Received: 10 August 2022 | Revised: 7 November 2022 | Accepted: 15 November 2022

DOI: 10.1002/lio2.1005

ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

Analysis of T1-T2 stage oropharyngeal squamous cell carcinoma treated with transoral robotic surgery

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Abstract

Objective: Transoral robotic surgery (TORS) has become an effective treatment for early-stage oropharyngeal squamous cell carcinomas (OPSCCs). We aimed to analyze the clinical safety and efficacy of TORS for human papilloma virus (HPV)-positive and HPV-negative OPSCC in China.

Methods: Patients with OPSCC of pT1-T2 stage who underwent TORS from March 2017 to December 2021 were analyzed.

Results: A total of 83 patients (HPV-positive, $n = 25$; HPV-negative, $n = 58$) were included. The median age of the patients was 57.0 years and 71 were men. The majority of primary tumor sites were palatine tonsils (52, 62.7%) and base of tongues (20, 24.1%). Three patients have a positive margin. A total of 12 (14.5%) patients received tracheotomies, the average duration of tracheostomy tube use was 9.4 days, and nasogastric tube was 14.5 days. No patient had a long-term tracheotomy. The 3-year overall survival (OS), disease-free survival (DFS), and recurrence-free survival (RFS) for all 83 patients were 89.5%, 80.1%, and 83.3%, respectively. The OS at 3 years between the HPV-positive group and HPV-negative group were 100% versus 84.3% ($P = .07$), while the DFS and RFS between two groups also showed no significant difference. Among multivariate cox regression analysis of all potential risk factors, smoking was the significant risk factors for disease recurrence ($P < .05$).

Conclusion: Transoral robotic surgery achieved encouraging oncologic outcomes and safety in T1-T2 stage OPSCC treatment, regardless of HPV status.

Level of Evidence: 4

KEYWORDS

clinical outcome, head and neck cancer, HPV status, oropharyngeal squamous cell carcinomas, transoral robotic surgery

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1 | INTRODUCTION

In the past, radiotherapy (RT) was the main treatment option for oropharyngeal squamous cell carcinomas (OPSCCs). Resection of oropharyngeal lesions by traditional invasive surgery could lead to a variety of dysfunctions, including speech disorders, swallowing difficulties, and malocclusion due to mandible dehiscence.[1] With the development of surgical technology, minimally invasive surgical techniques are gradually applied in clinical practice and robotic surgery is one of the latest technologies in head and neck surgeries. In 2005, Weinstein et al.[2] reported the first DaVinci robotic system-assisted transoral robotic surgery (TORS), which was soon proved to be able to shorten recovery time, maximize anatomical structure restoration, and minimize functional loss.[3] Patients with OPSCC who are treated with TORS have been reported to have a high quality of life at 1 year after the surgery.[4] The proportion of patients with cT_1-T_2 stage OPSCC who underwent primary surgery has increased from 56% (318/568) to 82% (837/1021) in the United States between 2004 and 2013.[5]

There has been a rapid increase in the incidence of OPSCC among young men in the last two decades and human papilloma virus (HPV) infection has caused an epidemic increase in the incidence of OPSCC worldwide.[6,7] In recent years, TORS was commonly used in the treatment of HPV-positive OPSCC, which may be associated with the regional high incidence of HPV infection. However, according to epidemiological reports in Asia, the incidence of HPV-positive OPSCC in South Asia and East Asia was 25.8% and 38.7%, respectively, which was obviously lower than that of 67.2% reported in North America.[8–10] In China, studies reported that only 10.8%–20.8% of oropharyngeal cancer samples were detected to be HPV positive.[11–13] Patients with HPV-negative OPSCC tended to be elder and more likely to have a long history of smoking or alcohol exposure. Compared with HPV positive OPSCC, HPV-negative patients could have more advanced tumor at first diagnosis and have higher risk of tumor progression.[3,14] Moreover, concurrent chemoradiotherapy (CRT) recommended by the NCCN guidelines are less satisfactory in HPV-negative patients and the traditional open surgery may lead to more complications.[3,15–17] Therefore, it is urgent to explore more effective treatment for HPV-negative oropharyngeal cancer patients with good oncological outcomes and improved quality of life. Whereas HPV-negative patients are less studied in the application of TORS, it remains unclear whether surgery should play an important role in this population.[18] Therefore, we aimed to explore whether both HPV-positive and HPV-negative patients could receive favorable therapeutic effect through our clinical practice of TORS.

2 | MATERIALS AND METHODS

2.1 | Patient recruitment and data collection

We retrospectively analyzed our single-institution's experience of TORS in patients with pathological T_1-T_2 stage OPSCC in the past 5 years (March 2017–December 2021). The staging of the tumor was based on the American Joint Committee on Cancer (AJCC) pathological staging manual, the eighth edition.[19] This study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center. Informed consents of all patients have been received for the study. Only patients with primary tumor developed at the oropharynx and diagnosed histologically as squamous cell carcinoma were included in the analysis. The exclusion criteria included the patients younger than 18 years, other cancer history besides the OPSCC within recent 5 years, and received other treatments for cancer in other hospitals.

Patient's demographic information, HPV status, smoking history, tumor site, pathologic TNM classification, treatment, perioperative complication, and follow-up information were recorded. Patients were divided into HPV-positive and negative groups according to the HPV status of their primary tumors. Overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS), local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), and risk factors of recurrence were analyzed and compared between two groups.

2.2 | HPV identification

The American Society of Clinical Oncology (ASCO) recommend HPV deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) testing for HPV infection or P16 immunohistochemistry (IHC) as a substitute index.[10,20,21] Therefore, P16 IHC or HPV DNA detection of the surgical specimens was used to define HPV status. The sample with the diffuse positive staining of nuclear nucleus and cytoplasm of >70% tumor cells was determined to be p16 positive. A commercially available qualitative PCR-based assay specialized for generalized HPV genotyping was used and high-risk type HPV16/18 was classified.

2.3 | Statistical analysis

All continuous variables were compared using the student's *t*-test and categorial variables were compared using the chi-square or Fisher's exact test. The OS, DFS, and RFS of the two groups were described by Kaplan-Meier method and the univariate survival analysis was performed by the bilateral log-rank test. Risk factors for recurrence were assessed using multivariate Cox regression model. A P value <.05 was considered to be statistically significant. All statistical analyses were performed using SPSS (SPSS, Inc., Chicago, IL) Windows 22.0 version.

3 | RESULTS

3.1 | Patients' demographic and clinical characteristics

A total of 129 patients underwent TORS for oropharyngeal cancer between March 2017 and December 2021 were recruited in this study, of which 13 (10.1%) were other types of cancers and excluded. A total of 116 (89.9%) were OPSCC, while 24 (28.9%) of them were

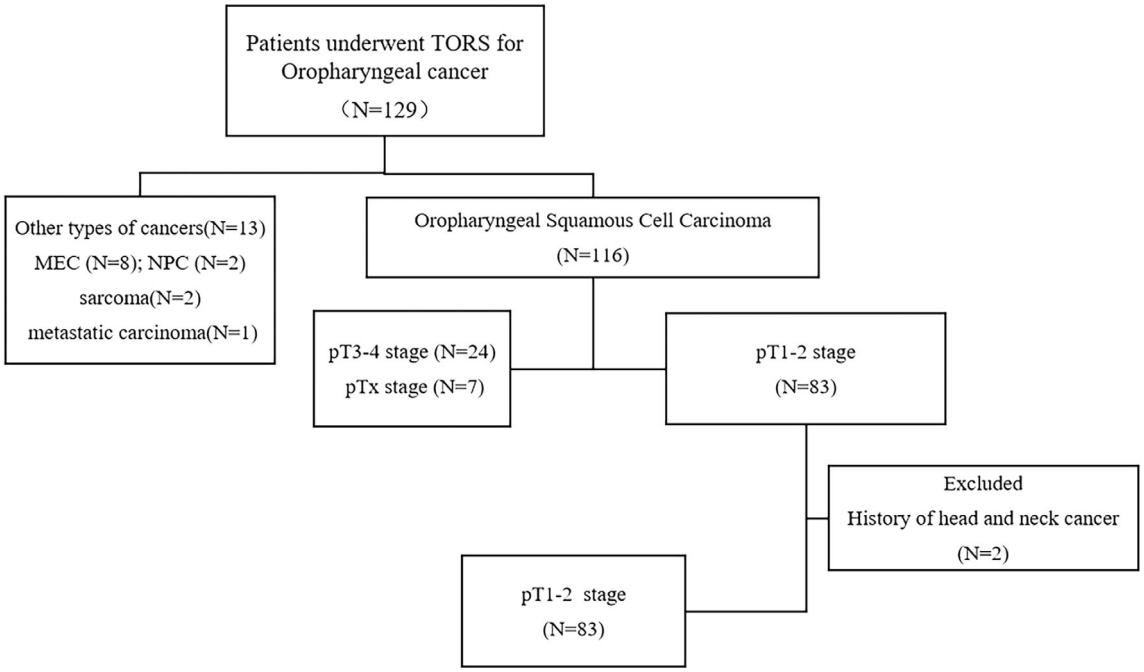


FIGURE 1 Flow diagram of included patients.

diagnosed with pT3-4 stages and analyzed separately. Seven patients were excluded because other treatment before surgery in other hospitals. Two patients were excluded due to histories of other head and neck cancers. Together, this left 83 patients with pT1-T2 stage OPSCC which were included in the final analysis (Figure 1). Patients were divided into two groups according to their HPV status, which included 25 HPV-positive patients and 58 HPV-negative patients. P16 IHC was assessed in 15 patients and HPV DNA detection was used in the rest 68 patients.

Overall, the majority (71, 85.5%) were men and the average age of morbidity was 57.0 years old ($SD = 10.0$). Patients in HPV-negative group tended to have older ages at onset than ones in HPV-positive group (60.6 vs 48.5, $P < .001$). The primary tumors in most patients located at the palatine tonsils (52, 62.7%) and bases of the tongue (20, 24.1%). Smoking consumption history was recorded in 45 (54.2%) patients, most of them were in the HPV-negative group (37/45, 82.2%). According to the AJCC staging guideline (the eight edition), 19 patients were classified into pT_1 stage (22.9%) and the rest 64 patients were pT_2 stage (77.1%). (Table 1)

3.2 | Treatments

The average robotic operation time was 34.7 ± 28.4 min, there was no significant difference between the two groups, but there was more blood loss in the HPV-negative group (42.3 ± 22.9 ml vs 68.3 ± 43.6 ml $P < .05$). In our cohort, neck dissection was performed in 69 (83.1%) patients during the same surgical episode as TORS, including 61 patients (84.8%) with unilateral neck dissection and 8 (15.2%) with bilateral neck dissection. In addition to TORS, 12 (14.5%) patients also received tracheotomies to avoid potential dyspnea, tumor sites of which are mostly located at the base of the tongue (8/12, 66.7%). The average duration of tracheostomy tube use was 9.4 ± 2.8 days and no patient had a long-term tracheotomy tube. Nasogastric tubes were placed in all patients and the average time to decannulation was 14.5 ± 16.1 days. No difference of tracheotomy tube and nasogastric tube placement was found between the HPV-positive and HPV-negative groups. Furthermore, we found that eight patients maintained the nasogastric tube with over one month (30–130 days) and six of them had tumors located at tonsils, which suggested that the swallowing function of patients with large-sized tonsil tumors would recover slowly. None of the patients underwent intraoperative free flap reconstruction and mandible dehiscence. The average postoperative hospital stay was 5.0 ± 2.9 day and there was no significant difference between the HPV-positive and HPV-negative groups.

Among postoperative adjuvant treatments, 60 patients (72.3%) were treated with surgery alone, while 5 (6.0%) received postoperative RT and 18 (21.7%) underwent postoperative CRT. Basically, postoperative RT or CRT were prescribed for these patients due to pathological adverse features or multiple lymph node metastasis, including three with perineural invasion, two with vascular invasion, eight with extranodal extension (ENE+), three with positive margin and seven with multiple lymph node metastasis. Patients undergoing RT after TORS received a mean dose of 62.5 ± 6.2 Gy on the tumor bed (range 50–70 Gy) and a mean of 57.2 ± 13.7 Gy on anterior neck field (range 0–66 Gy). There was no significant difference in radiation dose between the HPV-positive and HPV-negative groups. Further, concurrent chemotherapy with cisplatin was administered at dose of 80–100 mg/m^2 according to three-week dosing scheme, a mean dose

TABLE 1 Demographic and clinical data of all included patients.

Variable	No. (%)
Age (mean ± SD)	57.0 ± 10.0
Sex	
Male	71 (85.5)
Female	12 (14.5)
HPV status	
Positive	25 (30.1)
Negative	58 (69.9)
Smoking (>10 package/year)	
Yes	45 (54.2)
No	38 (45.8)
Tumor site	
Tonsil	52 (62.7)
Base of tongue	20 (24.1)
Soft palate	9 (10.8)
Others[a]	2 (2.4)
Pathologic T classification	
T1	19 (22.9)
T2	64 (77.1)
Pathologic T classification	
N0	32 (38.6)
N1	28 (33.7)
N2	23 (27.7)
Stage AJCC 8th edition	
I	29 (34.9)
II	29 (34.9)
III	8 (9.7)
IV	17 (0.5)
Treatment methods	
Surgery	60 (72.3)
Surgery +RT or CRT	23 (27.7)

Note: Age is presented as mean ± SD. Sex, HPV status, smoking history, pathologic TNM stage, and treatment methods are presented as No. (%).
Abbreviations: AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy; HPV, human papilloma virus; RT, radiotherapy; SD, standard deviation; TNM, tumor node metastasis.
[a]The tumor site is posterior pharyngeal wall.

of 241.7 ± 62.2 mg/m^2 (range 150–356). In the HPV-positive group, a mean dose of 240.6 ± 70.8 mg/m^2 cisplatin was administered to selected patients for adjuvant chemotherapy; while in the HPV-negative group, the mean dose was 242.1 ± 61.7 mg/m^2.

3.3 | Complications

According to postoperative pathological findings, three tumor specimens demonstrated positive margins. Among them, one positive margin occurred in the HPV-positive group and two in the HPV-negative group. Combined with the patient's wishes and the risk of a second operation, the patients received adjuvant CRT.

Only one patient in HPV-positive group had wound dehiscence on the third day after surgery, for which secondary debridement was then performed without further adverse sequelae. Postoperative bleeding occurred in two patients, both in HPV-negative group, including one during hospitalization and another one after discharge. Given the limited amount of bleeding, the doctor evaluated the wounds and hemostasis by gauze compression was utilized. Taken together, the treatment, postoperative recovery and complications of the HPV-positive and HPV-negative groups were given in Table 2.

3.4 | Follow-up and survival outcomes

The median follow-up period was 29.5 months (7.0–62.6 months). The mean duration of follow-up for the HPV-positive group was 30.8 ± 13.3 months, whilst 29.0 ± 17.3 in the HPV-negative group. In the whole cohort, seven patients died (8.4%), including five patients who died from the tumor and two patients who had non-tumor-related deaths (one intestinal perforation and one viral pneumonia). Fourteen patients developed disease recurrence (16.8%) during the follow-up period. Table 3 includes detailed information regarding the 14 patients who developed disease recurrence. In the HPV-positive group, two recurrences but no deaths occurred, while 12 recurrences and 7 deaths occurred in the HPV-negative group, which however, has not reached statistical significance between two groups.

The survival of the whole cohort was favorable. The 1-year OS, DFS, and RFS were 100%, 90.0%, and 91.4%, respectively. The 3-year OS, DFS, and RFS were 89.5%, 80.1%, and 83.3%, respectively. Meanwhile, according to the site of disease recurrence, LRFS, and RRFS were analyzed. The 1-year LRFS and RRFS were 93.7% and 94.9%, respectively. The 3-year LRFS and RRFS were 91.1% and 85.9%, respectively. The detail data is shown in the Table 4 and the survival Kaplan-Meier curves for 3-year OS, DFS, RFS, LRFS, and RRFS are shown in Figures 2 and S1. Compared with HPV-negative patients, patients with HPV-positive tumors received slightly better prognoses, however, the difference of survival rates didn't show statistical significance. (3-year OS: 100% vs 84.3%, $P = .07$; 3-year DFS: 92.0% vs 74.9%, $P = .13$; 3-year RFS: 92.0% vs 79.5%, $P = .20$; 3-year LRFS: 96.0% vs 88.9%, $P = .47$; 3-year RRFS: 95.8% vs 81.2%, $P = .22$; Table 4 and Figure 3).

3.5 | Risk factors for recurrence

Multivariate Cox regression model was used to analyze the risk factors for recurrence and variates including HPV status, age, smoking history, T stage, positive lymph nodes, the AJCC stage, and postoperative treatment were selected in the analysis. Among all potential risk factors, smoking was the only significant risk factors for disease recurrence in our study ($P < .05$) with a hazard ration (HR) of 3.51 (95% confidence interval [CI]: 1.07, 11.51; Table 5).

TABLE 2 Treatment, postoperative recovery, and complications of the two groups.

Characteristic	Overall ($N = 83$)	HPV+ ($N = 25$)	HPV− ($N = 58$)	*P*-value
Tracheotomy	12 (14.5)	3 (12.0)	9 (15.5)	.68
Neck dissection	69 (83.1)	22 (88.0)	47 (81.0)	.44
Positive margin	3 (3.6)	1 (4.0)	2 (3.4)	.66
Operation time (min)	34.7 ± 28.4	26.7 ± 23.7	38.1 ± 29.7	.15
Bleeding (ml)	60.5 ± 40.3	42.3 ± 22.9	68.3 ± 43.6	.02
Postoperative hospital stay (day)	5.0 ± 2.9	5.6 ± 3.7	4.7 ± 2.4	.10
Nasogastric tube (day)	14.5 ± 16.1	13.6 ± 10.5	16.4 ± 24.9	.13
Adjuvant RT/CRT	23 (27.7)	10 (40.0)	13 (22.4)	.10
Complication	3 (3.6)	1 (4.0)	2 (3.4)	.66
Recurrence	14 (16.9)	2 (8.0)	12 (20.7)	.16
Death	7 (8.4)	0 (0)	7 (12.1)	.07

Note: Conventional continuous variables are presented as mean ± SD and categorical variables as No. (%). *P*-value <.05 was considered to be statistically significant.
Abbreviations: HPV+, HPV-positive group; HPV−, HPV-negative group.

TABLE 3 Details of patients with recurrence

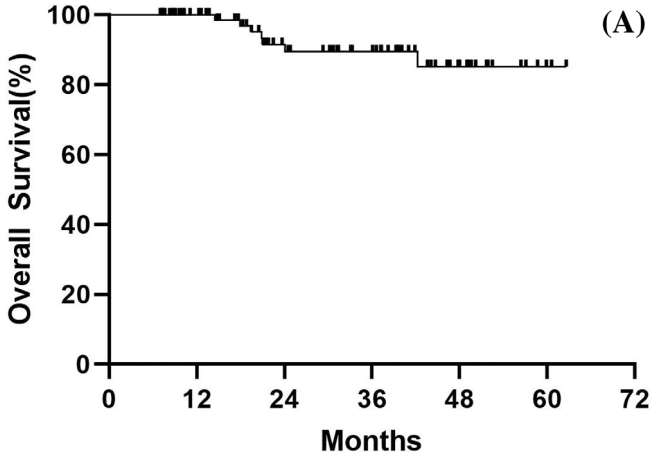
Sex	Age	HPV status	TNM stage	The site of recurrence	Time (RFS)	Treatment
M	59	−	T2N2	Regional	33.3	Surgery
M	54	−	T2N2	Regional	52.0	None
F	64	−	T1N0	Local	29.8	Surgery
M	55	−	T2N0	Regional, distant	16.0	CRT
M	42	+	T2N2	Local	2.8	Surgery, CRT
M	51	+	T2N1	Regional	4.0	Surgery, CT
M	52	−	T2N2	Local, Regional	5.2	CT
M	63	−	T2N1	Regional, distant	15.4	Immunechemotherapy
M	66	−	T2N2	Regional	8.5	CRT
F	65	−	T2N2	Local	5.4	Immunechemotherapy
M	64	−	T2N2	Local	5.0	Immunechemotherapy
M	57	−	T1N0	Regional	7.3	CRT
M	54	−	T1N	Regional	30.5	Surgery
M	57	−	T2N2	Local	11.2	CT

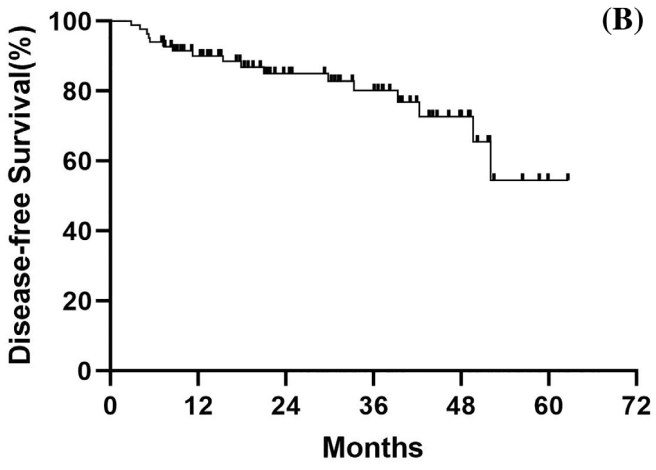
Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; F, female; HPV; human papilloma virus; M, male; RFS, recurrence-free survival; TNM, tumor node metastasis.

TABLE 4 Details of survival outcomes

	Overall (%)		HPV+ (%)		HPV− (%)		
	1-year	3-year	1-year	3-year	1-year	3-year	*P*-value
OS	100	89.5	100	100	100	84.3	.07
DFS	90.0	80.1	92.0	92.0	89.1	74.9	.13
RFS	91.4	83.3	92.0	92.0	89.1	79.5	.20
LRFS	93.7	91.1	96.0	96.0	92.6	88.9	.47
RRFS	94.9	85.9	95.8	95.8	89.4	81.2	.22

Note: Values are presented as percentage (%). *P*-value <.05 was considered to be statistically significant.
Abbreviations: DFS, disease-free survival; HPV−, HPV-negative group; HPV+, HPV-positive group; LRFS, local recurrence-free survival; OS, overall survival; RFS, recurrence-free survival; RRFS, regional recurrence-free survival.





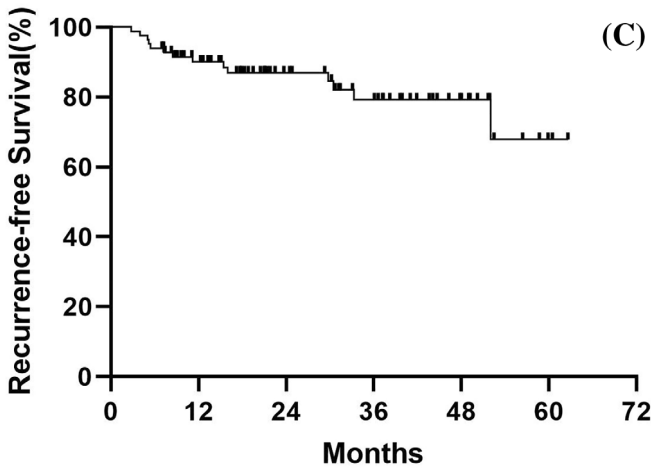
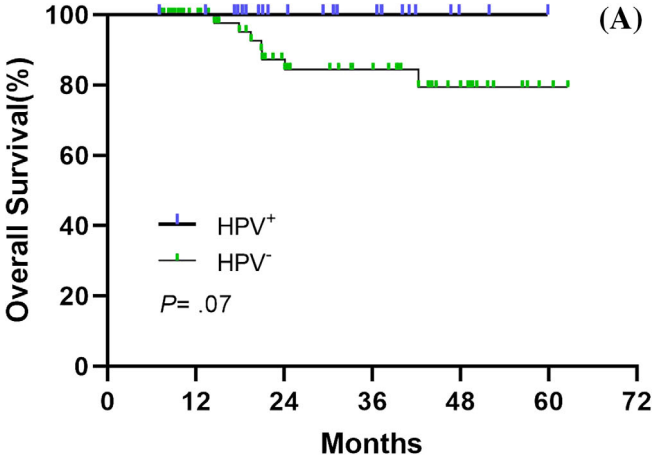
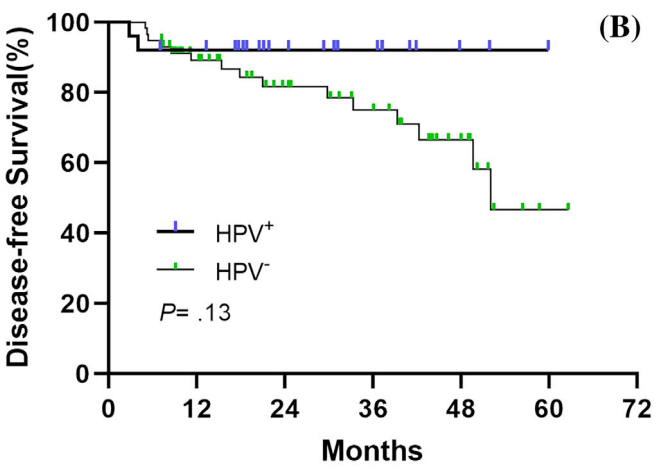


FIGURE 2 Kaplan-Meier survival curve analysis for (A) overall survival, (B) disease-specific survival, and (C) recurrence-free survival of total patients.





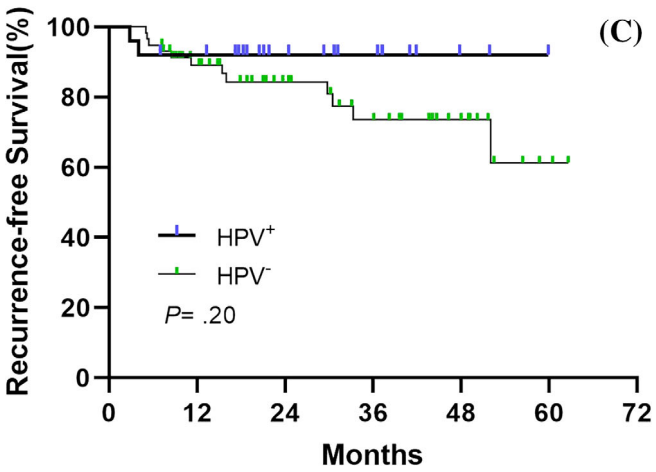


FIGURE 3 Kaplan-Meier survival curve analysis for (A) overall survival, (B) disease-specific survival, and (C) recurrence-free survival by human papilloma virus status.

4 | DISCUSSION

Transoral robotic surgery has been considered as a reasonable option for the treatment of selected patients with early-stage oropharyngeal cancer.[4,22–24] In the last 5 years, our medical center has successfully performed over one hundred TORSs. By detailed data collection and follow-up, we conducted this clinical application analysis of TORS for T1-T2 stage OPSCC patients and it is the first clinical study of TORS in Chinese population with the largest patient cohort.

In our cohort, 83 patients underwent TORS as the primary treatment for OPSCCs with pT1-T2 stages. Among them, 30.1% of patients were HPV-positive patients and 69.9% of patients were

TABLE 5 Multivariable analysis of prognostic factors of recurrence.

	Multivariable survival analysis	
Covariate	**HR (95% CI)**	***P*-value**
HPV status		
Positive		Ref.
Negative	0.81 (0.20, 3.20)	.57
Smoking history		
No		Ref.
Yes	3.51 (1.07, 11.51)	**.039**
Older than 60 years		
No		Ref.
Yes	1.33 (0.35, 5.01)	.67
T stage		
T1		Ref.
T2	0.81 (0.20, 3.20)	.76
Positive lymph nodes		
No		Ref.
Yes	2.21 (0.20, 23.94)	.51
AJCC stage		
I + II		Ref.
III + IV	0.30 (0.02, 3.75)	.35
Adjuvant RT/CRT		
No		Ref.
Yes	0.83 (0.19, 3.70)	.81

Note: *P*-value <.05 was considered to be statistically significant.
Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; CRT, chemoradiotherapy; HPV, human papilloma virus; HR, hazard ratio; RT, radiotherapy.

HPV-negative status, which might reflect the regional epidemiology of OPSCC in East Asia.[25–27] After a median follow-up of 29.5 months, the prognosis of our patients is favorable. The 3-year OS and DFS were 89.5% and 80.1%, respectively, which were similar to the data from other studies with the 3-year DFS of 89% ~ 95.1% and the 3-year OS of 92.4%–100%.[22,28–30]

Whether HPV infection could affect the clinical outcomes of patients undergoing TORS is an important issue that needs to be evaluated. Interestingly, there was no significant difference in the OS, DFS, and RFS between the HPV-positive and HPV-negative groups in our study. In a prospective study with 50 patients with OPSCC, 37 were HPV-positive and 17 were HPV-negative. The OS and DFS of the two groups were compared and no differences were found.[31] Similar results were obtained in other studies.[18,32] Therefore, evidences from our study and previous reports suggest that both patients with HPV-positive and HPV-negative OPSCC of local early-stage could benefit from the TORS approach. In addition to the survival outcomes, there was no significant difference in the operative time of TORS, postoperative hospital stays, postoperative complications between two groups. However, large prospective studies are needed to validate the efficacy of TORS in OPSCC, regardless of HPV status. In further studies, we will continue to track the long-term treatment outcomes of our cohort.

Reports have showed a noninferior survival for TORS compared with the traditional invasive operation, and furthermore, TORS has the advantages of reducing the demand of free flap reconstruction, reducing complications, and shortening the postoperative hospital stay.[33,34] Compared with previous analyses,[4,35] similar recovery data are observed in our study. In our cohort, the average durations of both tracheostomy tube and nasogastric tube use were short and none of the patients underwent intraoperative free flap reconstruction. Postoperative complications occurred in only three patients and two of them were postoperative bleeding, which were considered to be caused by the deep cough. Therefore, it is necessary to use nebulizer therapy for patients suffering from viscous sputum and expectoration difficulty. Besides, margin status has been demonstrated to be an important prognostic factor, especially in HPV-negative OPSCC, the positive rate of surgical margin was more easily obtained, up to 17.3%.[36–38] In our series, only three patients have carcinoma in situ in the postoperative pathological analysis. Reports showed that HPV-negative OPSCCs located at the base of the tongue are more likely to have positive surgical margins in TORS.[14,37] However, in our 58 HPV-negative patients, tonsillar tumors stood a higher proportion, which might explain a low rate of positive margin in our data. Together, these suggest that TORS achieves satisfactory R0 resection in patients with T1-T2 stage OPSCC and postoperative complications are controllable.

Transoral robotic surgery should be performed with caution to ensure that the tumor is fully resected and wound laceration avoided. For lesions located at the tonsil, the excision extension should include the tonsillar fossa, the retromolar pad, the root part of the soft palate, the tongue base close to the tonsil, and part of the posterior pharyngeal wall. In cases with a large tongue and small operation space, part of tonsil and soft palate tissue can be removed first to enhance lesion exposure and operation site accessibility. Secondly, to avoid postoperative wound tearing and risk of postoperative hemorrhage, surgical suture should be placed carefully. In most cases, it could be difficult to close all the wounds. Therefore, suturing the major part, instead of the whole wound, could avoid the occurrence of wound laceration and postoperative dysphagia caused by a forced stitch. It is difficult to stitch the lower pole of the tonsil and the lateral wall of the pharynx, which is usually the most likely place for wound tearing. In such cases, a suture can be placed on the lateral wall of the pharynx to the tongue root tissue.

In terms of postoperative treatments, postoperative CRT was considered as the presence of pathologic ENE or positive margin. These results are similar to those described in other studies.[35,39] Nevertheless, the satisfactory outcomes among patients with HPV-positive OPSCC has led to the development of de-escalated therapeutic strategies.[40] Several studies have shown that TORS alone is safe and effective in patients with HPV-positive cancer, and has the potential to become a de-intensification therapy.[41–43] This is particularly important because some studies showed that the postoperative adjuvant therapy is

associated with worse swallowing-related QOL scores and the addition of RT/CRT didn't improve the oncological outcome.[44,45] Therefore, further researches to evaluate the effectiveness of withdrawal or reduction in the intensity of adjuvant therapy are warranted.

In contrast to HPV-positive OPSCC, the survival outcomes for HPV-negative OPSCC received definitive RT or CRT were still disappointing.[5,17,46] This might be related to the low radiosensitivity of HPV-negative OPSCC.[47] Recently, an analysis based on the National Cancer Data Base (NCDB) and Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2016 support the frontline surgery in patients with T1-2N1-2bM0 HPV-negative oropharyngeal cancer, which had improved OS as compared with the group who received CRT (5-year OS: 74.0% vs 62.9%, $P = .012$).[48] For oncologic results of stage III-IV patients treated with TORS, it can be found that compared with CRT, the survival results obtained by primary treatment with TORS and the adjuvant therapy under the condition of detailed pathological staging are more encoraging.[48–50] In our cohort, the survival rates of 58 patients with HPV-negative OPSCC were not statistically different from those of the HPV-positive group. The results presented in our study and previous findings suggested that HPV-negative patients might benefit from TORS. Hence, instead of definitive RT or CRT, TORS could be considered for suitable patients with HPV-negative OPSCC.

The local recurrence is a critical issue that matter the therapeutic efficiency and prognosis of OPSCC. Both HPV-positive group and HPV-negative group appear to achieve satisfactory locoregional control in the results of LRFS (96.0% vs 88.9%, $P = .47$), which indicates that the treatment of TORS is feasible and has a good advantage in the local control for oropharyngeal cancer of T1-T2 stage. However, studies revealed that HPV-negative OPSCC composed a significant proportion of the OPSCC patients who failure in the first treatment.[18,51]A noticeable correlativity was found between disease control and HPV by Moore EJ et al., with a 3-year local control rate of 92% for HPV-relative group vs 52% for HPV-negative patients.[36] Although the oncologic and perioperative outcomes showed in our study are encouraging and provide effective evidence for the treatment of TORS in the HPV-negative population, it is important to recognize that the management of intensification strategy in HPV negative OPSCC remains inherently more challenging than HPV-positive OPSCC.

According to the Cox regression models we performed, HPV status is not a risk factor for disease recurrence, and smoking history was the only risk factors that had significant effects on recurrence. Smoking has gradually fallen out of the mainstream of risk factors of OPSCC in developed countries. However, in China, smoking is still an important risk factor for OPSCC.[52] Another study has reported that smoking status was considered the only independent prognostic factor for survival.[53] HPV-negative patients make up the majority of our cohort, and these patients tended to be elder and have a long history of smoking. In addition, smoking during RT might affect the persistence of RT and reduce the disease control rate.[54] Therefore, smoking history should be carefully recorded when considering the prognosis of patients with OPSCC.

There are some limitations in this study. First, the follow-up period was short and the 5-year survival rates are still under investigation. Second, the retrospective nature of our analysis might bring some bias and further prospective trials are needed. Third, our study cohort was not compared with the CRT cohort, which may affect the generality of this study. Fourth, due to the limitation of retrospective analysis, the collection of swallowing and speech assessment data was unavailable and we will improve the collection of this part of data in further prospective studies.

5 | CONCLUSION

In recent years, TORS have become an effective method of OPSCC treatment. HPV-related oropharyngeal cancer is not a major morbidity group in China. HPV-negative OPSCC with a more aggressive tumor biology and present more therapeutic challenge. Our study demonstrates that excellent disease control and functional preservation can be achieved with TORS as primary therapy. TORS achieved favorable safety and efficacy in the oncological outcomes of T1-T2 stage OPSCC, regardless of HPV status. Therefore, the technique is safe and feasible, and worthy of clinical promotion.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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How to cite this article: Li H, Zhang X, Chen W, et al. Analysis of T1-T2 stage oropharyngeal squamous cell carcinoma treated with transoral robotic surgery. *Laryngoscope Investigative Otolaryngology*. 2023;8(1):103-112. doi:10.1002/lio2.1005