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Original Article

Minimal benefit of tonsillectomy in T1-T2 tonsillar squamous cell carcinoma treated with chemoradiotherapy

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Abstract

Background: Chemoradiotherapy (CRT) has become the mainstay of treatment for tonsillar squamous cell carcinoma (SCC). Pre-CRT tonsillectomy is frequently performed, mostly for small primary tumors (T1-T2). However, the benefits of pre-CRT tonsillectomy remain unclear.
Methods: A retrospective review was performed in 66 patients with T1-T2 tonsillar SCCs treated by CRT from 1997 to 2009. The efficacy of pre-CRT tonsillectomy was analyzed with regard to oncological and functional outcomes.
Results: Thirty patients (45.5%) received tonsillectomy (pre-CRT tonsillectomy group), and 36 patients (54.5%) did not (CRT group). Except for a trend toward more T1 cases (33.3% vs. 13.9%, $p = 0.061$) and significantly less chemotherapy use (60% vs. 86.1%, $p = 0.016$) in the pre-CRT tonsillectomy group, there were no differences between the two groups in terms of age, gender, N classification (nodal status), overall stage, radiation dose, duration, or technique. In the pre-CRT tonsillectomy group, eight cases (26.7%) achieved an adequate operative margin judged by the surgeon, and only one (12.5%) had a negative pathological margin. In long-term follow-up, there were no statistically significant differences between the two groups regarding local (93.3% vs. 91.7%, $p = 0.82$) or regional control (93.3% vs. 94.4%, $p = 0.84$). The pre-CRT tonsillectomy group did not have a better 5-year disease-specific survival rate (83.3% vs. 94.4%, $p = 0.177$) or 5-year overall survival rate (70% vs. 94.4%, $p = 0.017$). There were no differences in complications or functional results (feeding tube and tracheostomy dependence), and quality of life demonstrated no significant difference.
Conclusion: Pre-CRT tonsillectomy contributes little to oncological and functional outcomes in patients with T1-T2 tonsillar SCC.

Keywords: chemoradiotherapy; quality of life; surgical margin; tonsillar squamous cell carcinoma; tonsillectomy

1. Introduction

Tonsillar squamous cell carcinoma (SCC) is the most common type of oropharyngeal cancer, and its incidence has been reported to be increasing in Western countries along with the prevalence of human papilloma virus (HPV) infection.[1,2] Early tonsillar SCCs can be treated by either surgery or radiotherapy (RT), while advanced cases usually require a

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combination of treatments, such as surgery followed by adjuvant therapy or chemoradiotherapy (CRT). Because of excellent radiosensitivity at this tumor subsite, CRT has become the mainstay of treatment for tonsillar SCCs in recent years, and the use of open surgery has declined.[3,4] However, optimal treatment strategy remains under debate.[5]

Despite the common use of definitive CRT as the treatment for tonsillar SCC, tonsillectomy is still frequently performed first, mostly for T1-T2 tumors. Common reasons for tonsillectomy before CRT include: (1) tissue diagnosis for occult primary tumors presenting with metastatic neck disease or as asymmetric tonsils; (2) the feasibility of transoral tumor removal; (3) the belief that optimal oncological outcomes with the combination of tonsillectomy reduce tumor burden before CRT treatment. Yildirim et al[6] reported excellent oncological outcomes in 120 patients who underwent tonsillectomies followed by RT. However, there was no control group for comparison in their study. Holliday et al[7] analyzed the Surveillance Epidemiology and End Results registry, and found that patients with early tonsillar SCC may have had better survival benefits with pre-CRT tonsillectomy compared with those who received a biopsy only. However, their study did not include data on locoregional control or functional outcomes.

Therefore, the benefits of pre-CRT tonsillectomy require further clarification, especially for small T1-T2 tonsillar SCCs for which transoral removal could be feasible. The aim of this study was to evaluate the efficacy of pre-CRT tonsillectomy in a retrospective cohort of patients with T1-T2 tonsillar SCCs. The oncological and functional outcomes were analyzed to determine the effect of pre-CRT tonsillectomy before definitive CRT treatment.

2. Methods

2.1. Population selection

This retrospective analysis included patients with T1-T2 tonsillar SCCs treated between 1997 and 2009 in Taipei Veterans General Hospital. Approval for this study was obtained from the Institutional Review Board (2012-03-037BC). One hundred and sixteen consecutive patients were included. Forty-eight patients were excluded, including 21 treated with surgery alone, four with open surgery including mandibulotomy or mandibulectomy, two with chemotherapy only, and 21 with transoral surgery and neck dissection. Another two patients were excluded for distant metastasis (DM) at diagnosis. The remaining 66 patients treated with CRT with or without pre-CRT tonsillectomy were included in this study.

2.2. Patient characteristics and tumor status

Tumors were staged according to the 2002 criteria of the American Joint Committee on Cancer, and the patient characteristics are summarized in Table 1. Thirty patients (45.5%) received pre-CRT tonsillectomy (pre-CRT tonsillectomy group) and the other 36 (54.5%) received CRT only (CRT group). There was a trend toward more T1 tumors in the pre-CRT tonsillectomy group compared with the CRT group (33.3% vs. 13.9%, $p = 0.061$). Otherwise, no statistically significant differences were observed between the two groups in terms of age, gender, N classification or overall stage.

Table 1
Patient characteristics.

	Pre-CRT tonsillectomy ($n = 30$)	CRT ($n = 36$)	p
Age	56.8	55.6	0.680
Gender			0.486
Male	22 (73.3%)	29 (80.6%)	
Female	8 (26.7%)	7 (19.4%)	
T classification			0.061
T1	10 (33.3%)	5 (13.9%)	
T2	20 (66.7%)	31 (86.1%)	
N classification			0.352
N0	13 (43.3%)	9 (25.0%)	
N1	2 (6.7%)	6 (16.7%)	
N2	14 (46.7%)	20 (55.6%)	
N3	1 (3.3%)	1 (2.8%)	
Overall stage			
Stage I–II	13 (43.3%)	9 (25%)	0.116
Stage III–IV	17 (56.7%)	27 (75%)	

CRT = chemoradiotherapy.

2.3. Treatment plans

The CRT treatment data are shown in Table 2. RT was delivered at 2 Gy per fraction, 5 d/wk, for a total dose of 52–75 Gy to the primary site and/or positive neck level, and 50 Gy to the N0 neck level. Both sides of the neck were included in treatment portals, and RT was administered as 6 MV X-rays from a linear accelerator. Accelerated fractionation of the RT was not performed. There were no differences in RT between the two groups, including total dosage, duration, and technique (Table 2).

Induction or concurrent cisplatin-based chemotherapy was given to some patients. Induction chemotherapy (ICT) was delivered in two courses; the regimen mainly consisted of cisplatin (60 mg/m^2) and 5-fluorouracil (600 mg/m^2/

Table 2
Chemoradiotherapy treatment data.

	Pre-CRT tonsillectomy ($n = 30$)	CRT ($n = 36$)	p
RT dose (Gy)	67.74	68.09	0.763
RT duration (d)	49.4	51.5	0.136
RT technique			0.380
IMRT	16 (53.3%)	19 (52.8%)	
3D	5 (16.7%)	11 (30.9%)	
2D	6 (20%)	5 (13.9%)	
Not determined	3 (10%)	1 (2.8%)	
Chemotherapy			0.016
Yes	18 (60%)	31 (86.1%)	
No	12 (40%)	5 (13.9%)	
Median follow-up time (mo)	65.5 (range 7–187)	56 (range 6–126)	0.743

CRT = chemoradiotherapy; IMRT = intensity modulated radiotherapy; RT = radiotherapy.

d continuous infusion for 4 days). In concurrent CRT, cisplatin (20 mg/m^2/d) and 5-fluorouracil (600 mg/m^2/d) were delivered for 4 days every 3 weeks concomitantly with the RT. Chemotherapy was given less frequently in the pre-CRT tonsillectomy group than in the CRT group (60% vs. 86.1%, $p = 0.016$). Among the 18 patients in the pre-CRT tonsillectomy group who received chemotherapy, only four (22.2%) underwent ICT. In contrast, 14 (45.2%) of the 31 patients in the CRT group who received chemotherapy underwent ICT. The median follow-up time was 65.5 months for the pre-CRT tonsillectomy group and 56 months for the CRT group ($p = 0.743$).

2.4. Tissue diagnosis status and margin of tonsillectomy

In the CRT group, tissue diagnosis was established by punch biopsy at our clinic. In the pre-CRT tonsillectomy group, the diagnosis of SCC was pathologically proven in six patients (20%) prior to tonsillectomy. Among the other 24 patients (80%), seven underwent tonsillectomy to identify the primary tumors with metastatic neck disease, and 17 underwent tonsillectomy directly with grossly visible tonsillar tumors. Tonsillectomy was performed by dissection with either electrocautery or cold instruments along the tonsil capsule. When gross invasion of the tonsil capsule was found, the dissection was carried out including a cuff (2–4 mm) of surrounding soft tissue to remove the tumor as completely as possible.

The margin status of the tonsillectomy specimen was obtained according to the surgical records and pathology reports. The operative margin was judged by the surgeon and classified into adequate, inadequate, and not mentioned. A negative pathological margin was defined as no tumor cells being found within 2 mm from the cut margin. A close margin was defined as tumor cells or cell dysplasia within 2 mm of the cut margin, and a positive margin was defined as the presence of tumor cells at the resection border of the specimen.

2.5. Outcome measurements

Disease-specific survival (DSS) and overall survival (OS) were calculated using the Kaplan-Meier product limit method. Follow-up times were defined as the duration between the date of treatment initiation and events or last contact. OS was defined as the time from diagnosis of the primary cancer to death by any causes. DSS was defined as the time to death from cancer or treatment-related events. Functional results were determined by the dependence of feeding and tracheostomy tubes at >6 months after completion of treatment. Major complications were defined as treatment-related events, such as massive bleeding, neutropenic fever, or osteoradionecrosis, which necessitated a second operation, prolonged hospitalization, or were life-threatening.

Quality of life (QOL) assessments were only available for 15 patients (six in the pre-CRT tonsillectomy group and nine in the CRT group) at posttreatment 1 year, using the European Organization for Research and Treatment of Cancer Core QOL questionnaire (EORTC QLQ-C30) and head- and neck-specific QOL questionnaire (EORTC QLQ-H&N35).[8]

2.6. Statistical analyses

All analyses were performed using PASW statistical software version 18 (SPSS Inc., Chicago, IL, USA). Differences in categorical variables between the two groups were determined using Pearson's Chi-square or Fischer's exact test. The Mann-Whitney U test was used to compare the means because of non-normality in the distribution. DSS and OS were compared by the log-rank test. All tests were two-sided, and the results were considered significant at $p < 0.05$.

3. Results

3.1. Margin status in the pre-CRT tonsillectomy group

Among all patients in the pre-CRT tonsillectomy group, the operative margin was considered to be adequate in eight cases (26.7%) and inadequate in four cases (13.3%). In the other 18 cases (60%), the status of the operative margin was not mentioned. Under pathological examination, a negative pathological margin was achieved in only two cases (6.7%), while close and positive margins were noted in eight (26.7%) and nine (30%) cases, respectively. In the other 11 cases (36.7%), the pathological margin was not determined due to fragmentation of the tumor specimen. Of note, among the eight patients whose operative margin was considered to be adequate, only one (12.5%) had a negative pathological margin (Table 3).

3.2. Oncological outcomes

The oncological and functional outcomes are summarized in Table 4. After long-term follow-up, the disease control rates were almost equivalent between the two groups. There was no significant difference in 5-year DSS rate between the pre-CRT tonsillectomy and CRT groups (83.3% vs. 94.4%, $p = 0.177$) (Fig. 1). However, a trend toward a higher rate of DM (10% vs. 0%, $p = 0.059$) and a poorer 5-year OS (70.0% vs. 94.4%, $p = 0.017$) were observed in the pre-CRT tonsillectomy group.

3.3. Complications and functional outcomes

Long-term complications and functional outcomes are listed in Table 4. The incidence rates of major complications were 20.0% and 16.7% in the pre-CRT tonsillectomy group and CRT group, respectively ($p = 0.727$). Of the six cases

Table 3
Operative and pathological margin statuses.

Pathological margin	Operative margin			
	Adequate	Inadequate	Not mentioned	
Negative	1 (12.5%)	0	1	2 (6.7%)
Close[a]	4 (50%)	0	4	8 (26.7%)
Positive	3 (37.5%)	1	5	9 (30%)
Not determined	0	3	8	11 (36.7%)
Total	8 (26.7%)	4 (13.3%)	18 (60%)	30

[a] Close margin: <2 mm from cut margin or margin dysplastic change.

Table 4
Patient outcomes.

	All ($n = 66$)	Pre-CRT tonsillectomy ($n = 30$)	CRT ($n = 36$)	p
Disease control				
Local control	92.4%	93.3%	91.7%	0.82
Regional control	93.9%	93.3%	94.4%	0.842
DM	3 (4.5%)	3 (10%)	0	0.059
Survival				
5-y DSS	89.4%	83.3%	94.4%	0.177
5-y OS	83.3%	70.0%	94.4%	0.017
Complication	12 (18.2%)	6 (20.0%)	6 (16.7%)	0.727
Functional results				
Tube feeding	2 (3.0%)	2 (6.7%)	0	0.203
Tracheostomy	0	0	0	

CRT = chemoradiotherapy; DM = distant metastasis; DSS = disease-specific survival; OS = overall survival.

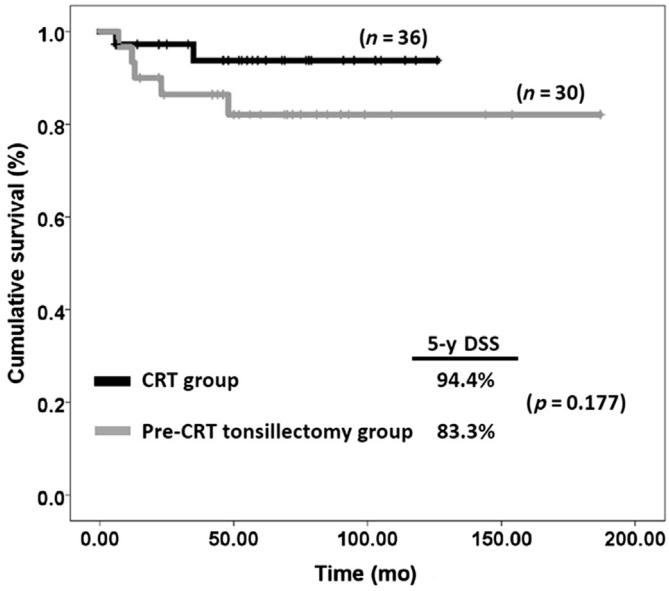

Fig. 1. The Kaplan-Meier curves of disease-specific survival (DSS) of pre-CRT tonsillectomy ($n = 30$) and CRT ($n = 36$) groups in a T1-T2 tonsillar squamous cell carcinoma cohort. CRT = chemoradiotherapy; DSS = disease-specific survival.

with complications in the pre-CRT tonsillectomy group, two involved massive postoperative bleeding, one from the tonsillectomy wound and the other from ruptured esophageal varices owing to procedure-related stress. The other complications in this group included two of mandibular osteoradionecrosis, one of neutropenic fever during ICT, and one of aspiration pneumonia. In the CRT group, neutropenic fever during concurrent CRT occurred in three patients, and acute renal failure and pneumonia in one and two patients, respectively.

Respiratory and swallowing functional outcomes were evaluated by tracheostomy and feeding tube dependence. No patient was tracheostomy-dependent in either treatment group, and feeding tube dependency was not significantly different between the pre-CRT tonsillectomy and CRT groups (6.7% vs. 0%, $p = 0.203$). Of the 15 patients who had available data on 1-year QOL results posttreatment, there was no significant difference between the two groups in global health status, all functional scales, and all symptom and single-item scales on the EORTC QLQ-C30 questionnaire (Table 5). There were also no significant differences in most items of the EORTC QLQ H&N 35 questionnaire between the two groups, except for a trend toward fewer sense problems ($p = 0.06$) in the pre-CRT tonsillectomy group compared with the CRT group.

4. Discussion

In this study, the results of CRT treatment with or without pre-CRT tonsillectomy were compared in a cohort of 66 patients with T1-T2 tonsillar SCCs. Our data indicated that pre-CRT tonsillectomy did not contribute to additional benefits regarding disease control, survival, complications, functional, or QOL outcomes. The locoregional control rates were higher

Table 5
Posttreatment 1 year quality of life.

	Pre-CRT tonsillectomy ($n = 6$)	CRT ($n = 9$)	p
EORTC QLQ-C30			
Global health scale	66.5 ± 36.2	77.7 ± 16.6	0.72
Physical function	90.8 ± 10.2	94.8 ± 7.3	0.38
Role function	94.3 ± 13.9	92.6 ± 12.1	0.65
Emotional function	88.8 ± 10.2	91.7 ± 22.2	0.13
Cognitive function	86.2 ± 16.2	92.6 ± 12.1	0.42
Social function	88.7 ± 17.6	85.2 ± 22.7	0.89
Symptom scale			
Fatigue	11.0 ± 13.9	8.6 ± 13.2	0.64
Nausea/vomiting	2.8 ± 6.9	0	0.22
Pain	11.2 ± 13.6	11.1 ± 18.6	0.74
Single item			
Dyspnea	0	0	>0.99
Insomnia	33.2 ± 36.5	7.3 ± 14.6	0.77
Appetite loss	0	3.7 ± 11	0.41
Constipation	22.2 ± 40.4	11.0 ± 23.3	0.60
Diarrhea	0	0	>0.99
Financial difficulties	16.5 ± 18.1	11.1 ± 33.3	0.17
EORTC QLQ-H&N35			
Pain	9.7 ± 15.1	8.2 ± 11.0	0.75
Senses problems	12.5 ± 8.9	23.1 ± 9.8	0.06
Speech problems	11.0 ± 12.0	11.0 ± 18.2	0.61
Social eating	11.0 ± 14.5	13.9 ± 13.8	0.80
Social contact	5.5 ± 13.4	5.2 ± 10.5	0.93
Less sexuality	38.8 ± 49	7.3 ± 14.6	0.18
Teeth	33.2 ± 36.5	22.1 ± 37.2	0.37
Opening mouth	5.5 ± 13.5	11.0 ± 23.3	0.74
Dry mouth	44.2 ± 40.2	55.2 ± 37.2	0.58
Sticky saliva	22.0 ± 26.9	62.7 ± 38.9	0.49
Coughing	16.5 ± 18.1	3.7 ± 11.0	0.11
Felt ill	5.5 ± 13.5	11.0 ± 16.5	0.49
Pain killers	16.7 ± 40.8	11.1 ± 33.3	0.77
Nutrition supplements	33.3 ± 51.6	33.3 ± 50.0	>0.99
Feeding tube	0	0	>0.99
Weight loss	16.7 ± 40.8	0	0.22
Weight gain	66.7 ± 51.6	33.3 ± 50.0	0.22

Data are expressed as mean ± standard deviation.
CRT = chemoradiotherapy; EORTC = European Organization for Research and Treatment of Cancer; QLQ = quality of life questionnaire.

than 90% in both groups. Consistent with our results, Mendenhall et al[9] reported 503 tonsillar SCC patients in whom CRT achieved 88% and 84% local control rates in T1 and T2 cases, respectively. Reported series of intensity-modulated radiation therapy also achieved comparable results.[10–13] Taken together; these data indicate that CRT already provides excellent treatment results for patients with T1-T2 tonsillar SCCs.

In this retrospective study, we considered pre-CRT tonsillectomy to be a debulking biopsy procedure, because adequate surgical margins were seldom achieved in the pre-CRT tonsillectomy group (Table 3). CRT was considered as the definitive treatment for T1-T2 tonsillar SCCs in this study, given that patients who received pre-CRT neck dissection were excluded and the RT dose in both treatment groups was equivalent (Table 2). Poor surgical exposure in a conventional tonsillectomy setting may be the main reason why 56.7% of the cases in the pre-CRT tonsillectomy group, not including 36.7% with an undetermined margin status, did not achieve a negative pathological margin, especially in the area near the lower pole of the tonsillar fossa and the base of the tongue. It is worth noting that most adequate operative margins judged by the surgeon were not consistent with the final negative pathological margins. Moreover, the tonsillectomy specimens were frequently poorly orientated due to fragmentation, making it difficult to determine the pathological margin in more than one third of the cases (Table 3).

It has been reported that transoral lateral oropharyngectomy using conventional or robotic instruments can achieve a high rate (>85%) of negative pathological margin,[14–18] and deintensification by omitting the use of chemotherapy or reducing the dose of RT.[16,18] Further studies are needed to elucidate whether these modern surgical techniques contribute to improved CRT treatment results for T1-T2 tonsillar SCCs. In the study by Yildirim et al,[6] tonsillectomies followed by RT achieved excellent oncological results. Among 120 patients included in their study, 24 (20%) received extended tonsillectomy, resulting in a higher rate (51%) of negative pathological margins. The median RT dose was 66 Gy to the primary site, and only 12 patients (10%) received chemotherapy. In the current study, pre-CRT tonsillectomy only removed the primary tumors along the tonsil capsule or a cuff of surrounding soft tissue without wide operative margins. As mentioned earlier, only 20% of the patients in the pre-CRT tonsillectomy group already had tissue diagnosis. Therefore, as high as 80% of the patients in this group received the surgery for diagnostic intent. This can explain the high positive margin rate in our study. Although chemotherapy was not performed in 40% of the patients in the pre-CRT tonsillectomy group, there was no reduction in the dose of RT compared with the CRT group. The long-term benefit of omitting chemotherapy remained minimal in the current study.

Given that six (20%) of the 30 patients in the pre-CRT tonsillectomy group already had a tissue diagnosis and 17 (56.7%) demonstrated gross visible tonsillar tumors, pre-CRT tonsillectomy was performed mainly based on the belief that optimal oncological outcomes can be achieved by reducing tumor burden before CRT treatment. However, this concept was not supported by our data. In fact, the survival rate of the pre-CRT tonsillectomy group in this study was poorer due to the higher DM rate. It is plausible that the higher proportion of patients receiving ICT in the CRT group may have contributed to the lower DM rate. Because the roles of ICT in improving distant control and survival are still inconclusive from randomized control trials,[19,20] this explanation should still be regarded as hypothetical for this study.

Feeding and tracheostomy tube dependence have been used as indicators of functional outcomes for patients treated with CRT.[21] Given the equivalent RT dose, it is not surprising that the major complication, feeding tube and tracheostomy-dependent rates were also similar between the two treatment groups at 6 months posttreatment. The posttreatment QOL as evaluated by the EORTC QLQ questionnaires in a small subgroup of our patients also showed no significant differences in most scales, indicating that pre-CRT tonsillectomy contributed no advantage in posttreatment QOL. The only trend of difference was observed with regard to fewer senses problems in the EORTC QLQ-H&N 35 in the pre-CRT tonsillectomy group which included a higher percentage (40%) of patients who did not receive chemotherapy (Table 5). Broglie et al[22] also recently demonstrated more senses problems and dry mouth in patients undergoing primary CRT compared with those treated with surgery and postoperative RT. It is possible that the platinum-based chemotherapy caused dysgeusia due to related neuropathy which contributed to the higher senses problems scores in our CRT group.[23]

Because pre-CRT tonsillectomy was only minimally beneficial in the current study, we suggest that a biopsy under topical anesthesia should be the first choice for the diagnosis of grossly visible tonsillar SCC. Pre-CRT tonsillectomy can then be reserved for patients presenting with cervical metastasis of unknown primary origin or suspicious asymmetric tonsils to allow for a higher tumor detection rate.[24–29]

A major limitation of this study is the small sample size, which resulted because we included only a homogenous patient cohort with early T1-T2 tonsillar SCCs. Owing to the retrospective design, pre-CRT tonsillectomy was decided by the surgeons according to the feasibility of removal and their preference. Selection bias is also obvious, as seen by the higher percentage of T1 patients in the pre-CRT tonsillectomy group. In addition, patients with better performance status and less comorbidity may also have been selected for pre-CRT tonsillectomy. However, such bias toward favorable patients may not have affected our conclusion that pre-CRT tonsillectomy contributes little to oncological and functional results of CRT treatment for early T1-T2 tonsillar SCCs. Another limitation is that data on the HPV status of most patients in our series (80.5%) were not available. It was not until 2005 that HPV status was routinely checked in our department of pathology. HPV has been demonstrated to be an indicator of better outcomes in patients with oropharyngeal cancer treated with CRT.[30–32] Nevertheless, the prevalence of HPV tonsillar SCC is relatively low (12.6%) in Taiwan compared with that in Western countries.[33] Future investigations should stratify

patients by HPV status in order to minimize the confounding effects on tumor control and survival.

In conclusion, pre-CRT tonsillectomy contributes little to locoregional control and survival rates, because CRT already provides excellent treatment results for patients with T1-T2 tonsillar SCC. Pre-CRT tonsillectomy did not reduce the frequency of major complications or improve functional outcomes and post-CRT QOL. Our results suggest that when CRT is chosen as the primary treatment, pre-CRT tonsillectomy is not necessary if the tumor is obviously visible or tissue diagnosis has been obtained. Future studies should focus on the benefits of novel surgical techniques, such as transoral lateral oropharyngectomy or robotic surgery, in deintensification or improving CRT treatment results.

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