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Usefulness of Narrow-band Imaging for Detecting the Primary Tumor Site in Patients with Primary Unknown Cervical Lymph Node Metastasis

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Objective: We sometimes experienced patients with primary unknown cervical lymph node metastasis. In such cases, if computed tomography, magnetic resonance imaging, laryngoscopy and gastrointestinal endoscopy cannot detect a primary site, there is no other effective method to identify a possible primary tumor. We investigated whether narrow-band imaging can detect a possible primary tumor in such.
Methods: Forty-six patients with primary unknown cervical lymph node metastasis were surveyed about primary tumors, from January 2003 to December 2006. All cervical lymph nodes were histologically proved to be squamous cell carcinoma by fine-needle aspiration cytology. Narrow-band imaging combined with magnifying endoscopy was used to identify the primary site in the head and neck region and cervical esophagus. Histological analysis was performed for all suspicious lesions by a biopsy specimen.
Results: Twenty-six lesions were suspected to be cancerous lesions by narrow-band imaging in the head and neck region. Sixteen lesions in 16 (35%, 16/46) patients were squamous cell carcinoma. Ten lesions were located in the hypopharynx and the remaining six lesions were located in the oropharynx. White light endoscopy could not point out any lesion.
Conclusions: Narrow-band imaging endoscopy can detect possible primary cancer in patients with primary unknown cervical lymph node metastasis.

Key words: NBI – pharynx – primary unknown cancer – neck lymph node metastasis

INTRODUCTION

In the head and neck region, we sometimes treat patients with cervical lymph node metastasis where a primary tumor cannot be identified by laryngoscopy, computed tomography (CT) and magnetic resonance imaging (MRI). Primary unknown cervical lymph node metastasis (PUCLNM) is reported in 2–9% of metastases in the head and neck region. Additional work-up including upper gastrointestinal endoscopy can detect possible primary lesions in about 10% of the patients, but the possible primary site is not identified in 90% of the patients with PUCLNM.

The inability to find the primary tumor makes it difficult to decide on the most appropriate treatment for the patient, and the clinician must consider different options for the initial treatment. In some cases, the primary tumor is detected during treatment for the lymph node metastasis, but the primary site remains unidentified in some. In cases where the primary tumor is detected after the start of

treatment, it is impossible to switch the treatment. Thus, to stage and evaluate the treatment strategy, the clinician should be able to detect the primary site before starting treatment.

To find a primary lesion, blind biopsy (1–3) or tonsillectomy (4) is sometimes used in patients with PUCLNM. However, these surveillance methods do not always detect the primary lesion. In the case of PUCLNM, whole-neck irradiation will be indicated after cervical lymph node excision because we cannot pinpoint the primary cancer-based treatment strategy (5–7). Whole-neck irradiation causes adverse events such as salivary gland disorder, severe mucositis and taste disorder. In addition, if primary cancer could be detected after irradiation, re-irradiation would not be needed; this is important because surgery after irradiation increases the risk of leakage of the anastomosis.

Muto et al. (8,9) reported that narrow-band imaging (NBI) can detect superficial cancer in the oropharynx and hypopharynx. Although NBI is expected to help identify the primary lesion in patients with PUCLNM, there are no reports on this issue. We surveyed primary lesions in such patients using NBI endoscopy of the gastrointestinal tract.

PATIENTS AND METHODS

From January 2003 to December 2006, 46 consecutive patients with PUCLNM were surveyed about the primary site using a gastrointestinal NBI endoscope in National Cancer Center Hospital East, Chiba, Japan. Written informed consent for the examination was obtained from all patients.

The definition of PUCLNM was in accordance with the report by Greenberg (10) as follows.

- It is proven to have malignant cells histologically.
- We cannot identify a primary tumor using ocular inspection or pharyngolarynx fiberoscopy.
- We cannot identify a primary tumor by CT or MRI.
- Other organs except the head and neck do not show a carcinoma.

In all patients, the possible primary tumor could not be detected by examination using CT, MRI, pharyngolaryngoscopy and standard white-light gastrointestinal endoscopy.

We used a magnifying videoendoscope (Q240Z, Olympus Medical Systems, Tokyo, Japan) and sequential RGB light source with NBI function (CLV-Q260SL, Olympus Medical Systems). The magnifying endoscope had a capability of $\times 80$ optical magnification. The NBI system has been described in detail in previous studies (8,9). In this system, the central wavelengths of NBI were 415 and 540 nm, and each had a bandwidth of 30 nm.

During the survey of the primary site in the head and neck region including the cervical esophagus, if the lesions showed both a well-demarcated brownish area and an irregular microvascular pattern (11), we diagnosed cancer. After this examination, we took a biopsy specimen to confirm the histological diagnosis.

RESULTS

The patients' characteristics are shown in Table 1. Thirty-eight patients were men and eight were women. Their median age was 66 years (range, 38–81 years). Twenty-eight cases were N2 and 18 cases were N3. Thirty-one patients had metastatic lymph nodes in the upper jugular area (Level II), 13 had middle jugular lymph node metastasis (Level III) and 2 had lower jugular lymph node metastasis (Level IV).

Twenty-six lesions were suspected to be the cancerous site in 25 patients. Sixteen lesions in 16 patients were confirmed histologically as squamous cell carcinoma. Histological assessment of all of the possible primary lesions showed the similar feature of squamous cell carcinoma. Thus, primary cancer in the head and neck region was detected in 16 patients (35%) by NBI endoscopy. The patients' characteristics are shown in Table 2. Ten patients had metastatic lymph nodes in the upper jugular area, five had middle jugular lymph node metastasis and one had lower jugular lymph node metastasis. Nine cases were N3 and seven cases were N2. All of the lesions detected were superficial neoplasia. Ten lesions were located in the hypopharynx and the remaining six lesions were located in the oropharynx (three were tonsil). All lesions were T1 stage or Tis, and all lesions were <2 cm in size. Biopsy specimens revealed that one lesion was intraepithelial cancer and the other had invaded to the subepithelial layer.

Table 1. Patient characteristics

	Patients
Age (years)	66 (38–81)
Gender	
Male	38
Female	8
N stage	
N2a	4
N2b	20
N2c	4
N3	18
Levels of cervical metastasis	
Upper jugular (II)	31
Middle jugular (III)	13
Lower jugular (IV)	2

Thirty-eight patients were males and eight were females. Median age was 65 years (range, 38–81 years). Twenty-eight cases were N2 and 18 cases were N3. Thirty-one patients had metastatic lymph node in the upper jugular area (Level II), 15 had middle jugular lymph node metastasis (Level III) and 2 cases had lower jugular lymph node metastasis (Level IV).

Table 2. Characteristics of possible primary lesions detected by NBI

	Primary	Endoscopic findings	*n* (levels)	Treatment
1	Oropharynx	Superficial	3 (II)	CRT
2	Oropharynx	T1	3 (II)	CRT
3	Hypopharynx	Superficial	3 (II)	RT
4	Oropharynx	Superficial	3 (III)	CRT
5	Hypopharynx	Superficial	3 (II)	CRT
6	Hypopharynx	Superficial	3 (II)	EMR + ND
7	Hypopharynx	Superficial	3 (II)	CRT
8	Hypopharynx	Superficial	3 (II)	Surgery + ND
9	Oropharynx	Superficial	2b (III)	Surgery + ND
10	Oropharynx	T1	2a (II)	Surgery + ND
11	Hypopharynx	Superficial	2b (IV)	Surgery + ND
12	Hypopharynx	T1	2a (II)	Surgery + ND
13	Hypopharynx	Superficial	2b (II)	EMR + ND
14	Hypopharynx	Superficial	3 (III)	RT
15	Oropharynx	Superficial	2c (II)	Surgery + ND
16	Hypopharynx	Superficial	2b (III)	EMR + ND

Nine cases were N3 and seven cases were N2. Five cases were treated by concurrent chemoradiation therapy and in nine cases, primary site was removed by surgery or endoscopic resection and they underwent neck dissection for lymph node metastasis. NBI, narrow-band imaging; CRT, chemoradiation therapy; EMR, endoscopic mucosal resection; ND, neck dissection.

Five patients were treated by concurrent chemoradiation therapy (CRT). Two patients were treated with a chemotherapy regimen comprising 5-fluorouracil (800 mg/m^2, days 1−5) and cisplatin (80 mg/m^2, day 1). Two patients were treated with tegafur-gimeracil-oteracil potassium (60 mg/m^2, days 1−14) and cisplatin (20 mg/m^2, day 1). One patient was treated with cisplatin (80 mg/m^2, day 1). The irradiation field covered the whole neck, and the total radiation dose was 70 Gy (2 Gy/fr). Two patients were treated by radiation therapy (total 70 Gy) alone. For the other nine patients, the primary site was removed by surgery or endoscopic resection, followed by neck dissection of the lymph node metastasis. No patient received whole-neck irradiation after neck dissection.

Treatment of the 20 patients who cannot detect cancer lesion were CRT (for N3 or N2b), and neck dissection and close follow-up with NBI endoscopy (for N2a or N2b).

Figure 1 shows a representative case where the primary cancer was detected by NBI. This patient had a swollen lymph node (2.5 cm in size) on the left side of the upper jugular area (Level II) (Fig. 1). The specimen taken using a fine-needle aspiration method from the swollen lymph node revealed squamous cell carcinoma, which was confirmed later as metastatic. CT scan, MRI, laryngoscopy and standard gastrointestinal endoscopy could not detect any primary site. NBI detected easily a well-demarcated brownish area in the uvula to the right anterior palatine arch (Fig. 2B). In contrast, the conventional white-light image made it difficult to visualize the cancerous lesion (Fig. 2A). Magnifying the observation with NBI revealed easily an irregular microvascular pattern inside the lesion (Fig. 2D), but magnifying the observation with white light made it difficult to see this irregular microvascular pattern (Fig. 2C). We diagnosed cancer for this lesion. The biopsy specimen revealed squamous cell carcinoma, which was similar histologically to that of the metastatic lymph node. Treatment of this patient involved neck dissection and resection for primary disease, and we were able to avoid irradiation of the whole neck.

Figure 1. Computed tomographic scan shows lymph node metastasis at left upper jugular area.

DISCUSSION

We report for the first time that NBI endoscopy can detect possible primary cancer in patients with PUCLNM. Information about the primary site is very important for deciding on the appropriate treatment because the treatment strategy may differ for each primary site. Our data indicate that NBI can be helpful to the clinician when deciding on the treatment.

According to Greenberg (10), primary unknown carcinoma is defined when primary tumor cannot be detected by an autopsy. However, this definition cannot be applied in clinical decision-making. We defined a PUCLNM as one for which we could not detect any primary site by CT, MRI, laryngoscopy and gastrointestinal endoscopy (11). Although recent advance in technologies of CT, MRI and PET makes it possible to detect a small lesion precisely, the primary cancer is detected in only 2−9% of the patients with PUCLNM (1,2,12,13). Positron emission tomography (PET) or CT is also useful to detect occult cancer, but this primary site is too small to point out with PET. Random biopsy in the head and

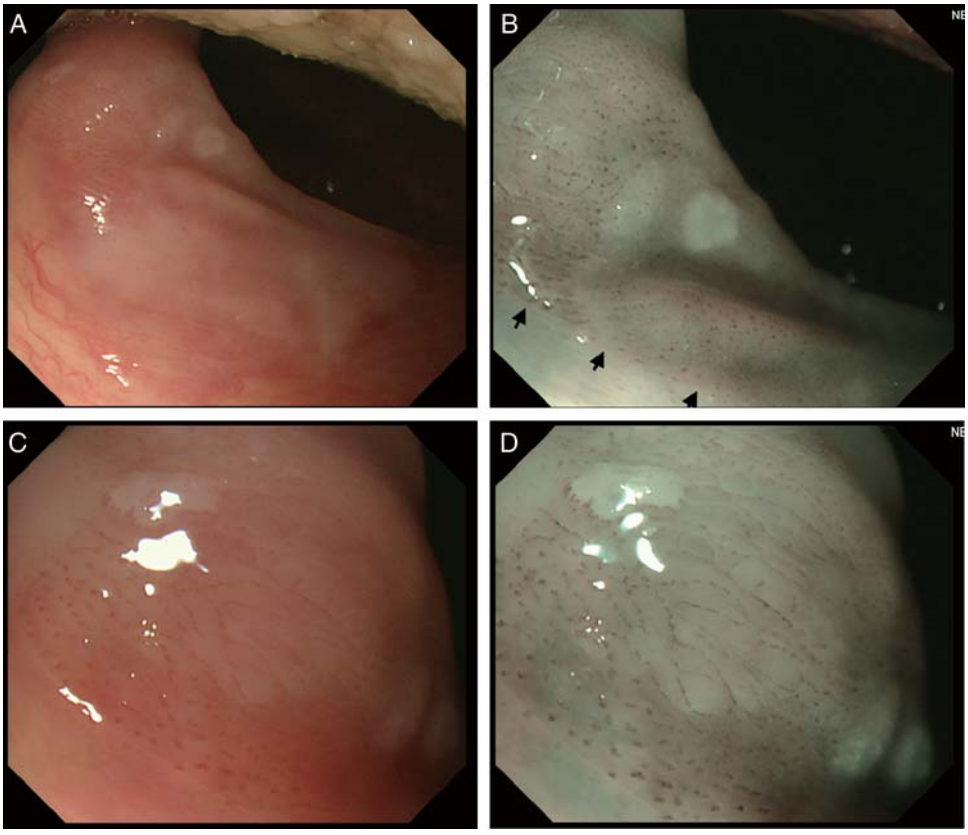

Figure 2. (A–D) Endoscopic findings. Conventional white-light image (A), narrow-band imaging (NBI) image (B), magnifying conventional white-light image (C) and magnifying the NBI images (D). NBI detected a well-demarcated brownish area in the uvula to right anterior palatine arch (B). In contrast, conventional white-light image was difficult to visualize the cancerous lesion (A). Magnifying the observation with NBI revealed an irregular microvascular pattern inside the lesion (D).

neck region may be useful for detecting possible primary cancer in patients with PUCLNM, but the detection rate is only around 10% (1,2). However, tonsillectomy is very useful to detect the primary cancer but tonsillectomy can detect only tonsil cancer. Because only 3 of 16 cases have a cancerous lesion on tonsil in this study, NBI endoscopy was better than tonsillectomy to detect occult tumor.

In the esophagus, Lugol chromoendoscopy is useful for detecting superficial squamous cell carcinoma. However, Lugol's solution cannot be applied in the head and neck region because of the risk of aspiration into the airway. NBI is now recognized as a useful and safe method for detecting superficial squamous cell carcinoma in the head and neck region because it uses no solution and improves the visibility. Muto et al. (8,9,16) reported that both a well-demarcated brownish area and an irregular microvascular pattern are typical characteristics of the superficial squamous cell carcinoma in the head and neck region. In this study, we evaluated the lesion according to these two endoscopic characteristics, and we were able to confirm 64% (16/25) of the lesions in the suspicious cancerous area as squamous cell carcinoma. This positive rate is better than that from a random biopsy (~10%). Finally, possible primary cancer could be detected in 35% (16/46) of the patients. These results indicate that NBI should be applied when surveying the primary site in patients with PUCLNM. Moreover, it is not impossible to detect cancerous lesion only using white-light endoscopy by trained endoscopist but NBI endoscopy is very easy for beginners to detect lesion.

Nine of 16 patients underwent surgery or endoscopic resection of the primary site and subsequent lymph node dissection. In such cases, post-operative whole-neck radiation is one treatment option (13–15). However, the indications for post-operative radiation therapy for PUCLNM are still controversial because these patients are at high risk for developing metachronous multiple cancers in the head and neck region (16). If they received radiation therapy as a post-operative radiation therapy, there is no radiotherapy treatment option for the later appearance of a metachronously developed second primary cancer in the head and neck region (14–16). The clinician must thus plan the post-operative radiation therapy carefully.

We cannot conclude with certainty whether the lesions detected by NBI were the true primary sites unless we identify their clonality. As a next step, we will compare the clonality of both primary sites and metastatic lymph nodes. In this study, at least, histological assessment showed the same histological features of the primary site and metastatic lymph

node. Clinically, histological accordance would be enough to consider whether the lesion is primary.

Although we could not evaluate the depth of invasion in all patients, we know that micro-invasive cancer can metastasize to the lymph node. The risk of lymph node metastasis of superficial squamous cell carcinoma is unknown, but collection of data from a large number of cases should help clarify this.

In conclusion, our data indicate that NBI has the potential to identify primary cancer in patients with PUCLNM. Identification of the primary site provides helpful information for deciding on the treatment strategy.

Conflict of interest statement

None declared.

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