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Usefulness and pitfall of Narrow band imaging combined with magnifying endoscopy for detecting an unknown head and neck primary site with cervical lymph node metastasis

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ABSTRACT

Objective: Cervical nodal metastasis from clinically undetectable primary squamous cell carcinoma (SCC) accounts for 1–2% of head and neck malignancies. We retrospectively evaluate the ability of Narrow band imaging combined with magnifying endoscopy (NBI-ME) to detect the primary sites of superficial SCC in the head and neck region.
Methods: This was a report of 11 patients. We performed with NBI-ME to detect unknown primary sites in the head and neck.
Results: Among 11 patients, primary sites were detected in eight. Primary sites were detected in the head and neck in 6 (54.5%) of 11 patients on NBI-ME, all 6 primary lesions were a flat lesion. Two patients in whom primary lesions could not be detected on NBI-ME, one had submucosal tumor like lesion, the other featured by a detectable primary lesion 19 months after neck dissection.
Conclusion: NBI-ME can be recommended as an essential procedure for the detection of primary lesions in patients with primary unknown cervical lymph node metastasis.

1. Introduction

Gastrointestinal endoscopy (GIE) is essential for the diagnosis of squamous cell carcinoma arising in the esophagus, oropharynx, and hypopharynx. Narrow band imaging (NBI) is a novel optical technique that uses narrow bandwidth filters in a red–green–blue sequential illumination system (CV-260SL processor and CLV-260SL light source, Olympus Optical Co. Ltd, Tokyo, Japan) to illuminate intraepithelial papillary capillary loops, thereby enhancing the diagnostic capability of GIE. NBI can more clearly depict capillary patterns as well as boundaries between different types of tissue, factors that are essential for the early diagnosis of tumors [1,2]. Since April 2006 we have used an upper GIE combined with NBI to examine the head and neck region and have reported that this technique permits more detailed examinations than a conventional otolaryngologic endoscope [3]. Cervical node metastasis from clinically undetectable primary squamous cell carcinoma (SCC) accounts for 1–2% of head and neck malignancies [4–6]. We retrospectively evaluate the ability of NBI combined with magnifying endoscopy (NBI-ME) to detect the primary sites of superficial SCC in the head and neck region.

2. Patients and methods

We reviewed the medical records of patients who were given a diagnosis of cervical lymph node metastasis from an unknown primary site at the Department of Otorhinolaryngology, Kitasato University Hospital from September 2006 through December 2009. No patient had evidence of an obvious primary tumor on prior evaluations, including physical examination, these evaluations were performed by several otolaryngologists. The oral cavity, pharynx and larynx were examined for primary lesions, mainly on

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Table 1
Characteristics of patients with cervical lymph node metastasis from an unknown primary tumor.

	Patients
Age (years)	70 (51–84)
Gender	
Male	10
Female	1
N stage	
N2b	3
N3	8
Levels of cervical metastasis	
Upper jugular	4
Middle jugular	6
Lower jugular	1

the affected side. Lesions were assessed with the use of whole-body computed tomography (CT), and video ENT endoscope system (EPX2201 processor and light source unit; FUJINON Co., Saitama, Japan) and an optical endoscope (ER270FP: distal end diameter: 3.5 mm; FUJINON). Patients were excluded if they had a history of head and neck cancer or if the histopathological diagnosis of the primary site or neck mass was not squamous-cell carcinoma. Patients with only supraclavicular lymph node swelling were also excluded. We excluded patients whose primary tumors could be diagnosed on white light endoscopy without examination by NBI endoscopy. To detect primary sites in the head and neck, NBI-ME was performed with the use of a high-definition video endoscope system (CV-260SL, processor, CLV-260SL light source; Olympus Optical Co., Tokyo, Japan) and an optical magnifying endoscope that could magnify objects up to 80 times (GIF H260Z video endoscope: distal end diameter: 10.5 mm; Olympus). Written informed consent was obtained from all patients. Screening was done in the following order: (i) the oral cavity was examined without the use of mouth gear, allowing the subject to move the tongue, and (ii) the oropharyngeal, hypopharyngeal, and laryngeal regions were examined during vocalization, while the subject wore mouth gear. We initially performed screening by NBI endoscopy and white light endoscopy. If a brownish area was found, NBI-ME was done to confirm atypical blood vessels. After the completion of screening examinations for superficial cancers in the head and neck region, we obtained biopsy specimens [7]. We then examined the esophagus, stomach, and duodenum. The epipharynx was not examined because NBI-ME is not transnasal endoscopy.

3. Results

3.1. Patient characteristics

The patient's characteristics are shown in Table 1. The study group comprised 11 patients (10 men, 1 woman), 51–84 years of age (median, 70 years). The characteristics of patients whose primary site was detected are shown in Table 2. The primary tumors were located in the oropharynx in 5 patients, the hypopharynx in 2, and the larynx in 1. These patients demonstrated primary lesions at the ipsilateral sites of the neck masses presented at same. TNM stage was classified according to the 2002 Union for International Cancer Control (UICC) guidelines [8]. Patient 1–6 in whom NBI-ME detected primary lesions had superficial flat type lesion, two patients in whom primary lesions could not be detected on NBI-ME, patient 7 had submucosal tumor like lesion, patient 8 had superficial protruded type lesion. Lymph node metastasis was N3 in 8 patients and N2b in 3. No patients had distant metastasis or primary tumors in the esophagus, stomach, or duodenum.

3.2. Detection of primary sites in the head and neck on NBI-ME

Primary sites were detected in the head and neck in 6 (54.5%) of 11 patients on NBI-ME. Although the detection rate did not differ between NBI and NBI-ME, well-demarcated brownish areas and irregular microvascular patterns of superficial cancer spread were better visualized by NBI and NBI-ME than by white light endoscopy. Furthermore, NBI-ME allowed definitive visualization of both of these characteristics [9]. In all 6 patients in whom primary lesions were confirmed on NBI-ME, the presence of a flat lesion with a brownish area and proliferation of atypical vessels strongly suggested cancer. SCC was diagnosed on biopsy. An NBI diagnosis of superficial SCC required the presence both a well-demarcated brownish area and an irregular microvascular pattern [10–12]. Images of primary tumors detected on NBI-ME that were located at the base of the tongue (patient 2) and hypopharynx (patient 4) are shown in Figs. 1 and 2. ENT endoscopy showed clinically significant lesions in the hypopharynx (Fig. 2a). Conventional white-light examination showed a slightly reddish area with mild mucosal irregularity (Fig. 1a) and reddish spots with whitish lesion (Fig. 2b). NBI endoscopy showed a well-demarcated brownish area (Figs. 1b and 2c). NBI at maximum magnification (×80) showed an irregular microvascular pattern (Fig. 1c) and NBI at low power magnification shows irregular-shaped microvessels on the surface of the lesion (Fig. 1d). Pathologic examination of specimens (patient 2) revealed squamous cell carcinoma (Fig. 1d). In patient 2, the lesion extended from the root of the tongue to the epiglottic vallecula. A flat lesion was present at the root of the tongue. The primary tumor was therefore considered to arise from the root of the tongue. The patients in whom primary lesions could not be detected on NBI-ME, patient 8 had submucosal tumor like lesion, patient 9 had superficial protuded type lesion. In patient 8, NBI endoscopy showed no irregular vessels on the surface of the palatine tonsils (Fig. 3a), which were not swollen. Neck dissection with concurrent tonsillectomy was performed on the affected side. Specimens of the resected palatine tonsil stained with hematoxylin and eosin are shown in Fig. 3b and c. SCC was found to invade the tonsillar fossa, but not the surface of the palatine tonsil.

Table 2
Characteristics of possible primary lesions detected.

Case	Age (y)	Gender	Primary	Endoscopic findings	Node size	Neck level
1	70	Male	Base of tongue[a]	Superficial, flat type	N3	Middle jugular
2	70	Male	Base of tongue[a]	Superficial, flat type	N3	Middle jugular
3	51	Male	Palatine tonsil[a]	Superficial, flat type	N3	Upper jugular
4	84	Male	Hypopharynx[a]	Superficial, flat type	N3	Lower jugular
5	78	Male	Hypopharynx[a]	Superficial, flat type	N2b	Middle jugular
6	60	Male	Palatine tonsil[a]	Superficial, flat type	N3	Upper jugular
7	71	Male	Palatine tonsil	Submucosal tumor like	N2b	Middle jugular
8	53	Female	Supraglottic[b]	Superficial, protruded type	N2b	Middle jugular

[a] Primary site were detected with NBI-ME.
[b] Detectable primary lesion developed 19 months after neck dissection.

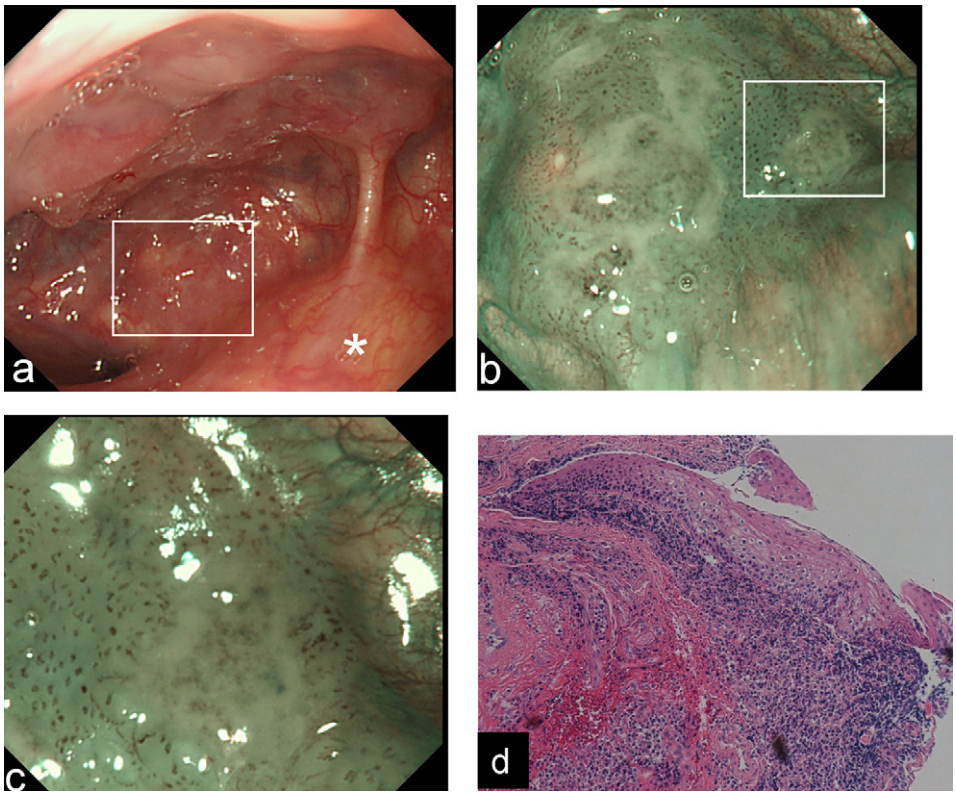

Fig. 1. Patient 1. (a) Conventional endoscopy shows reddish spots with gentle upheaval at the right base of the tongue (arrows). Asterisk (*) indicates epiglottis. (b) Narrow band imaging endoscopy shows both a brownish area and scattered brown dots with gentle upheaval at the right base of the tongue in the same square as (a). (c) Narrow band imaging endoscopy at maximum magnification (×80) shows irregular-shaped microvessels on the surface of the lesion in the same square as (b). (d) Squamous-cell carcinoma invaded the subepithelium (hematoxylin-eosin stain; original magnification at low power).

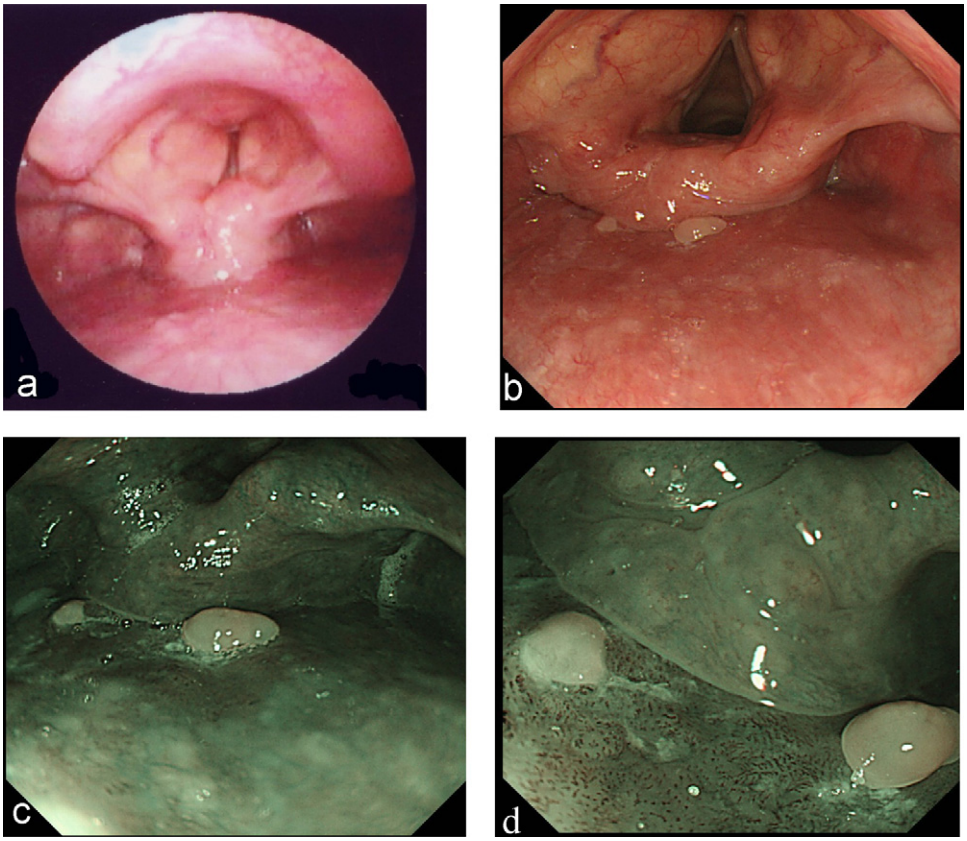

Fig. 2. Patient 4. (a) ENT endoscopy shows clinically significant lesions in the hypopharynx (a). (b) Conventional endoscopy shows reddish spots with whitish lesion. (c) Narrow band imaging endoscopy shows a well demarcated brownish area. (d) Narrow band imaging endoscopy at low magnification shows irregular-shaped microvessels on the surface of the lesion.

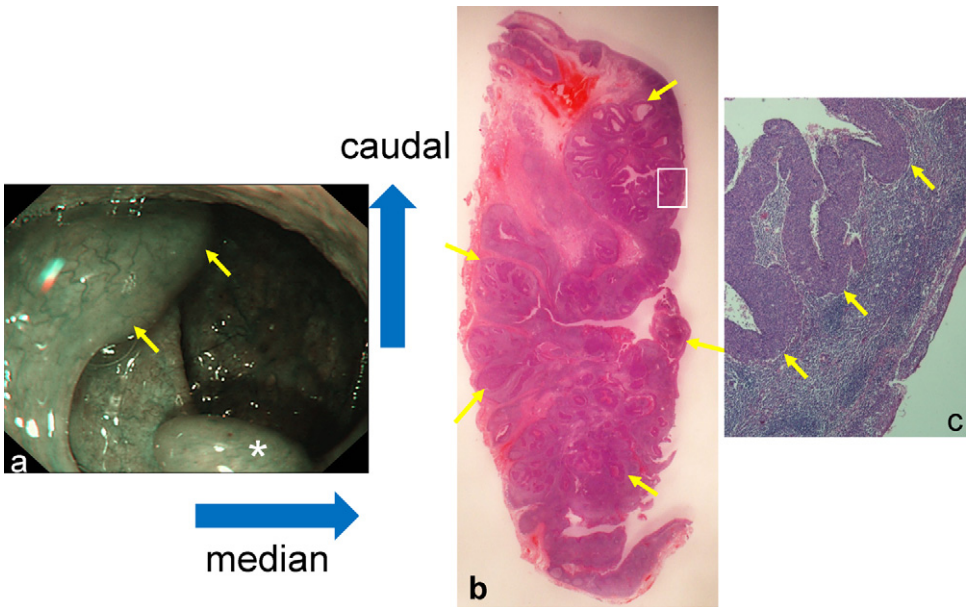

Fig. 3. Patient 8. (a) Narrow band imaging endoscopy shows normal capillary vessels on the surface of left palatine tonsil (arrows). Asterisk (*) indicates uvula. Left palatine tonsil (arrows). (b) Resected left palatine tonsil with histologic mapping. The arrows indicate squamous cell carcinoma with subepithelial invasion (hematoxylin–eosin stain; original magnification at low power). (c) The arrows indicate subepithelial invasion by squamous cell carcinoma, but no involvement of the surface (hematoxylin–eosin; original magnification at medium power).

Patient 9 was recommended to undergo a tonsillectomy because of the diagnosis of the primary tumor, but the patient refused. Neck dissection was therefore performed. Chemoradiotherapy was recommended, but also refused. The patient was therefore observed with no further treatment. After 19 months, a submucosal lesion developed in the supraglottis (Fig. 4a and b). NBI endoscopy showed no evidence of irregular vessels on the lesion surface. However, biopsy demonstrated a diagnosis of SCC for the primary lesion.

4. Discussion

Several reasons may account for cervical lymph node metastasis in the absence of a primary tumor. Small tumors in particular sites, such as the tonsillar fossa or the base of the tongue, can be easily missed on physical and radiographic examinations owing to the anatomic complexity of the region and the intrinsic limitations of currently available diagnostic techniques. Small tumors hidden in the crypts of lymphoid tissue of the tonsillar fossa and base of the tongue can acquire an early metastatic phenotype and spread to the regional lymph nodes while still undetectable clinically [13]. However, there is no general consensus on what should be included in an optimal diagnostic workup [14,15]. Sixteen studies evaluated the role of fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET) in the detection of unknown primary tumors. FDG-PET detected 24.5% (74/302) of tumors that were not apparent after conventional examinations [16]. Superficial squamous cell carcinomas of the thoracic esophagus infiltrating the deep submucosal layer, 67.9% (19/28) were FDG-PET positive, while only 15.4% (2/13) tumors infiltrating only the mucosa or shallow submucosal layer were PET positive. Furthermore, non-flat (elevated or depressed) tumors showed significantly stronger (73.7%: 14/19) FDG uptake than flat ones (31.8%: 7/22) [17]. FDG-PET/CT was not performed in any patient in our series because the necessary equipment was unavailable at our hospital. Patients 1–6 in whom NBI-ME detected primary lesions had superficial flat type, might be FDG-PET negative. Therefore, we studied whether NBI-ME was useful for detecting

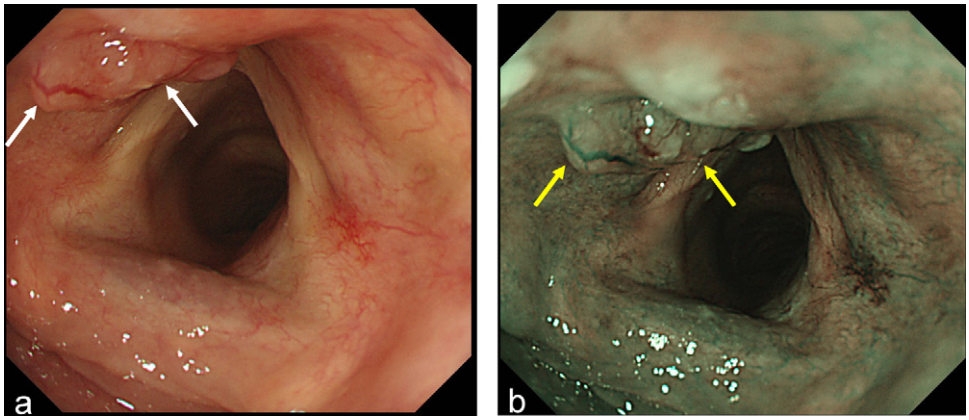

Fig. 4. Detectable primary lesion developed 19 months after neck dissection (Patient 9). (a) Conventional endoscopy shows dilated, regular-shaped vessels associated with a massive submucosal lesion arising in the supraglottis (arrows). (b) Narrow band imaging endoscopy shows dilated regular-shaped vessels associated with a massive submucosal lesion in the supraglottic region (arrows). As compared with conventional white light endoscopy, NBI endoscopy provided better visualization of blood vessels on the surface of the supraglottic mass and demonstrated the presence of dilated regular-shaped vessels; however, no atypical blood vessels were apparent.

primary sites. Cervical lymph node metastasis from an unknown primary site was defined as no evidence of a primary lesion on physical examination, the whole body CT scanning, or ENT endoscopy. Before NBI-ME, all patients had a diagnosis of head and neck cancer with an unknown primary site. Our results showed that NBI-ME can identify primary lesions in patients who have head and neck cancer of unknown origin. In all 6 patients in whom NBI-ME detected primary lesions, the presence of cancer was strongly suggested by the proliferation of irregular vessels, and biopsy yielded a diagnosis of SCC. In these 6 patients, the primary lesions cannot be detected because their atypical vessels are invisible on ENT endoscopy. Although these primary lesions were flat, they lacked ulceration and induration on palpation. These lesions were also not visualized on CT scanning of the neck.

Tonsillectomy offers a significantly higher likelihood (40.7%; 11/27) of finding occult tonsillar tumors than deep tonsil biopsy (11.6%; 11/95) [18]. In patient 7, squamous-cell carcinoma was present in the tonsillar fossa, but not on the surface of the palatine tonsil. Therefore, the primary lesion would probably have gone undetected if the tonsil had not been resected. In patient 8, a superficial, protruded type lesion was detected in the supraglottis 19 months after neck dissection. Cervical lymph-node metastasis appeared before detection of the primary lesion, which was superficial, protruded type. Diagnosis of the primary lesion was therefore extremely challenging.

In Patient 1, histopathological examination of a biopsy specimen showed that the tumor invaded beyond the epithelium. The primary lesion was resected only in patient 7, in whom the tumor extended beyond the epithelium. Because the primary lesions were not resected in the other 7 patients, the depth of invasion remains unclear. However, even superficial lesions in the head and neck for which a primary site could not be detected before the introduction of NBI-ME can apparently cause multiple metastases to the ipsilateral and other groups of cervical lymph nodes (N2b) in the neck. The incidence of positive lymph node metastasis tend to increase markedly as superficial esophagus cancer infiltrates reached the submucosal (e.g. m1: 0% (0/199), m2: 3.3% (5/153), m3: 12.2% (28/230), sm1: 26.5% (58/219), sm2: 35.8% (133/372), sm3: 45.9% (260/567)) [19]. In contrast to esophageal cancer, head and neck cancers have no lamina muscularis mucosae and therefore cannot be directly compared with esophageal cancer. However, because even superficial cancers of the esophagus can be associated with lymph-node metastasis, superficial cancers of the head and neck might also have a risk of lymph-node metastasis.

To the best of our knowledge, however, the incidence of lymph-node metastasis associated with head and neck superficial lesions has not been assessed previously. Further studies are therefore needed. NBI-ME can detect possible primary cancer in 35% (16/46) of the patients with primary unknown cervical lymph node metastasis, however the authors only studied patients in whom a diagnosis could be made on NBI [20]. In the present study, NBI-ME successfully detected primary lesions in 54.5% (6/11) of the patients who had primary tumors in the head and neck that were undetectable on conventional diagnostic techniques. Two patients in whom primary lesions could not be detected on NBI-ME, one had sub mucosal tumor like lesion (patient 7), the other featured by a detectable primary lesion 19 months after neck dissection (patient 8). NBI-ME is a diagnostic technique that can depict superficial irregular vessels, but may be not useful for the detection of submucosal tumors that lack irregular vessels on their surface or for detecting primary lesions that are found after the start of therapy. NBI-ME can be recommended as an essential procedure for the detection of primary lesions in patients with primary unknown cervical lymph node metastasis.

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