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ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

Tumor detection with transoral use of flexible endoscopy for unknown primary head and neck cancer

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Abstract

Objectives: With the advent of new optical technologies, early pharyngolaryngeal cancerous lesions can be better visualized. Although the conventional transnasal approach offers great views of the hypopharynx and larynx, the visualization of the oropharynx and palatine tonsils is limited. Through the transoral insertion of a flexible video-laryngoscope, direct views of the oropharynx and oral cavity can be obtained. Thus, transoral examination may contribute to primary detection of cancers of unknown primary (CUP).

Methods: Eighty-five CUP patients from Tokai University were included retrospectively in this study, from 2006 to 2017. Starting in 2010, we employed the transoral examination in addition to our conventional method. The primary detection rates were compared before and after 2010. Oropharyngeal primaries were further analyzed for tumor subsite and p16 status.

Results: The overall primary detection rate did not improve with the addition of transoral examination. However, greater numbers of oropharyngeal primaries were detected. The oropharyngeal lesions detected by transoral examination were mainly p16 positive, located on the palatine tonsil.

Conclusion: Transoral examination is a noninvasive, easy method to adopt in an outpatient setting, and a promising technique to improve tumor detection in this era of human papillomavirus-associated head and neck cancers.

Level of Evidence: 3.

KEYWORDS

endoscopy, human papillomavirus, narrow band imaging, oropharynx, primary tumor detection, transoral examination, unknown primary

1 | INTRODUCTION

As a result of recent advances in optical technology such as narrow band imaging (NBI) systems, microscopic morphological changes of the intraepithelial papillary capillary loop can be visualized noninvasively. These changes suggest early mucosal lesions, such as intraepithelial neoplasia or squamous cell carcinoma (SCC) of the head and neck.[1,2] A flexible video-laryngoscope with NBI enabled us to detect tiny cancerous lesions in the pharyngo-larynx, which would otherwise be impossible to visualize macroscopically or with normal white light examination (WL).[3-5] New optical devices can therefore contribute to the detection of the primary lesions in cancer of unknown primary (CUP).[6,7] Recent systematic review and meta-analysis showed NBI has a considerable diagnostic accuracy in patients affected by head and neck CUP.[8]

To detect the primary lesion of CUP, we initially used a transnasal video-laryngoscope and hooded fiberscope, which yielded a primary detection rate of only 40%. For exposing closed sites, we developed a head position from a combination of Killian's position, head torsion and the Valsalva maneuver. By using this method together with transnasal NBI starting in 2006, we were able to obtain an improved detection rate of primary lesions of CUPs, especially for hypopharyngeal primary sites.[9] In contrast, there were only a few cases whose primary sites were detected in the oropharynx. The palatine tonsils are located anterior to the posterior pillars in tangential manner. Therefore, they cannot be visualized well upon transnasal examination with video-laryngoscope. We thought it is necessary to improve the examination method to obtain more direct visualization of the oropharynx.

Transoral insertion of a flexible video-laryngoscope allows direct views of the oral cavity, palate, and palatine tonsils. The combination of transnasal and transoral examination may allow the detection of lesions in larynx, hypopharynx, and oropharynx. Since 2010, we have employed this transoral examination in addition to the conventional method to identify the primary lesion of CUP. We have already reported two cases of tiny human papillomavirus (HPV)-related tonsillar primary lesions successfully detected with the transoral use of an NBI video-laryngoscope.[10] The advent of transoral examination may help improve the detection rate of primary lesions of CUPs. In this study, we investigated the usefulness of transoral examination by comparing it with the conventional method.

2 | MATERIALS AND METHODS

Patients with cervical lymph node metastasis from CUPs, who were referred to our hospital between January 2006 and June 2017, were retrospectively analyzed.

Starting in 2006, we used a hooded fiberscope and transnasal endoscopy both with WL and NBI with Killian's position in combination with head torsion and the Valsalva maneuver as the conventional method for CUP patients in the outpatient setting (Figure 1A). After 2010, this was modified by combining transoral examination with the conventional method (Figure 1B).

In addition to the irregular surfaces, masses and ulcers detected by WL, well-demarcated brownish areas and irregular microvascular patterns[2] detected by NBI were defined as suspicious primary lesions. When suspicious lesions were detected, biopsy under local anesthesia with optical devices was performed, and then primary lesions were decided by pathological diagnosis. The detection rates of primary

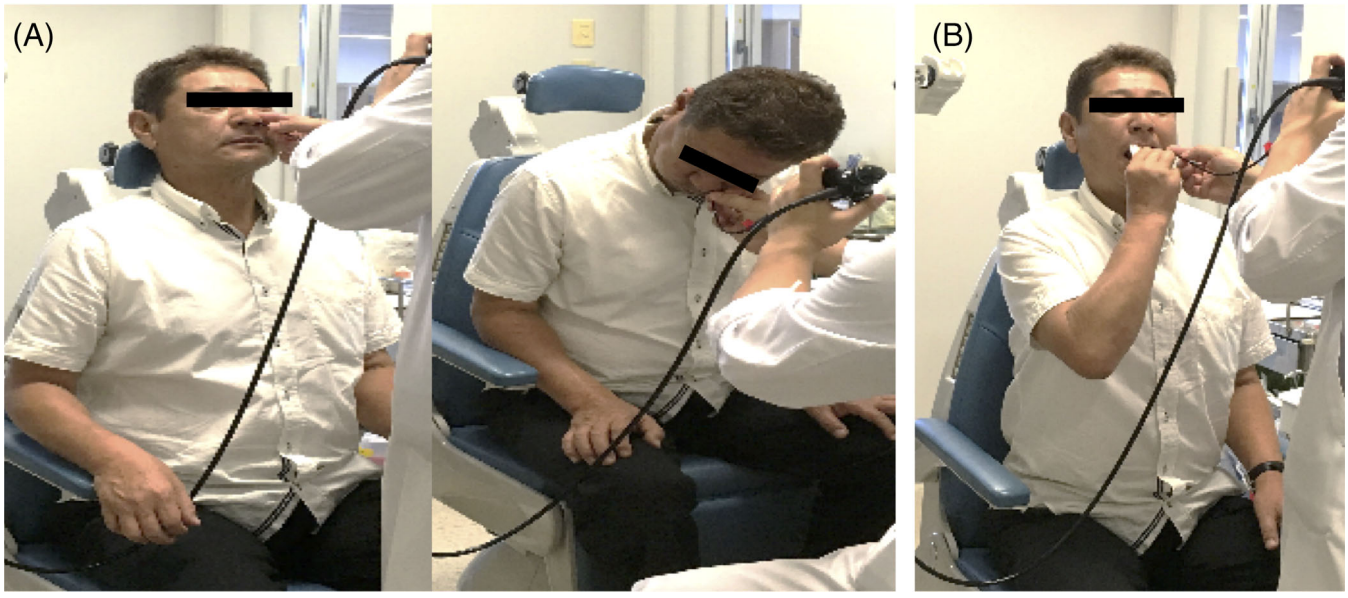

FIGURE 1 Examination method. (A) Conventional method. Transnasal flexible endoscopy with head torsion and the Valsalva maneuver was employed from 2006 to 2009. (B) Transoral examination. The patient is instructed to be in a sitting position, open the mouth, and extend the tongue outward. This new method was employed in combination with the conventional method from 2010

tumors at the initial hospital visit of the period before and after employing transoral examination were assessed.

For the patients after 2010, p16 status was examined retrospectively. In addition, for patients whose primary sites were detected in the oropharynx, the tumor subsites and detection methods were examined retrospectively.

2.1 | Optical devices

We used an ENF TYPE VH and ENF TYPE VQ (Olympus, Tokyo, Japan) NBI endoscopes. These flexible endoscopies were developed for otolaryngological use. Although these outside diameters are small: 3.9 mm (VH) and 3.6 mm (VQ), these can provide high-definition imaging of WL and NBI. The system can be switched between WL and NBI easily by pressing the button on the handle. Both WL and NBI were employed to explore the primary lesions. All examinations were performed by at least two head and neck surgeons.

2.2 | Transoral examination

In the outpatient setting, we placed patients in a seated position and instructed them to open their mouth. We then instructed patients to pull their tongue forward by themselves using small gauze. Physicians inserted the endoscope transorally and examined in sequence the dorsum of the tongue, bilateral lingual edge, buccal mucosa, oral floor, soft palate, bilateral palatine tonsil, posterior wall, and base of the tongue. Both WL and NBI were employed by simply switching the system. The procedure was well tolerated by patients, topical anesthesia with 4% xylocaine spray or nebulizer was employed only when patients felt a gag reflex or discomfort.

2.3 | Histopathological analysis

The biopsy specimens were fixed with 10% buffered formalin, cut into small sections after paraffin embedding, and stained with hematoxylin and eosin. To confirm the p16 status, immunohistochemical staining with an anti-p16 antibody was performed (CINtec p16 Histology; Roche, Basel, Switzerland). The lesions showing continuous, diffuse staining of the nucleus and cytoplasm were considered p16 positive.

2.4 | Statistical analysis

Chi-squared test was employed to compare the primary detection rates. $P < .05$ was considered statistically significant.

2.5 | Ethical statement

All subjects gave their informed consent for inclusion in the study. This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the institutional review board (Tokai University, 17R-297).

3 | REPRESENTATIVE CASES

3.1 | Case 1

A 67-year-old woman was referred to our outpatient clinic for further examination of cervical lymph node metastasis. She had undergone tumor resection of the left cervical mass at her previous institution. She had no remarkable medical or family history, and she was a nonsmoker and a nondrinker. Pathological examination of the lymph node revealed a SCC. We were unable to detect any suspicious lesions upon macroscopic inspection and transnasal endoscopy using the conventional method. However, transoral examination revealed a tiny lesion at the superior pole of the left palatine tonsil (Figure 2A,B). The lesion could not be seen via transnasal approach because the lesion was located behind the posterior pillar (Figure 2C, Video S1). The biopsy specimen revealed a SCC, which was p16 positive.

3.2 | Case 2

A 49-year-old female visited our outpatient clinic for further examination and treatment of an enlarged cervical lymph node of 2 weeks duration on the right side of the neck. She had a medical history of dermatomyositis, was a nonsmoker and a nondrinker. Pathological examination of the lymph node revealed a SCC. Upon transoral examination, a tiny concavity with irregular microvascular patterns was detected at the inferior pole of the right palatine tonsil (Figure 3A-C). However, the concavity could not be seen via a transnasal approach (Figure 3D). The biopsy specimen revealed a p16 positive SCC.

3.3 | Case 3

A 52-year-old male was referred to our outpatient clinic for further examination and treatment of an enlarged cervical lymph node of a month's duration on the right side of the neck. He had no remarkable medical or family history, but had an 18 pack-year smoking history and was a social drinker. Multiple lymph nodes were palpable, with a maximum diameter of 40 mm, on the right side of the neck. We were unable to detect any suspicious lesions on macroscopic inspection and transnasal endoscopy with the conventional method. However, transoral examination revealed a tiny lesion on the right palatine tonsil (Figure 4A,B). The biopsy from the lesion revealed SCC, which was p16 positive. Transoral lateral oropharyngectomy[11,12] and ipsilateral neck dissection were performed. Pathological examination of the resected specimen revealed that the solid tumor grew within the palatine tonsil. The surface of the palatine tonsil was covered with normal mucosa, showing a minute mucosal defect (Figure 4C,D).

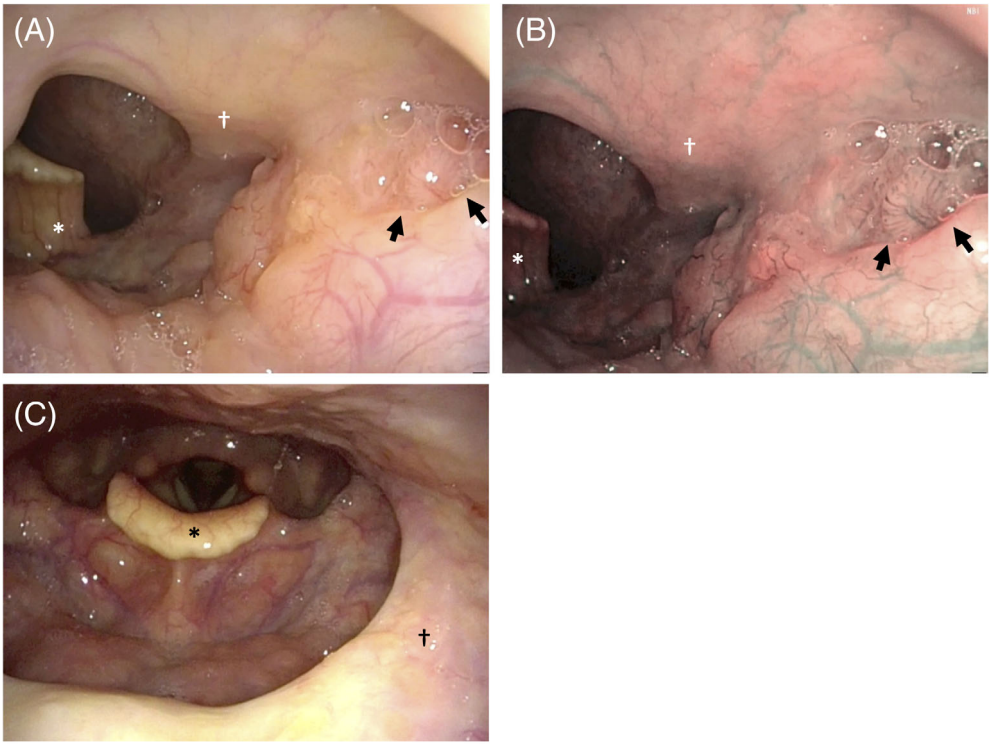

FIGURE 2 Endoscopic findings of case 1. (A) There was a subtle, irregular lesion at the superior pole of the left palatine tonsil (arrow). (B) The lesion was enhanced by NBI (†: posterior pillar, *: epiglottis). (C) The lesion located in front of the posterior pillar; therefore, it was invisible via transnasal examination

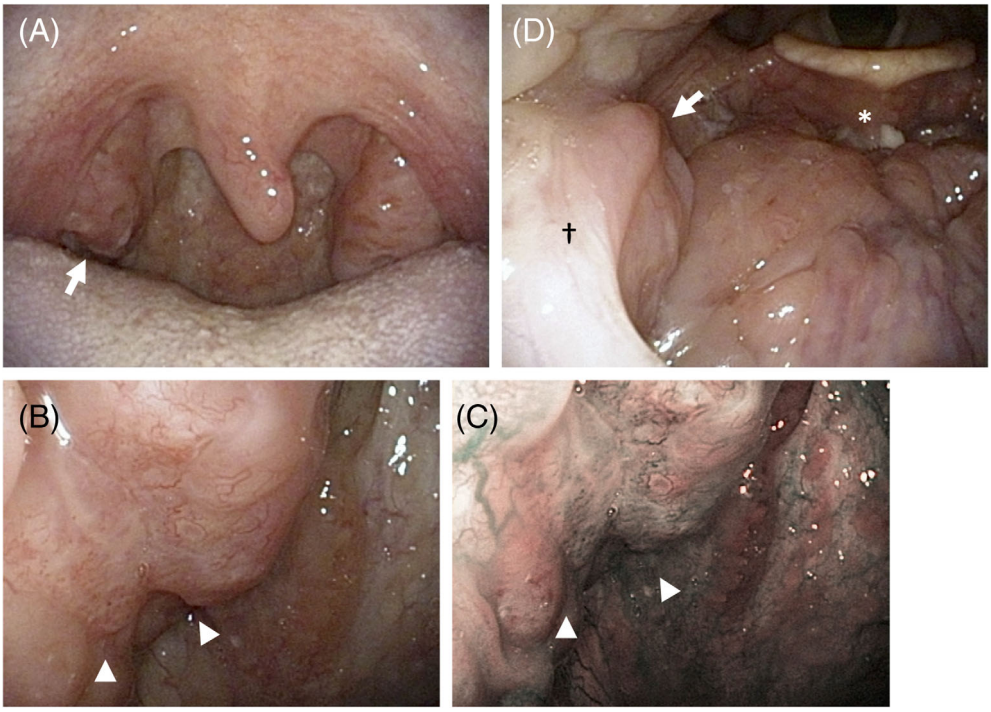

FIGURE 3 Endoscopic findings of case 2. (A) There was a tiny concavity at the inferior pole of the right palatine tonsil (arrow). (B) The concavity included irregular microvascular pattern (arrowhead). (C) The lesion was enhanced by narrow band imaging (NBI). (D) The lesion located inferior edge of the palatine tonsil (arrow), it was outside of a range of transnasal examination (†: posterior pillar, *: epiglottis)

4 | RESULTS

In total, 85 patients (62.9 ± 11.8 years old, 73 male/12 female) were enrolled in this study. None of the patients had p16 information from lymph nodes at the point of their initial hospital visit.

Between January 2006 and December 2009, 21 patients (61.4 ± 11.6 years old, 19 male/ 2 female) were enrolled in the study. They were examined using the conventional method. Between January 2010 and December 2016, 64 additional patients (63.5 ± 11.9 years old, 54 male/10 female) were enrolled and examined using the new method. All patients could undergo the examination without any complications.

In the first phase of the study, primary lesions were detected in 15 (71.4%) out of the 21 patients with CUP using the conventional

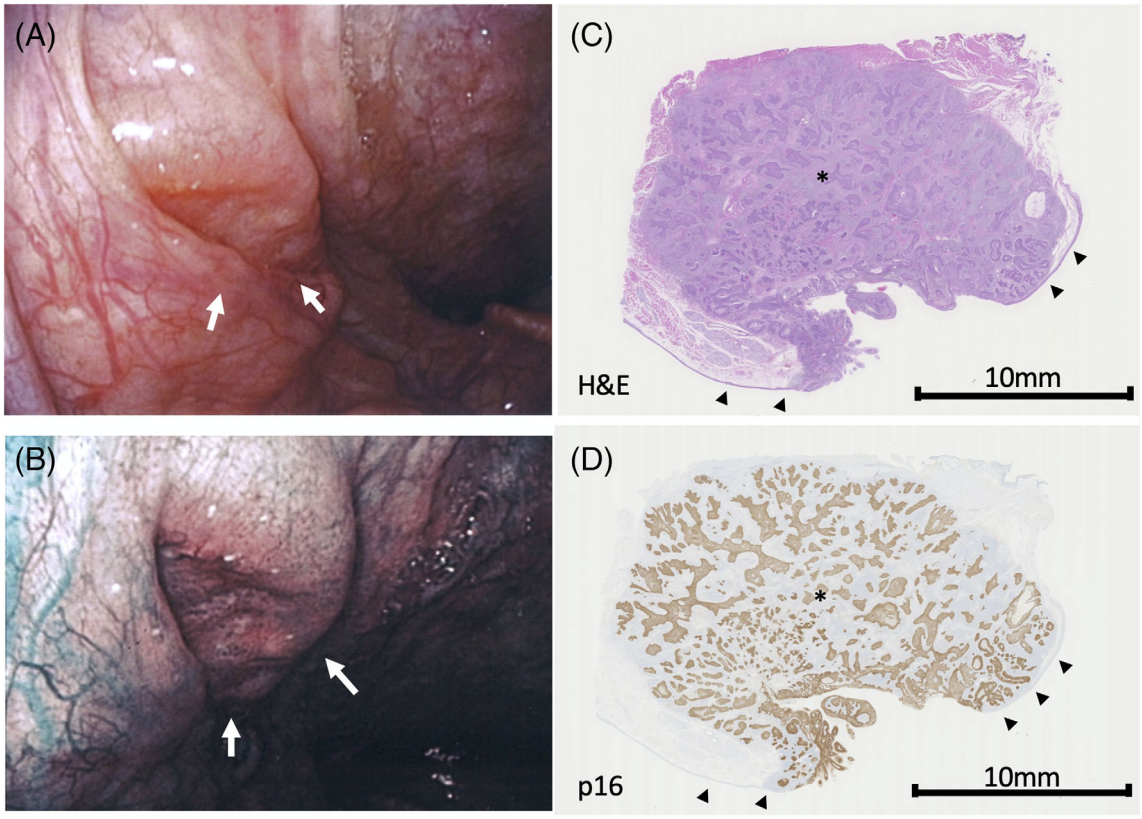

FIGURE 4 Endoscopic and pathological findings of case 3. (A) We detected a small irregular surface at the right palatine tonsil (arrow). (B) Narrow band imaging (NBI) enhancement (arrow). (C) Hematoxylin and eosin (H&E) staining. The tumor was covered with normal mucosa (arrowhead). It was mostly located within the palatine tonsil (*). (D) p16 staining. The tumor showed positive p16

method. The lesions were located at various sites as follows: hypopharynx (12), oropharynx (2), and esophagus (1). During follow-up, primary lesions were found in 3 (50%) out of the remaining six patients in whom primary lesions had not been initially detected (oropharynx, 1; esophagus, 1; nasopharynx, 1; Figure 5).

In the second phase, primary lesions were detected in 47 (73.4%) out of 64 patients with CUP using the new method. The lesions were located at various sites as follows: hypopharynx (19), oropharynx (20), nasopharynx (4), larynx (3), and parotid gland (1). During follow-up, primary lesions were found in 6 (35.3%) of the remaining 17 patients in whom primary lesions had not been initially detected (oropharynx, 2; nasopharynx, 2; esophagus, 1; lung, 1). In total, 19 out of 22 oropharyngeal primary lesions were p16 positive. In contrast, no p16 positive lesion was found in other primary cites except for 1 nasopharynx lesion (Figure 5).

Although the overall primary detection rate did not improve with the addition of transoral examination ($P = .857$), after 2010, 20 oropharyngeal primary sites were identified at the initial visit. Six lesions were at the base of the tongue, 13 on the palatine tonsils, and 1 on the soft palate. Five out of the six primary lesions of the base of the tongue primary were detected by transnasal examination, whereas the remaining one was detected by transoral examination. In contrast, 11 out of the 13 palatine tonsil primary lesions were detected by

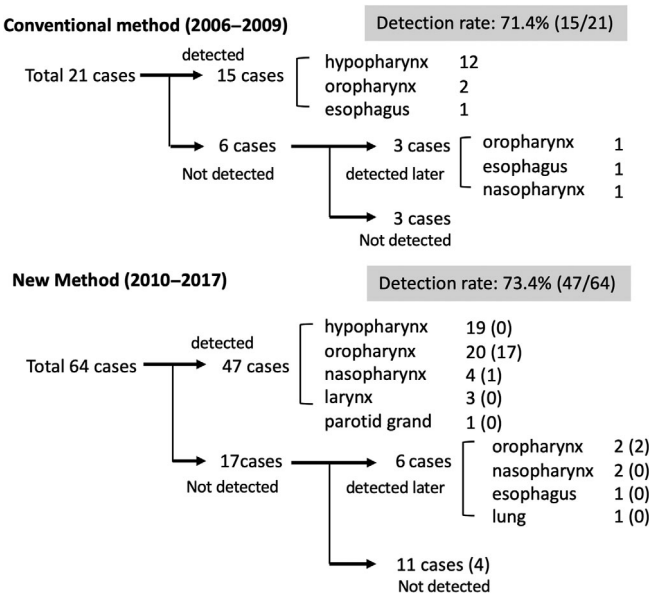

FIGURE 5 Tumor detection rate at the initial hospital visit. The detection rate using the new method was almost same as that of the conventional method. The new method could detect more oropharyngeal primary sites than the conventional method. Primary site and patient number (number of p16 positive cases)

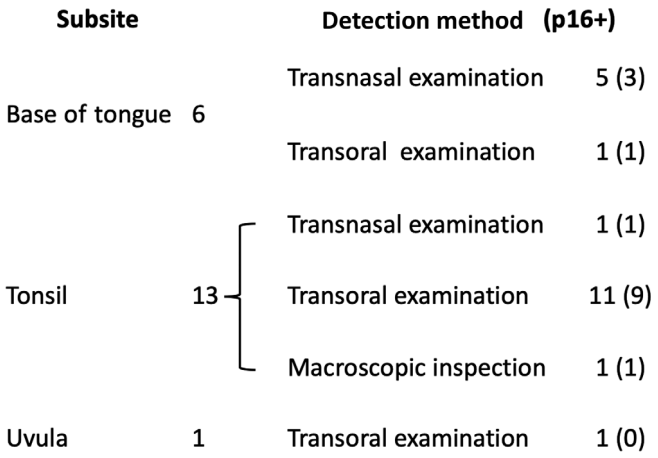

FIGURE 6 Oropharyngeal primary patients after 2010. The primary tonsillar lesions of patients were mainly detected using transoral examination. Primary site and patient number (number of p16 positive cases)

transoral examination, with 9 out of the 11 being p16 positive. One lesion located posterior to the palatine tonsil was detected by transnasal examination, whereas the remaining lesion was detected by macroscopic inspection (Figure 6).

5 | DISCUSSION

The primary detection rates varied from 45% to 80%, depending on the series.[13] Our methods have relatively good identification rates despite these being office-based methods.

We could detect 20 oropharyngeal primary lesions with addition of the new method, a much higher number than with the conventional method. Thus, the transoral examination contributed to the detection of the primary site of oropharyngeal lesions.

The palatine tonsils were the main subsites in the cases detected with transoral examination. Nine out of the 11 tonsillar cancers detected by transoral examination were p16 positive, considered to be HPV-related tonsillar cancers. HPV-related cancers commonly arise in the lymphatic tissue, mainly the palatine and lingual tonsils. Although the patients did not have pre-evaluated p16 status, retrospective p16 evaluation suggests p16 positive lesions are mainly oropharyngeal primary.

HPV infections reach the basal layer of tonsillar crypts, with subsequent carcinogenesis occurring deep inside the tonsil. HPV-related tonsillar cancers grow inside the tonsil, sometimes covered with normal mucosa, making them difficult to detect, and are often clinically diagnosed as CUPs.[10,14] As clarified in the UICC/AJCC TNM classification eighth edition,[15,16] p16 positive oropharyngeal cancer with no primary identified is classified into T0, CUP in the clinical situation. The incidence of HPV-related oropharyngeal cancer is expected to continue increasing.[17] Consequently, HPV-related oropharyngeal cancers showing CUP will also likely increase.

The palatine tonsil is well known as the primary site of CUPs; therefore, tonsillectomy is one of the recommended diagnostic strategies in the NCCN Clinical Practice Guidelines in Oncology.[18] However, both tonsillectomy and the associated general anesthesia are invasive interventions. Although endoscopic examination has limitations in detecting lesions completely covered with normal mucosa, it is a much less invasive strategy than the surgical approach.

To detect primary lesions of CUP, a work-up with diagnostic imaging, including computed tomography (CT) with contrast, magnetic resonance imaging with contrast, and positron emission tomography/computed tomography (PET/CT), is recommended.[18] However, compared to the transoral examination, these require a designated area and expensive equipment. In addition, palatine tonsils sometimes show physiological accumulation of FDG on PET scans, making it difficult to detect small tumors in the area. Therefore, minute examination is essential, even when every kind of imaging diagnosis is available.

This study does not aim to elucidate the usefulness of NBI compared to WL, as this has already been established.[8] However, previous studies have demonstrated the ability to detect a primary site in the palatine tonsil using a gastrointestinal fiberscope (GIF) with NBI.[6,7] It is reasonable to employ NBI examination in the detection of oropharyngeal primary lesions. The GIF requires complicated preparation and sedation, making it relatively invasive. In contrast, our transoral examination can be achieved noninvasively in an outpatient setting by an otolaryngologist or head and neck surgeon, without any complicated preparations. This makes our transoral examination an attractive alternative to GIF.

As shown in the representative cases, depending on the tumor location, the transnasal examination does not always provide sufficient visualization of the oropharynx. Specifically, the posterior pillar blocks the view of the palatine tonsil with this approach. Therefore, it is important to combine transoral examination with transnasal examination to achieve a more thorough screening.

The limitations of this study include its retrospective, single-institution design, lack of a control group, and the small number of patients enrolled. The clinical courses before the first hospital visit were not consistent; therefore, the patient population was subject to a risk of bias. Further prospective research with additional cases is necessary to elucidate the usefulness of transoral examination. However, this noninvasive, easy method is promising for primary detection of CUPs in this era of HPV-associated head and neck cancers.

6 | CONCLUSION

Transoral examination contributes to the detection of primary oropharyngeal lesions, especially HPV-related cancer. This is a noninvasive, easy method to adopt in outpatient settings, and a promising technique to improve tumor detection in this era of HPV-associated head and neck cancers.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Koji Ebisumoto, Akihiro Sakai, Kenji Okami: Conception and design. **Koji Ebisumoto, Akihiro Sakai, Daisuke Maki, Kenji Okami**: Development of methodology. **Koji Ebisumoto, Akihiro Sakai, Daisuke Maki, Tomoaki Murakami, Hiroaki Iijima, Mayu Yamauchi, Kosuke Saito, Takane Watanabe, Kenji Okami: Acquisition of data. Koji Ebisumoto, Akihiro Sakai**: Analysis and interpretation of data. **Koji Ebisumoto, Kevin Robinson, Kenji Okami**: Writing, review, and/or revision of the manuscript. **Koji Ebisumoto, Akihiro Sakai, Daisuke Maki, Kenji Okami**: Administrative, technical, or material support. **Kenji Okami**: Study supervision.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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