–2 tonsillar SCC can be effectively treated with either surgery or RT alone.² We thus further analyzed the 40 patients with advanced T3–4 tumors. In the primary surgery group, slightly better local control, more distant metastasis, higher feeding tube dependency and lower tracheostomy dependency, and more major complications were observed, compared with the organ preservation group (Table 4). However, none of the differences were statistically significant. This implies a similar efficacy between the two treatment groups, even in advanced T3–4 tonsillar SCC.

The optimal treatment for advanced tonsillar SCC is controversial. Parsons et al⁵ conducted a comprehensive literature review demonstrating similar oncological outcomes with both treatment modalities; however, the severe complication rate was significantly higher in the surgery group. In this study, the major complication rate in the primary surgery group was slightly but not significantly higher compared with the organ preservation group ($p = 0.216$, Table 2). Mandibular osteoradionecrosis was the most common complication encountered in both treatment groups, because 25 (58.1%) patients in the primary surgery group required PORT or POCRT (Table 3). However, other types of complications were distributed differentially between the two groups.

Whether transoral tonsillectomy before RT/CRT is the definitive treatment or the debulking management has long been debated clinically. In this study, although 19 (95%) of the 20 patients treated with tumor tonsillectomy had early T1–2 tumors, adequate surgical and pathological margins were hardly achieved, occurring in only three (15%) and one (5%) patient, respectively. Moreover, the mean RT dose in these 20 patients was significantly higher than in the primary surgery group (64.1 vs. 61.2 Gy, $p = 0.021$), and nine (45%) of them even received a dose higher than 66 Gy. Therefore, we grouped these 20 patients into the organ preservation group, considering RT/CRT as the primary treatment and tumor tonsillectomy as a debulking procedure. To evaluate the role of this debulking procedure, we compared their treatment results with the other 42 patients in the organ preservation group. Interestingly, tumor tonsillectomy did not contribute to improvements in oncologic outcomes, functional results, and

Table 5
Role of tonsillectomy in the organ preservation group ($n = 62$).

	No tonsillectomy (%) ($n = 42$)	Tonsillectomy (%) ($n = 20$)	p
T1–2	47.6	95	<0.001
N0–1	38.1	60	0.105
Chemotherapy	83.3	20.0	<0.001
Mean RT dose (range) (Gy)	68.9 (52–76)	64.1 (54–70)	<0.001
Disease control			
Local control	76.2	85.0	0.520
Regional control	85.7	95.0	0.412
Distant metastasis	14.3	10.0	0.978
5-year survival			
Disease-specific survival	69.4	80.0	0.707
Overall survival	62.9	70.0	0.745
Functional results			
Feeding tube dependent	16.7	5.0	0.258
Tracheostomy dependent	9.8	0.0	0.293
Major complications	14.3	25.0	0.311

RT = radiotherapy.

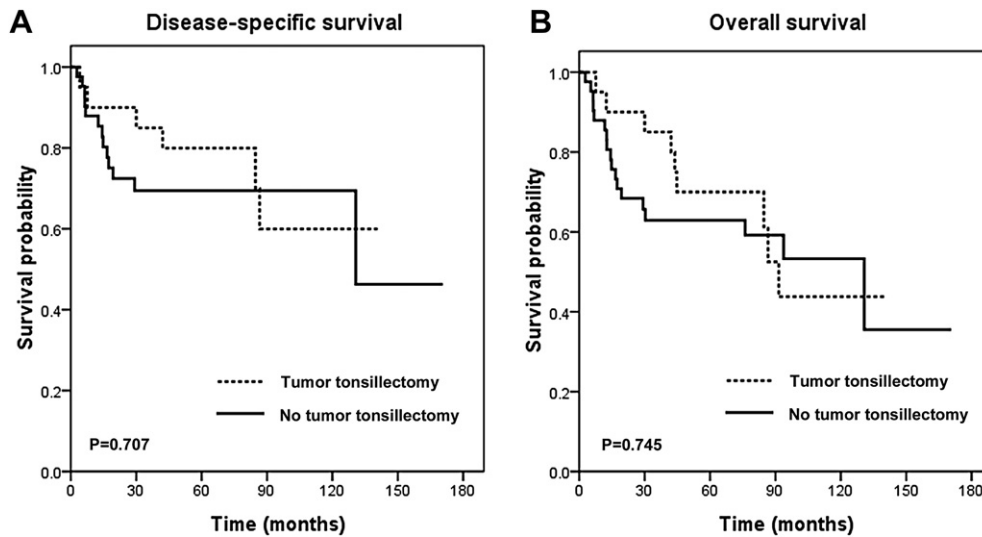


Fig. 2. (A) Disease-specific survival and (B) overall survival according to tumor tonsillectomy in the organ preservation group ($n = 62$).

major complications (Table 5). These results indicate that transoral tumor tonsillectomy, even if feasible, is not beneficial if organ preservation treatment is chosen.

Because of the retrospective design, human papillomavirus (HPV) infection status was not available in this study. HPV has been reported to play an important role in the pathogenesis of tonsillar SCC, and HPV-positive tumors have been shown to be associated with a better prognosis and higher radiosensitivity.^{14,15} It is reasonable to postulate that HPV-positive tonsillar SCCs may not require pre-RT/CRT tonsillectomy because of the superior radiosensitivity. The prevalence rate of HPV-related tonsillar SCCs has been reported to be lower in Chinese patients.^{16–18} In a recent study, Chuang et al¹⁸ found no significant prognostic impact of HPV infection in Chinese patients treated with primary surgery. Thus, the prognostic role of HPV infection in surgical patients remains to be elucidated. Routine screening for HPV status should be advocated to confirm its role in treatment selection for tonsillar SCC.

A major limitation of this study is the lack of detailed quality of life (QOL) analysis due to the retrospective study design, because functional outcome evaluation by feeding tube and tracheostomy dependency may not accurately reflect the patient's QOL. Because both primary surgery and RT/CRT organ preservation demonstrated equivalent oncological outcomes, QOL analysis may thus play a crucial role in future treatment selection. Mowry et al¹⁹ and Pourel et al²⁰ reported that long-term QOL for oropharyngeal cancer is similar, regardless of whether the patients received CRT or primary surgery. Tschudi et al²¹ reported that patients who were surgically treated had less pain, and fewer social eating and mouth opening problems compared with the nonsurgically treated patients. These results indicate that further prospective studies in a large patient population are warranted to clarify this important issue.

In conclusion, both primary surgery and RT/CRT organ preservation are effective treatments for tonsillar SCC, with equivalent outcome efficacy. Single modality treatment, either

surgery or RT/CRT, can be arranged for stage I–II diseases. Although in recent years RT/CRT is used more frequently for stage III–IV tonsillar SCC, primary surgery combined with adjuvant therapy still achieves equivalent outcomes. Therefore, treatment selection should be based on multidisciplinary pretreatment counseling and the facilities and personnel available at each institution. Tumor tonsillectomy before definitive RT/CRT organ preservation does not contribute to improved treatment outcomes, and is not indicated for patients with a pathological diagnosis of tonsillar SCC if RT/CRT organ preservation is chosen as the primary treatment.

Acknowledgments

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