Laryngoscope Investigative Otolaryngology

Avoidance of Postoperative Irradiation for Cervical Lymph Node Metastases of Human Papillomavirus-Related Tonsillar Cancer

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Background: Several reports have suggested that selected patients with human papillomavirus-related oropharyngeal cancer can be managed with surgery alone. We retrospectively reviewed tonsillar cancer cases to analyze treatment de-intensification after transoral resection.

Methods: Eighteen patients with tonsillar cancer who had undergone transoral resection were included. The patients' characteristics, p16 status, adverse features, clinical course, overall survival, and relapse-free survival according to p16 status were retrospectively examined.

Results: Four lesions showed positive surgical margins and one lesion showed close surgical margin; these patients were treated with postoperative irradiation. Seven p16-positive patients had multiple node metastases and two had extracapsular spread. No p16-positive patients agreed to postoperative irradiation, and recurrence within the surgical field was not observed. The five-year overall and relapse-free survival rates were 89% and 74%, respectively. The five-year relapse-free survival rates of p16-positive and p16-negative patients were 81% and 50%, respectively ($p = .075$).

Conclusions: Postoperative irradiation for cervical lymph node metastases might be avoidable in selected patients with human papillomavirus-related tonsillar cancer.

Key Words: Tonsillar cancer, transoral lateral oropharyngectomy, transoral videolaryngoscopic surgery, outcome, de-intensification.

Level of Evidence: 4.

INTRODUCTION

Recently, the overall incidence of head and neck cancer has decreased worldwide; however, the incidence of human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OPC) is continuously increasing. As a result, the clinical significance of HPV-related OPC is also increasing.[1] Accordingly, in Japan, HPV-related OPC has also increased in recent years, and almost 50% of OPC patients are currently considered to be HPV-related.[2]

HPV-related OPCs tend to be characterized by a small primary lesion with aggressive cervical lymph node metastases, arising within younger populations with good performance status.[3,4] HPV-related cancers show a better response to treatment and improved survival; therefore, HPV is considered to be an important prognostic factor in OPC.[4]

Considering the treatment strategy for OPC, chemoradiotherapy (CRT) has been widely applied compared to radical resection for the purpose of organ preservation. However, long-term toxicity, such as feeding tube dependency, residual tracheostomy, speech problems, and even treatment-related deaths, is common in patients treated with CRT. [5,6] Moreover, organ preservation with CRT does not always mean functional preservation. As mentioned above, HPV-related OPCs tend to arise in younger populations, and tend to show a good response to curative treatment. Hence, although HPV-related OPC might be overcome by CRT, the patient may continuously experience long-term toxicity, and avoiding long-term toxicity is therefore one of the most important clinical concerns.

Regarding tonsillar cancer, selected patients can be successfully treated with transoral lateral oropharyngectomy (TLO).[7,8] TLO can achieve a high local control rate with few complications for a subset of T1 or T2 tonsillar cancer patients; however, the restricted surgical access limits the indications of TLO. After the approval of robotic surgical systems in the United States, transoral robotic surgery (TORS) has been widely applied for transoral resection, especially for oropharyngeal cancer. TORS has the advantage of high-quality endoscopic optics with a 3-dimentional view and instrument mobility of the surgical robot. Weinstein et al.[9] reported that the use of TORS radical tonsillectomy improved the surgical access for tonsillar cancer, with negative margins, maintained postoperative swallowing function, and a low complication rate.

Currently, the use of robotic surgical systems for head and neck cancer is not approved by the JAPAN

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Pharmaceuticals and Medical Devices Agency; therefore, TORS is not applicable in Japan. To overcome this, Shiotani et al.[10] developed a new transoral surgical system, namely transoral videolaryngoscopic surgery (TOVS), in which an FK-WO retractor and Weerda distending laryngoscope or Crowe Davis retractor are used to open the operation field, and a rigid endoscope or high-definition videolaryngoscope with a flexible tip is used to visualize the operation field. The tumor is resected by bimanual use of several surgical instruments for laparoscopic surgery. Owing to the TOVS settings, we can obtain a wide surgical field and operability with tactile sensation. TOVS has attracted attention as an excellent non-robotic transoral surgical approach. Since 2012, we have applied TOVS for transoral resection of pharyngo-laryngeal cancers, including tonsillar cancer, in our institution.

Regarding T1 or T2 tonsillar cancer, there is no significant difference between transoral resection and radiotherapy concerning the overall survival (OS), disease-specific survival, and locoregional control rates,[11] and transoral resection is one of the standard treatments for T1 or T2 OPC today.[12] From the viewpoint of avoiding long-term toxicity related to CRT, the clinical significance of transoral resection as a less invasive treatment for HPV-related OPC might increase further.[13]

Weinstein et al.[14] analyzed the local control rate in OPC patients treated with TORS alone. Four out of 30 patients had perineural invasion or lymphovascular invasion; however, no patient experienced from local recurrence. In addition, despite 16 of the 30 patients being classified as having stage III or IV disease and being treated without postoperative CRT, no patients experienced local recurrence. Thus, some OPC cases might be successfully managed without postoperative treatment.

In this study, we retrospectively reviewed tonsillar cancer patients treated in our institution with transoral resection to discuss treatment de-intensification for HPV-related tonsillar cancer.

MATERIALS AND METHODS

Patients

This study included previously untreated tonsillar cancer patients who had undergone transoral en bloc resection at Tokai University Hospital between 2007 and 2015. Patients with a follow-up period of less than one year were excluded.

Eighteen patients were investigated. The patient characteristics, clinical TN and pathological N classification according to the American Joint Commission on Cancer (7th edition),[15] p16 status of the primary lesion, clinical course, surgical procedure, surgical margin status of the primary lesion, number of cervical lymph node metastases, presence or absence of extracapsular spread (ECS), five-year OS, and five-year relapse-free survival (RFS) rates for all cases, and five-year RFS according to p16 status were retrospectively examined.

Nodal status was assessed via palpation, ultrasonography of the neck, and computed tomography. To confirm the p16 status, immunohistochemical staining with anti-p16 was performed (CINtec p16 Histology; Roche, Basel, Switzerland). The lesions showing continuous, diffuse staining of nucleus and cytoplasm were considered positive. The other pathological features were examined based on the pathology reports.

Indication of Surgery

T1 and T2 tonsillar cancers not exceeding the pharyngeal constrictor muscle were indicated for transoral resection. The p16 status of the primary lesion was not a conclusive factor for determining the indication.

Regarding nodal status, N0, N1, and N2a cases were included, and no patient refused the surgery. We included several N2b cases who requested surgery; however, patients with distinct ECS, as determined through preoperative examination, were excluded. Patients with lymph node metastasis underwent therapeutic neck dissection concurrent with the transoral surgery. Elective neck dissection was not performed for N0 disease.

Postoperative radiotherapy or CRT was recommended for patients with adverse features, such as positive surgical margins, ECS, and multiple lymph node metastases on pathological examination. For N0 patients, we adopted a wait-and-see policy postoperatively and did not recommend any prophylactic treatment. The clinical flowchart is shown in Figure 1. After the transoral operation, the patients underwent follow-up examination for subsequent lymph node metastasis via palpation and ultrasonography once a month. To reveal metastatic lesions, computed tomography from the neck to abdomen was performed every six months.

Surgical Procedures

1. TLO

The operation field was expanded with a Crowe Davis retractor (Nagashima Medical Instruments, Tokyo, Japan). A

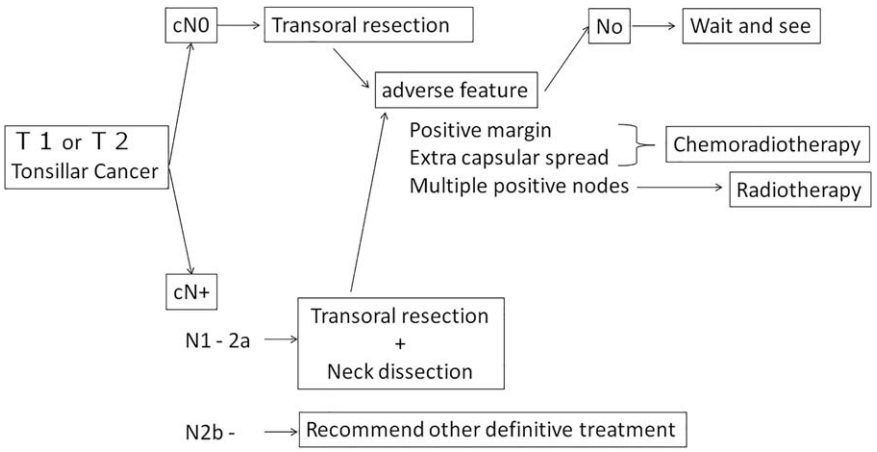

Fig. 1. Clinical flowchart for T1 and T2 tonsillar cancers
Patients without lymph node metastasis underwent transoral resection alone. Patients with lymph node metastasis underwent therapeutic neck dissection at the same time as the transoral surgery. Postoperative radiotherapy or chemoradiotherapy was adopted when adverse features were revealed.

surgical microscope (Carl Zeiss, Oberkochen, Germany) was used to visualize the operation field. The mucosal incision was made with a safety margin of 5–10 mm and the tonsillar lesion was resected with the pharyngeal constrictor muscle by using an electric scalpel (Colorado microdissection needle, Stryker Corporation, Kalamazoo, U.S.A.). The wound surface was covered with polyglycolic acid sheets using fibrin glue.

2. TOVS

The operation field was expanded with an FK-WO retractor (Olympus Medical Systems, Tokyo, Japan. Fig. 2A) or Crowe Davis retractor. A rigid endoscope (Karl Storz, Tuttlingen, Germany) or high-definition videolaryngoscope with flexible tip (Endoeye Flex; Olympus Medical Systems, Tokyo, Japan. Figs. 2B, 2C) was inserted into the operation field to provide a view of the oropharynx on the monitor. The resecting method used was same as TLO (Fig. 3).

Statistical Analyses

Kaplan-Meier survival curves were employed to assess the survival rates, and the log -rank test was employed to compare the survival rates. P values <0.05 were considered statistically significant, and all tests were two-sided. Statistical analyses were performed using StatMate software (Version 4; ATMS, Tokyo, Japan).

Ethics Statement

The Institutional Review Board of Tokai University Hospital, Japan, approved this retrospective study.

RESULTS

The clinical characteristics, clinical TN classifications, and pathological N classifications of the 18 patients are

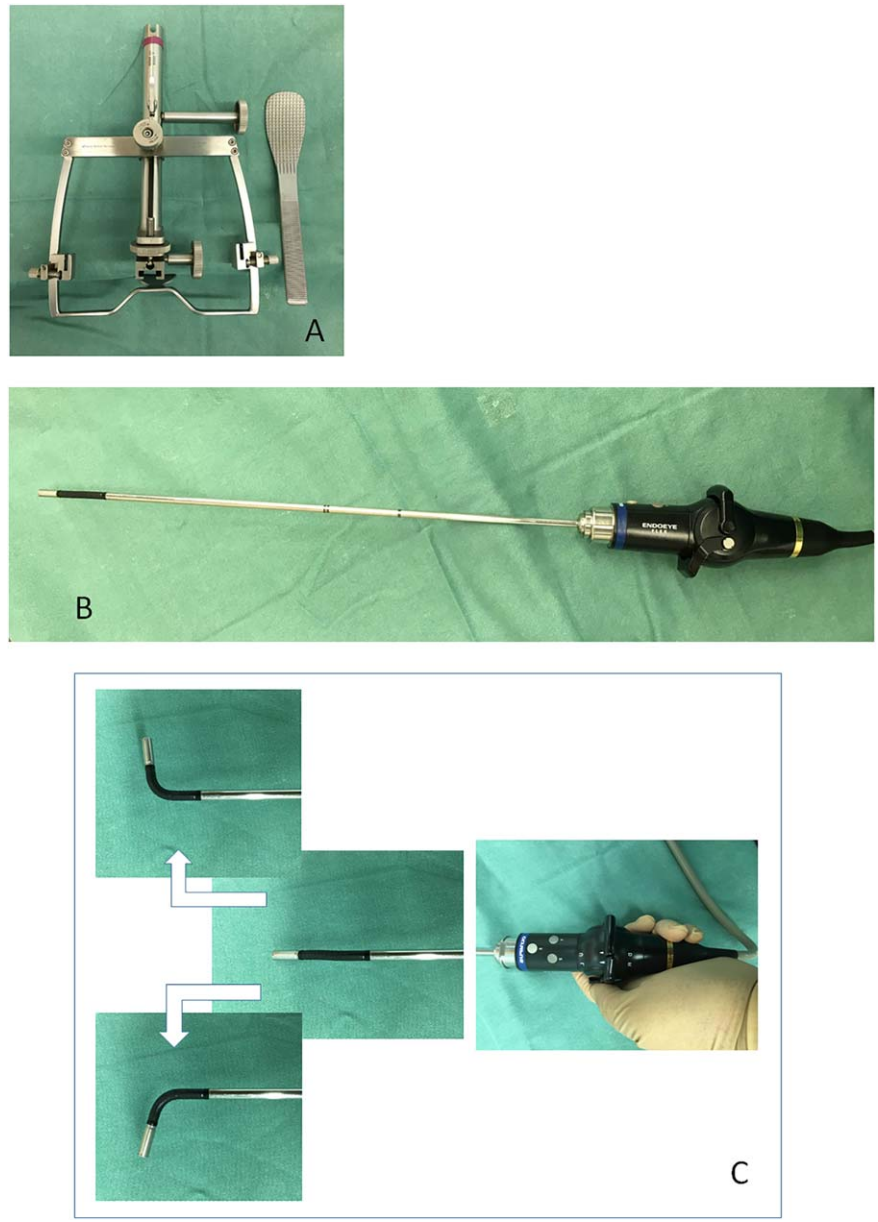

Fig. 2. Surgical procedure
A: FK-WO retractor. A short blade to expose the tonsillar lesion was adopted.
B: High-definition videolaryngoscope with flexible tip (Endoeye Flex; Olympus Medical Systems, Tokyo, Japan).
C: By manipulating the joy-stick, the tip of the rigid endoscope moves flexibly. It provides a good surgical view in the tangent direction and behind the tumor.

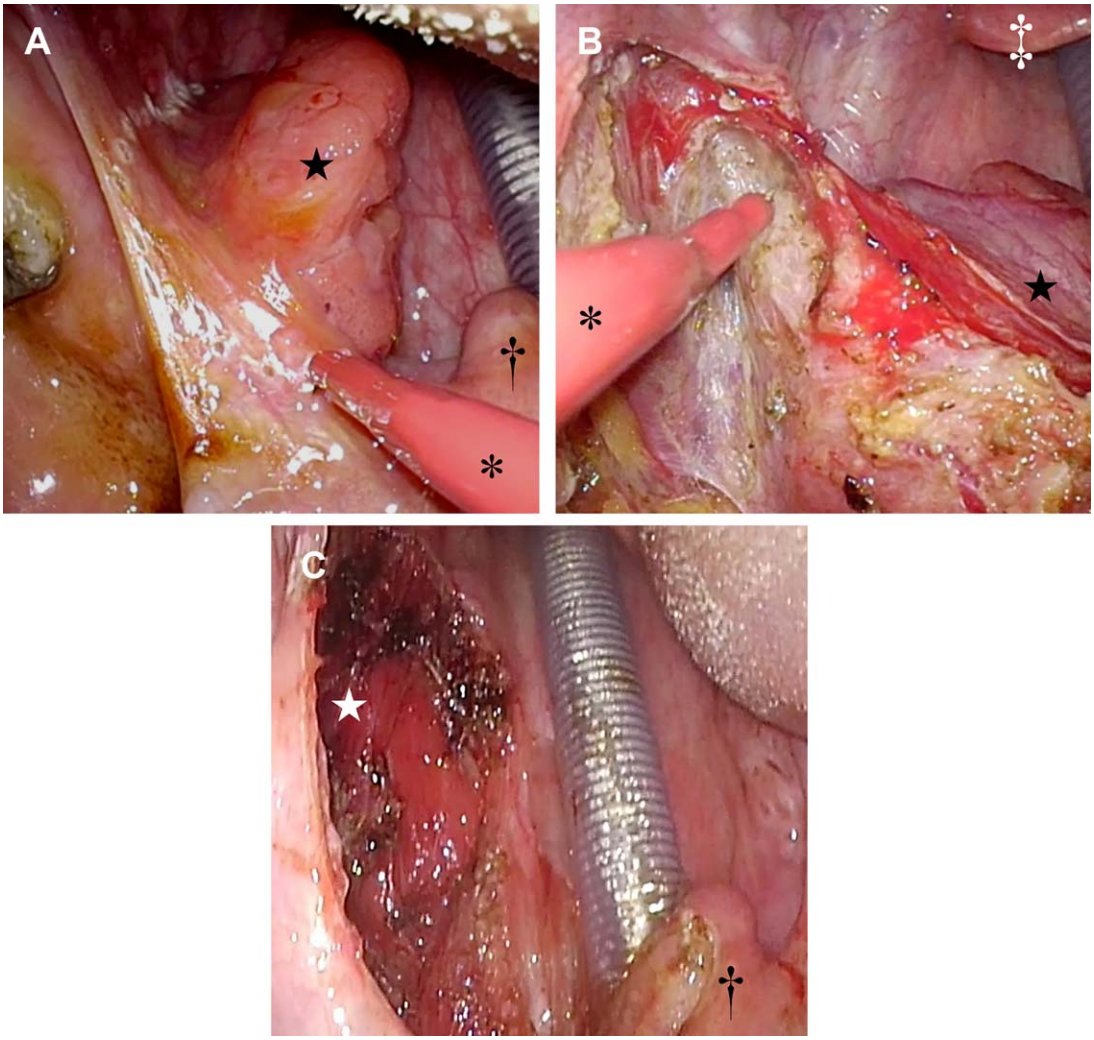

Fig. 3. Operative findings of radical tonsillectomy with transoral videolaryngoscopic surgery
A: The incision line was designed with a 5–10 mm safety margin. (★: tumor, †: uvula, ⋆:electric scalpel)
B: Owing to the use of videolaryngoscope with flexible tip, the lower pole of the palatine tonsil could be visualized well. (★: tumor, ⋆:electric scalpel, ‡: epiglottis)
C: As with transoral lateral oropharyngectomy, tumor resection was performed just beneath pharyngeal constrictor muscle. (†: uvula, ☆: stylopharyngeus muscle)

shown in Table 1. The median age of the patients was 62.5 ± 11.0 years. There were 11 males and seven were females. The median follow-up period for all cases was 32 months (range, 12–98 months). Regarding the TN classification, seven patients had T1 lesions, and the remaining had T2 lesions. N0, N1, and N2a lesions were seen in six, four, and one patients, respectively. Seven cases with N2b lesions were also included. There was no patient with distant metastasis. Immunohistochemical staining for p16 revealed that 14 of the 18 patients were p16-positive, considered to be HPV-related tonsillar cancer.

Of the total 18 primary lesions, 13 lesions were resected with negative surgical margin, whereas four lesions showed positive surgical margins; one was positive in the vertical margin, and three were positive in the horizontal margin. The other one lesion had a close horizontal margin. The patients with positive or close margins were treated with postoperative radiotherapy or CRT.

Seven out of 14 p16-positive patients had multiple node metastases, and two of these seven patients had ECS. For the patients with multiple lymph node metastases or ECS, we recommended postoperative radiotherapy or CRT, explaining the benefits of adjuvant therapy; however, all of the patients declined radiotherapy. Therefore, we adopted the "wait-and-see" approach for these patients.

Subsequent ipsilateral neck recurrence was observed in two patients with N0 tumors, and two patients experienced contralateral recurrence. All recurrent neck diseases were successfully treated with additional neck dissection. Only 1 p16-negative patient died of lung metastasis. A second primary cancer in the hypopharynx was detected in one patient. The five-year OS and RFS rates were 89% and 74%, respectively (Fig. 4). The five-year RFS of p16-positive and p16-negative patients were 81% and 50%, respectively ($p = .075$. Fig. 5).

TABLE 1.
Clinical characteristics of the patients.

Patient Age, sex	p16	cT	cN	pN	Surgical procedure	Margin status	Number of metastatic nodes	ECS	Postoperative treatment	Prognosis
72, M	+	2	0	NA	TLO	-	0	-	none	NED at 98 months
56, M	+	1	1	1	TLO	-	1	-	none	NED at 34 months
64, M	-	2	0	NA	TLO	HM close	0	-	RT	NED at 64 months
63, F	-	2	0	NA	TLO	HM+	0	-	RT	Subsequent ipsilateral neck recurrence at 10months
55, M	+	1	2a	2b	TLO	-	2	-	none	NED at 58 months
41, M	+	1	1	1	TLO	VM+	1	-	RT	NED at 51 months
52, M	+	1	2b	2b	TLO	HM+	7	-	CRT	NED at 48 months
87, M	-	2	2b	2b	TLO	-	4	-	none	Contralateral neck recurrence at 7 months, DOD at 35months
61, F	+	2	2b	2b	TOVS	-	6	+	none	Second primary lesion was detected in hypopharynx at 10 months
75, F	+	2	0	NA	TOVS	-	0	-	none	Subsequent ipsilateral neck recurrence at 10months
60, F	+	2	1	1	TOVS	-	1	-	none	NED at 28 months
54, M	+	2	2b	2b	TOVS	-	3	-	none	Contralateral neck recurrence at 26 months
73, F	+	1	0	NA	TOVS	-	0	-	none	NED at 22 months
78, F	+	2	1	2b	TOVS	-	2	+	none	NED at 21 months
66, M	-	2	2b	2b	TOVS	-	4	-	none	NED at 24 months
53, M	+	1	2a	2b	TOVS	-	2	-	none	NED at 19 months
62, M	+	1	2b	2b	TOVS	-	2	-	none	NED at 12 months
64, F	+	2	0	NA	TOVS	HM+	0	-	RT	NED at 17 months

Abbreviations: NA: not available, cT: clinical T classification, cN: clinical N classification, pN: pathological N classification, TLO: transoral lateral oropharyngectomy, TOVS: transoral videolaryngoscopic surgery, ECS: extracapsular spread. +: positive, -: negative, HM: horizontal margin, VM: vertical margin, RT: radiotherapy, CRT: chemoradiotherapy, NED: no evidence of disease, DOD: dead of disease

DISCUSSION

The indication of postoperative irradiation depends on the pathological lymph node status when complete resection of the primary site could be achieved. We generally do not apply this operation for patients with clinical N2b lymph node metastasis; however, several N2b patients requested to be treated surgically. Moreover, we recommend postoperative radiotherapy or CRT for patients with known adverse feature such as

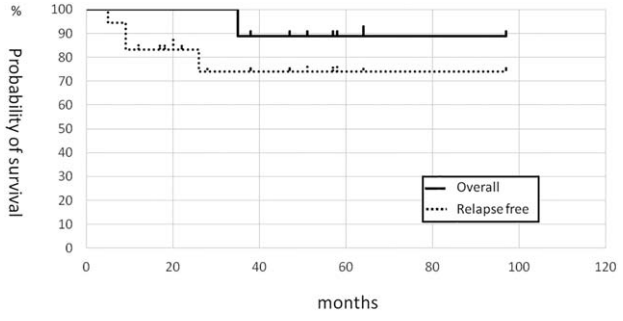

Fig. 4. Overall survival and relapse-free survival of all the cases. Survival probabilities determined by Kaplan-Meier estimates.

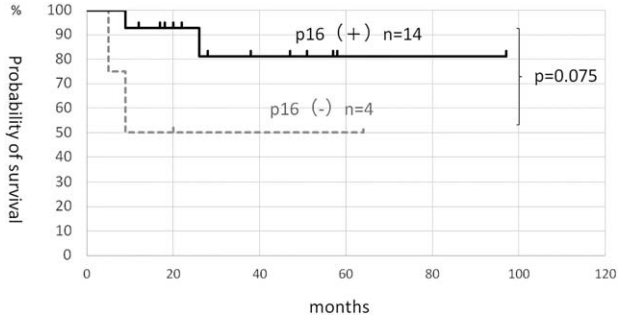

Fig. 5. Relapse-free survival according to the p16 status. Survival probabilities determined by Kaplan- Meier estimates. There was no statistically significant difference between the two groups.

multiple node metastases or ECS; however, the patients do not always agree with the standard postoperative treatment. Regarding HPV-related OPC, seven out of 14 patients had adverse features. Seven patients had multiple node metastases, and two of them had ECS. Despite the fact that they all refused postoperative therapy, only one patient experienced contralateral cervical lymph node metastasis 26 months after the initial operation.

Although this study included a small number of patients, our results suggest that selected OPC patients, especially those with HPV-related OPC, might be treated with surgery alone. Maxwell et al.[16] reported that ECS was not associated with a worse disease-specific survival rate in OPC patients. In addition, Kaczmar et al.[17] reported that conventional risk factors such as ECS, lymphovascular or perineural invasion, and surgical margin status (close or negative) did not affect the locoregional failure rate and the development of distant metastasis in HPV-related OPC patients who had been treated appropriately. These literatures support our opinion.

In this study, the RFS of p16-positive patients tended to be better than that of p16-negative patients; however, there were only four p16-negative patients included in this study. Other limitations of this study include its retrospective single institution study design and the small number of patients included. In addition, the enrolled patients were selected for transoral operation; therefore, the patient population was biased. Currently, we do not consider the p16 status as a decisive factor for the indication of transoral resection; according to NCCN clinical guideline,[12] HPV status should not be a routine consideration for the treatment at this time.

Finally, the long-term toxicity of CRT is known to significantly reduce the quality of life of patients with head and neck cancer; therefore, avoiding long-term toxicity is one of important clinical concerns. As HPV-related OPC tends to arise in younger populations and show a good response for curative treatment, OPC might be successfully treated with CRT; however, long-term toxicity continuously affects these patients. The harmful influence of such long-term toxicity might be more severe in HPV-related OPC patients, and the appropriate treatment selection and/or de-intensification on the basis of HPV status to avoid long-term toxicity will be discussed and proposed in the near future. Avoiding the postoperative irradiation as the de-intensification strategy may contribute to maintaining the patients' quality of life, and selected HPV-related OPC patients might be managed only with transoral resection and neck dissection.

CONCLUSION

Postoperative irradiation for cervical lymph node metastases might be avoidable in selected patients with human papillomavirus-related tonsillar cancer. The feasibility of the de-intensification strategy for HPV-related OPC will be validated by ongoing studies stratified by the HPV status.

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