possibility of selection bias. From the viewpoint of clinical practice, real-time detection and diagnosis are important. To avoid selection bias and to evaluate the actual diagnostic yield, we recorded the data during the procedure and completely separated the evaluation of white light imaging and narrow band imaging. We also conducted this study according to the Standards for Reporting of Diagnostic Accuracy checklist[29] to obtain high-quality data and to assess the generalizability and applicability of the results. Our data are therefore relevant to daily clinical practice.

Table A1. Rate of Superficial Cancer by Method of Detection in Back-to-Back Fashion

		Primary Examination WLI			Secondary Examination NBI			
Region	No. of Patients	No.	%	95% CI	No.	%	95% CI	*P*
Head and neck	13	1	8	0.2 to 36.0	10	77	46.2 to 95	< .001
Esophagus	105	58	55	45.2 to 65.0	100	95	89.2 to 98.4	< .001
			NBI			WLI		
Head and neck	15	15	100	78.2 to 100	5	33	11.8 to 61.6	< .001
Esophagus	107	104	97	92 to 99.4	85	79	70.5 to 86.6	< .001

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

Table A2. Size of Superficial Cancer by Method of Detection

	WLI Positive		NBI Positive		NBI and WLI Positive		Both Negative (false negative)	
Tumor Size (mm)	No.	%	No.	%	No.	%	No.	%
Head and neck region								
< 10	0	0	12	70	5	30	0	0
11-20	0	0	4	40	6	60	0	0
≥ 21	0	0	0	0	1	100	0	0
Total	0	0	16	57	12	43	0	0
Esophagus								
< 10	0	0	14	39	22	58	0	0
11-20	0	0	12	30	28	70	0	0
≥ 21	1	0.7	22	16	113	83	0	0
Total	1	0.5	48	23	163	77	0	0

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

Table A3. Median Procedure Time

	Primary WLI (seconds)		Primary NBI (seconds)		
Region	Median	Range	Median	Range	*P*
Head and neck	120	34-275	162	30-525	< .001
Esophagus	95	30-360	135	30-616	< .001
	Secondary WLI		Secondary NBI		
Head and neck	90	10-300	135	30-540	< .001
Esophagus	80	19-776	45	18-700	< .005

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

Japanese Journal of Clinical Oncology Advance Access published February 4, 2010

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010
doi:10.1093/jjco/hyp197

Original Article

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

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Received October 29, 2009; accepted December 24, 2009

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

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.

lesion was intraepithelial cancer and the other had invaded to the subepithelial layer.

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

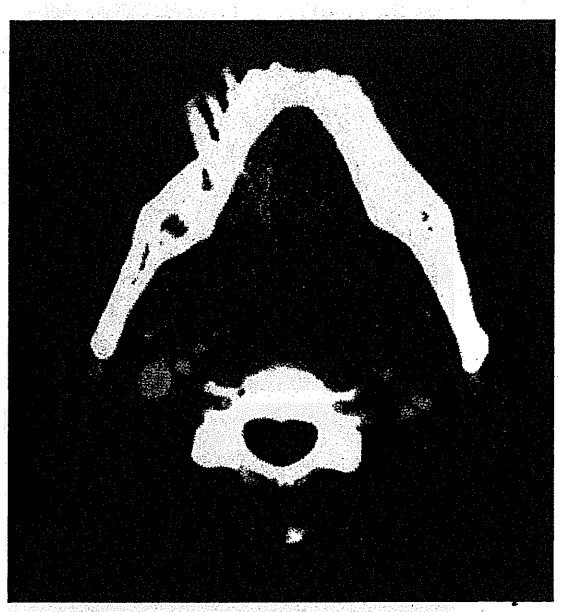

Figure 1. Computed tomographic scan shows lymph node metastasis at left upper jugular area.

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.

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

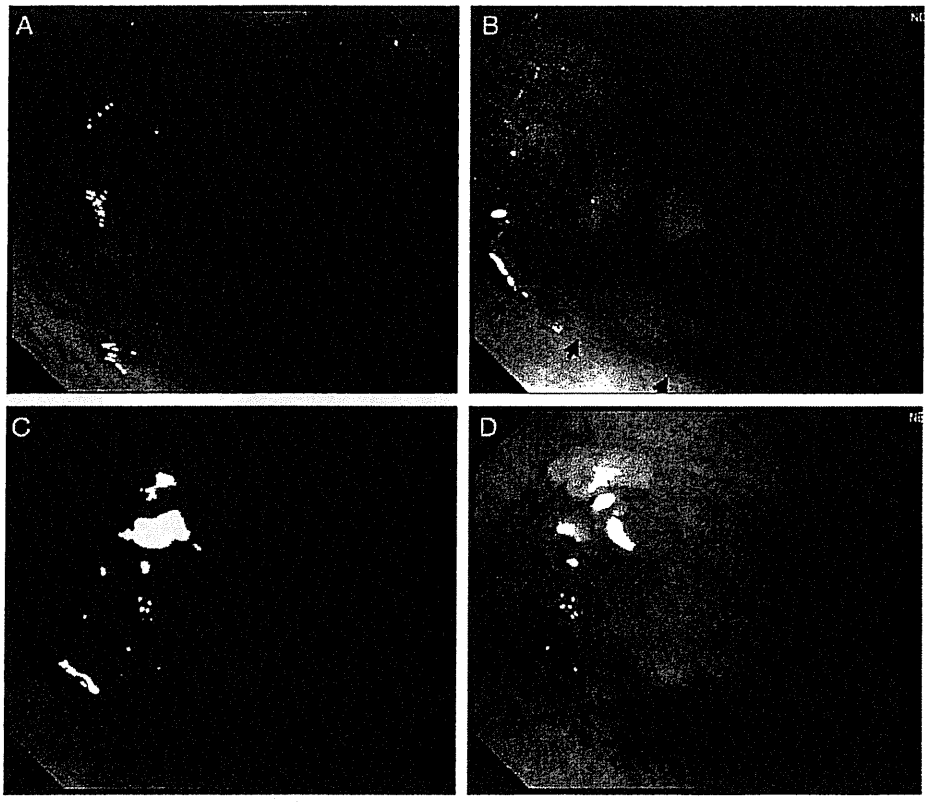

Figure 2. (A–D) Endoscopic findings. Conventional white-light image (A), narrow-band imaging (NBI) image (B), magnifying conventional white-light image (C) and magnifying the NBI images (D). NBI detected a well-demarcated brownish area in the uvula to right anterior palatine arch (B). In contrast, conventional 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).

also useful to detect occult cancer, but this primary site is too small to point out with PET. Random biopsy in the head and 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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Magnifying narrow-band imaging versus magnifying white-light imaging for the differential diagnosis of gastric small depressive lesions: a prospective study

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Background: The accurate diagnosis of gastric small depressive lesions (SDLs), including gastritis and cancerous lesions, is difficult with conventional endoscopy when using white-light imaging (WLI). Narrow-band imaging (NBI) is expected to make a more accurate diagnosis of gastric SDLs than WLI because it provides better visualization of the mucosal surface and microvascular architecture when combined with magnifying endoscopy.

Objective: To compare the real-time diagnostic accuracy of magnifying WLI and magnifying NBI for gastric SDLs.

Design: Prospective study.

Setting: National Cancer Center Hospital East, Kashiwa, Japan.

Patients: Fifty-seven lesions in 53 consecutive patients were analyzed: 30 cancers and 27 benign lesions.

Interventions: If previously undiagnosed gastric SDLs smaller than 10 mm were identified during an endoscopic examination, magnifying observation with both WLI and NBI was performed for each SDL. Endoscopic diagnosis of SDLs was made by each method on site.

Main Outcome Measurements: The diagnostic accuracy and the time required for diagnosis.

Results: The diagnostic accuracy was significantly higher for NBI than for WLI (79% vs 44%; $P = .0001$), as was its sensitivity (70% vs 33%; $P = .0005$). The diagnostic specificity of NBI (89%) was higher than that of WLI (67%), but the difference was not statistically significant. The time required for the diagnosis was equivalent with both methods.

Limitations: Single-center study, small sample size.

Conclusions: Adding NBI to the WLI examination is essential for making an accurate diagnosis of gastric SDLs compared with magnifying WLI alone. (UMIN Clinical Trials Registry identification number C000000421) (Gastrointest Endosc 2010;71:477-84.)

Gastric cancer is the fourth most common cancer and the second most common cause of cancer death worldwide.[1] Although the early detection of gastric cancer is necessary to improve patient survival, the identification of small gastric cancers is difficult.

The high-resolution endoscopic system has increased the probability of finding small, depressed lesions (SDLs) (≤10 mm) in the stomach. Because gastric SDLs include gastritis and cancer, their differential diagnoses are clinically important. However, the accurate diagnosis of SDLs

Abbreviations: DL, demarcation line; IMVP, irregular microvascular pattern; magnifying WLI, magnifying endoscopic observations combined with white-light imaging; NBI, narrow-band imaging; SDL, small depressive lesion; WLI, white-light imaging.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

0016-5107/$36.00
doi:10.1016/j.gie.2009.10.036

Received May 30, 2009. Accepted October 14, 2009.

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by conventional endoscopy is difficult, and the diagnosis of SDLs is usually confirmed by the histopathological examination of biopsy specimens, which increases the number of unnecessary biopsies. Real-time accurate endoscopic diagnosis should reduce the number of unnecessary biopsies. The most important clinical purpose is to detect a gastric cancer accurately at the SDL stage because such lesions are good candidates for minimally invasive endoscopic treatment, which can improve the patient's chance of survival markedly.

Magnifying endoscopy can visualize the microstructures and microvessels of the lesions. Endoscopic differential diagnosis based on the changes in these structures is useful for accurate diagnosis in the GI tract.[2-12] Yao et al[13] reported the following characteristic magnifying endoscopic findings of early gastric cancer: (1) there is a definite demarcation line (DL) between the cancerous lesion and normal areas and (2) an irregular microvascular pattern (IMVP) is present in the cancerous lesions. They also reported the usefulness of magnifying endoscopic observations combined with white-light imaging (WLI; magnifying WLI) and the diagnostic reliability of DL and IMVP findings in a prospective study.[14] However, it is not easy to accurately visualize and evaluate the magnifying endoscopic findings such as DL and IMVP because of the low contrast of WLI images. A novel technique and an excellent diagnostic capacity for magnifying endoscopy are required for an accurate diagnosis when using magnifying WLI.

In contrast, magnifying endoscopic observations combined with narrow-band imaging (magnifying NBI) provide a higher contrast image than does magnifying WLI.[15,16] Magnifying NBI is expected to improve the diagnostic accuracy for gastric SDLs. However, there has been no report of the diagnostic accuracy of magnifying NBI.

This prospective study was conducted to demonstrate the effectiveness of magnifying NBI in the differential diagnosis of gastric SDLs. For this purpose, the real-time diagnostic accuracy of magnifying NBI and conventional magnifying WLI was compared.

METHODS

This trial was conducted in accordance with the Standards for Reporting of Diagnostic Accuracy initiative. The protocol was approved by the Institutional Review Board of the Japanese National Cancer Center. Written informed consent was obtained from all participants who underwent a routine endoscopic examination with the NBI system. The UMIN Clinical Trials Registry identification number for this study is C000000421.

Eligibility criteria

The criteria for eligibility were gastric SDLs (≤10 mm) without ulceration that were detected during a routine endoscopic examination, age older than 20 years, no other serious complications, and the use of no medications that might interfere with obtaining a biopsy specimen.

Capsule Summary

What is already known on this topic

- Diagnosis of gastric small depressive lesions (SDLs), including gastritis and cancerous lesions, is difficult with conventional endoscopy when using white-light imaging (WLI).

What this study adds to our knowledge

- In a prospective study of 57 gastric SDLs, diagnostic accuracy and sensitivity were significantly higher for narrow-band imaging than for WLI.

Study design and examination

The primary endpoint was diagnostic accuracy, calculated from diagnostic sensitivity and specificity, and the secondary endpoint was the time required to establish a diagnosis. When we detected gastric SDLs during routine endoscopic examinations in patients from whom written informed consent was obtained, we registered those lesions.

In this study, we used high-resolution magnifying endoscopy systems: (1) a magnifying endoscope (GIF-Q240Z, GIF-H260Z; Olympus Medical Systems, Tokyo, Japan), (2) a video system center (EVIS LUCELA CV-260SL; Olympus Medical Systems), (3) a high-intensity luminous source (EVIS LUCELA CLV-260NBI; Olympus Medical Systems), and (4) a high-resolution liquid crystal monitor (OEV191H; Olympus Medical Systems).

SDLs were first examined by magnifying WLI, and their endoscopic diagnoses were determined according to the predetermined criteria and recorded immediately. After the first examination, we changed the light from the white light to the narrow-band light with just a single push of a button on the endoscope without changing the endoscope. An examination with magnifying NBI followed thereafter, and the diagnoses and records were processed similarly. Based on the diagnostic criteria, the assistant doctor recorded the presence or absence of DL or IMVP during the procedure in real-time and on-site to ensure the objectivity of the examination. We then applied these findings to the diagnostic criteria and provided endoscopic diagnoses. In each modality, the time from the start of the observation to the time when an endoscopic diagnosis was made was timed with a stopwatch. After all the records were complete, proper biopsies were performed on the SDLs (Fig. 1).

In this design, each imaging method (WLI and NBI) was examined by the same endoscope (GIF-Q240Z or GIF-H260Z; Olympus Medical Systems). This design allowed

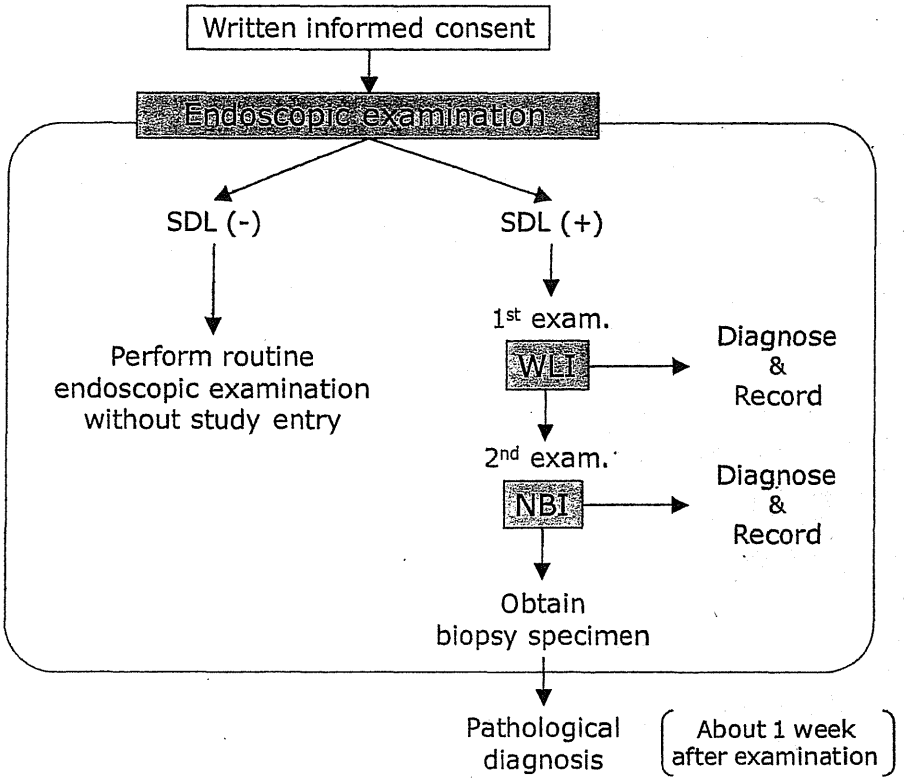

Figure 1. Protocol of the examinations in this study.

us to counteract any bias arising from differences in image quality obtained by using different types of endoscopes.

Five endoscopists participated in this study, and each endoscopist interpreted each lesion individually without consultation with the others. The endoscopists who participated in this study were required to have a level of knowledge and skills commensurate with those of a specialist accredited by the Japan Gastroenterological Endoscopy Society to ensure the quality of the examinations. They were shown magnified endoscopic images and videos for reference and considered the diagnostic criteria together to minimize variation between the endoscopists.

The criterion standard for the diagnosis was the results of the histopathological examination of the biopsy specimens, which were revealed about 1 week after the examination.

Diagnostic criteria for endoscopic findings

The endoscopic diagnostic criteria followed the classification established by Yao et al[13]: (1) a DL between the depressed lesion and the surrounding normal area and (2) an IMVP inside the lesion (Fig. 2). Nakayoshi et al[17] classified the microvessels found in gastric cancers into 2 patterns according to their histological type. However, in our preliminary observation, we found that irregular microvessels are a common finding, regardless of the histological type of the lesion. Therefore, we did not distinguish the microvascular patterns and used IMVP simply as one of the endoscopic criteria for gastric cancer in this study. Although DL and IMVP were reported originally as key findings in magnifying WLI,[13] we used these findings in both WLI and NBI in this study. The visibility of the DL and IMVP of the SDLs was classified into 3 categories: visible, illegible, or invisible. In both modalities, the SDLs were diagnosed according to the combination of the visibility of the DL and IMVP, as shown in Table 1 and as follows. (1) If both DL and IMVP were visible, the diagnosis was cancer. (2) If either DL or IMVP was illegible, the diagnosis was inconclusive. (3) If either or both DL and IMVP were invisible, the diagnosis was noncancer.

Criteria of the pathological diagnosis

The pathological diagnostic criteria were based on the revised Vienna classification[18]: C4 (mucosal high-grade neoplasia) or C5 (submucosal invasion by neoplasia) was diagnosed as carcinoma and C1 (negative for neoplasia), C2 (indefinite for neoplasia), and C3 (mucosal low-grade neoplasia) were diagnosed as noncarcinoma. The biopsy specimens were evaluated with hematoxylin–eosin staining.

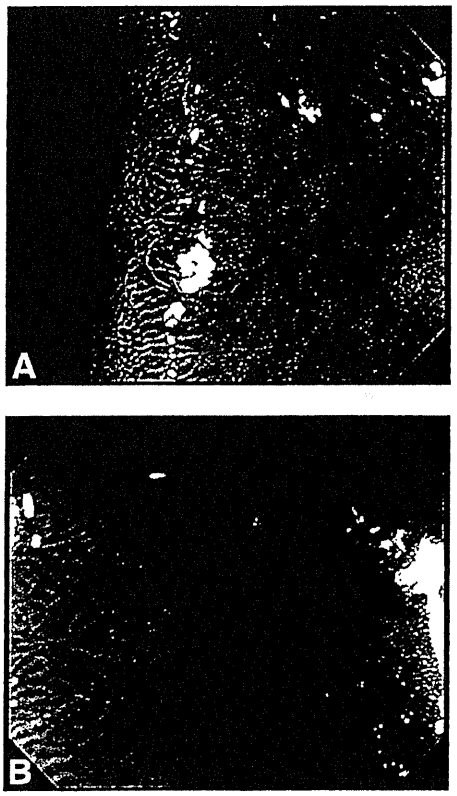

Figure 2. A typical finding of the DL and IMVP **(A, B)**. Magnifying NBI can clearly visualize the DL between the lesion and the surrounding normal mucosa (*arrows*) and IMVP within the lesion.

TABLE 1. Diagnostic criteria for endoscopic findings

Demarcation line	Irregular microvascular pattern		
	Visible	Invisible	Illegible
Visible	Cancer	Noncancer	Inconclusive
Invisible	Noncancer	Noncancer	Inconclusive
Illegible	Inconclusive	Inconclusive	Inconclusive

Statistical analysis

The estimated sample sizes required to achieve a power of the test of 80% and a 2-sided level of significance of 5% were 28 cancerous lesions and 69 noncancerous lesions.

The McNemar test was used for comparison of categorical variables, and the Wilcoxon signed-rank test was used for continuous variables.

All *P* values calculated in this analysis were 2 sided and were not adjusted for multiple testing. *P* values <.05 were considered significant. All statistical analyses were performed by using the Dr. SPSS II statistical software package (SPSS Japan Inc, Tokyo, Japan).

RESULTS

Characteristics of patients and lesions

A total of 60 lesions in 56 patients were examined in this study between March 2006 and February 2008. At the end of enrollment, 3 patients were excluded for the following reasons: no biopsy specimen was obtained for 1 lesion, pre-examination bleeding occurred in 1 lesion, and 1 lesion was larger than 10 mm. Ultimately, 53 patients and 57 lesions were analyzed: 30 cancerous lesions in 30 patients and 27 noncancerous lesions in 24 patients (Fig. 3).

The number of noncancerous lesions did not reach the statistically required number of 69, but enrollment was discontinued because the 2-year enrollment period had ended.

Endoscopic findings of all lesions

The results of endoscopic evaluation of the visibility of the DL and IMVP of all SDLs are shown in Table 2. In cancerous lesions, the numbers of lesions with visible DL or visible IMVP were significantly higher in magnifying NBI than in magnifying WLI ($P = .005$ and $P = .002$, respectively). In contrast, there is no statistical difference in visibility of DL and IMVP between magnifying WLI and magnifying NBI in the noncancerous lesions ($P = .25$ and $P = .07$, respectively).

In the magnifying NBI, the numbers of lesions with visible DL or visible IMVP were significantly higher in cancerous lesions than in noncancerous lesions (83% [25/30] vs 44% [12/27], $P = .003$ and 73% [22/30] vs 7% [2/27], $P < .0001$, respectively). DL could be seen in about half of the noncancerous lesions in both magnifying WLI and magnifying NBI (41% [11/27] and 44% [12/27], respectively).

Diagnostic accuracy (primary endpoint), sensitivity, and specificity

The diagnostic accuracy of magnifying WLI was 44%; a correct diagnosis was obtained for 25 (44%) of 57 lesions, an incorrect diagnosis for 14 (25%) of 57 lesions, and an inconclusive diagnosis for 18 (31%) of 57 lesions. In contrast, the diagnostic accuracy of magnifying NBI was 79%, and the corresponding diagnoses were 45 (79%) of 57 lesions, 8 (14%) of 57 lesions, and 4 (7%) of 57 lesions, respectively. The diagnostic accuracy was significantly better for magnifying NBI than for magnifying WLI ($P = .0001$; Fig. 4). Significantly more cases were diagnosed as inconclusive by magnifying WLI than by magnifying NBI (31% [18/57] vs 7% [4/57], respectively; $P = .001$).

The diagnostic sensitivity of magnifying WLI for small gastric cancer was significantly higher than that of magnifying WLI (23% vs 70%, respectively; $P = .0005$; Fig. 5). In contrast, although the diagnostic specificity of magnifying NBI was higher than that of magnifying WLI

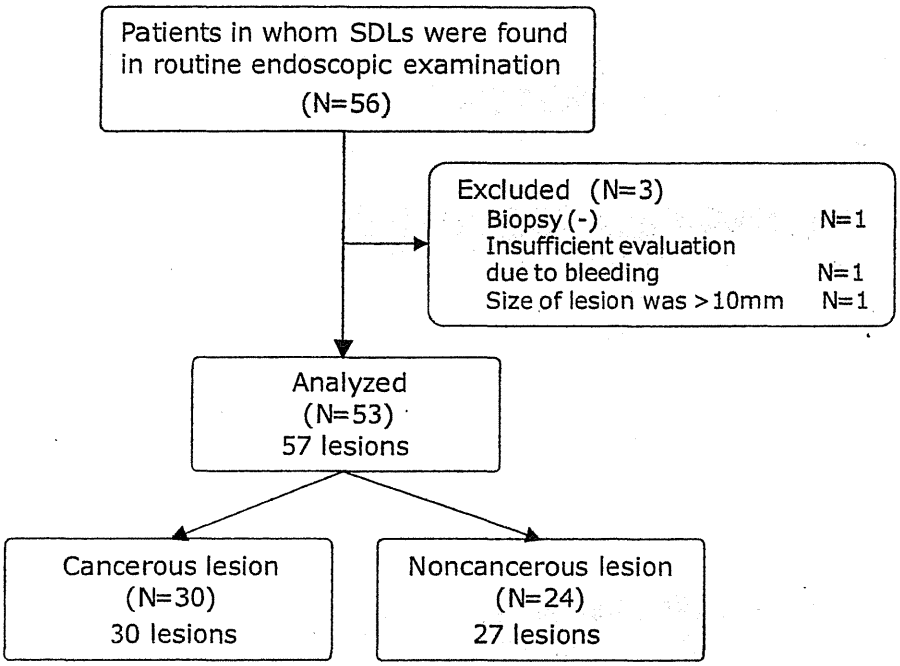

Figure 3. Study flow chart. N = number of patients.

TABLE 2. Endoscopic findings of all lesions

	Cancerous lesions (n = 30)			Noncancerous lesions (n = 27)			
	WLI	NBI	*P* value		WLI	NBI	*P* value
DL				DL			
Visible	11 (37)	25 (83)	.005*	Visible	11 (41)	12 (44)	.25†
Illegible	6 (20)	1 (4)		Illegible	4 (15)	0 (0)	
Invisible	13 (43)	4 (13)		Invisible	12 (44)	15 (56)	
IMVP				IMVP			
Visible	10 (33)	22 (73)	.002*	Visible	1 (4)	2 (7)	.07†
Illegible	8 (27)	3 (10)		Illegible	6 (22)	1 (4)	
Invisible	12 (40)	5 (17)		Invisible	20 (74)	24 (89)	

WLI, White-light imaging; *NBI*, narrow-band imaging; *DL*, demarcation line; *IMVP*, irregular microvascular pattern.
The numbers of lesions are shown. Values in parentheses are percentages of all the lesions.
*A *P* value was calculated as a comparison of visible and illegible + invisible.
†A *P* value was calculated as a comparison of invisible and illegible + visible.

(67% vs 89%, respectively), the difference was not significant ($P = .08$; Fig. 6).

Time required for diagnosis (secondary endpoint)

The median time required for diagnosis did not differ significantly between WLI and NBI ($P = .29$. The median time required for diagnosis, the secondary endpoint, was 95 seconds (range 10–265 seconds) for magnifying WLI and 99 seconds (range 15–285 seconds) for magnifying NBI (Fig. 7).

Adverse events

We did not observe any adverse events in this study during the endoscopic examinations or biopsy procedures. The endoscopic examinations were not discontinued in any patients.

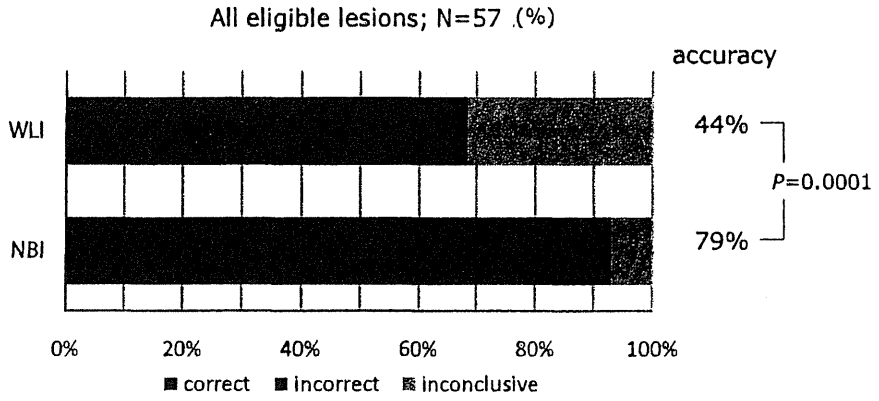

Figure 4. Diagnostic accuracy of magnifying WLI and magnifying NBI (primary endpoint). The numbers of lesions are shown. Values in parentheses are percentages of all the lesions.

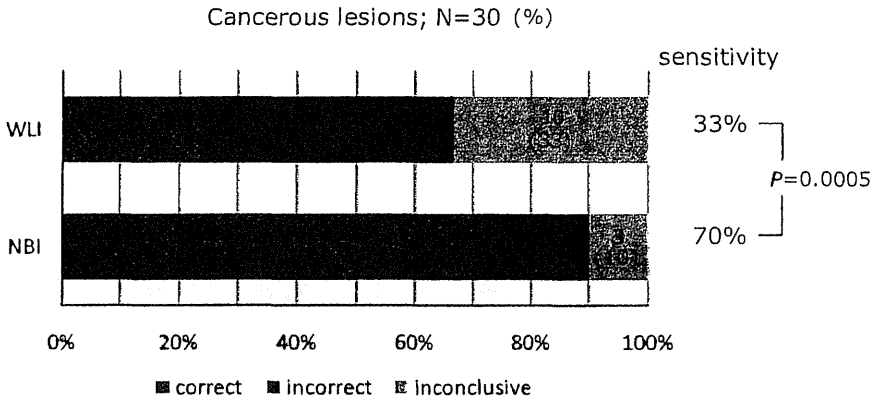

Figure 5. Diagnostic sensitivity of magnifying WLI and magnifying NBI. The numbers of lesions are shown. Values in parentheses are percentages of all the lesions.

DISCUSSION

The real-time diagnostic accuracy of magnifying NBI in the diagnosis of gastric cancer has not been reported. Most reports of endoscopic findings when using magnifying examination were made by reviewing only the best images selected by the investigators. Here, we performed the first prospective clinical investigation to compare the diagnostic accuracy of magnifying NBI and magnifying WLI used for the differential diagnosis of gastric SDLs. In this study, we demonstrated clearly that the visibility of DL and IMVP was superior in magnifying NBI compared with magnifying WLI in the differential diagnosis of gastric SDLs and that the DL and IMVP are valuable findings in the differential diagnosis of gastric SDLs. The feasibility of the NBI combination was verified because the observation time required to make a diagnosis was equivalent to that of magnifying WLI, and there was no interruption of the examination procedure in any patient. Taken together, our data from this study led us to conclude that NBI, rather than WLI, should be combined with magnifying endoscopy for the observation of gastric SDLs.

One of the most characteristic features of magnifying NBI is its ability to visualize the mucosal microarchitecture and microvessels in clear contrast to the background mucosa,[15,16] and this may result in a better visualization capacity than that of magnifying WLI. Supporting this possibility, in this study, magnifying NBI showed DL and IMVP in 83% and 73% of the cancerous lesion, respectively, whereas magnifying WLI showed only 37% and 33% of these findings ($P = .005$ and $P = .002$, respectively). These results also indicate that DL and IMVP are important endoscopic findings for the diagnosis of cancerous lesions in gastric SDLs.

In this study, although magnifying NBI showed significant superiority of diagnostic accuracy and sensitivity compared with magnifying WLI, we could not find a significant difference in the specificity. The main reason for the lack of a significant difference in diagnostic specificity may be the association with an insufficient number of

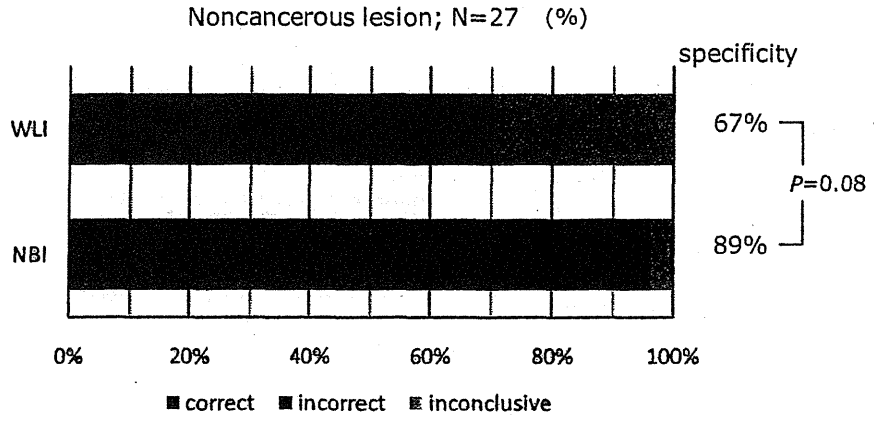

Figure 6. Diagnostic specificity of magnifying WLI and magnifying NBI. The numbers of lesions are shown. Values in parentheses are percentages of all the lesions.

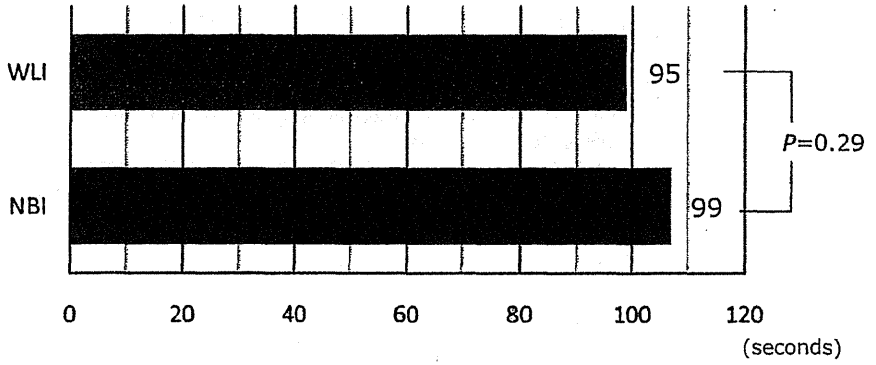

Figure 7. Time required for a diagnosis by magnifying WLI and magnifying NBI (secondary endpoint).

noncancerous lesions. Although the number of noncancerous lesions did not reach the statistically required number, we did not extend the enrollment period in this study because, judging from the rate of case collection, we considered that it would be difficult to achieve the required number of noncancerous lesions. The main reason was that we empirically excluded apparent benign lesions such as erosions and shallow ulcers from this study because this study targeted only SDLs that were suspected of being cancerous.

In this study, although the rate of misdiagnosis was lower with magnifying NBI than with magnifying WLI (14% [8/57] vs 25% [14/57]; $P = .15$), a considerable number of cases were misdiagnosed despite the clear visualization of magnifying NBI. Yao et al[14] reported that 25.3% of gastritis lesions were DL positive even by magnifying WLI. In this study, 41% and 42% of the noncancerous lesions were DL positive by magnifying WLI and magnifying NBI, respectively. Furthermore, in the stomach, the microvascular pattern shows many variations attributed to inflammatory changes. Therefore, it is sometimes difficult to judge the pattern of microvessels inside SDLs as cancerous IMVP or as an irregularity because of inflammatory changes. In this study, 17% of the cancerous lesions were negative for IMVP and 7% of the noncancerous lesions were positive for IMVP. This seems to be the main reason for misdiagnosis and thus may result in a limitation of DL- and IMVP-based diagnoses for gastric SDLs.

In this study, we performed magnifying WLI first and then magnifying NBI to compare their diagnostic accuracy. We chose this procedural order because we considered it unlikely that magnifying NBI would be conducted first followed by magnifying WLI in actual clinical practice. The possibility cannot be excluded that the results of the first examination influence those of the second examination when the comparative examinations are made in a fixed order. Therefore, the operators should be changed at each examination or each case should be randomized to either magnifying WLI or magnifying NBI. However, neither of these designs was adopted here because the former design seemed ethically equivocal for a real examination, and using the latter would make it technically difficult to identify and observe the target lesion by magnifying NBI alone. At least, this study was not a randomized comparison of

magnifying WLI and magnifying NBI for gastric SDLs. All lesions were examined with WLI followed by NBI sequentially, and then this study provided a comparison of the diagnostic yield of WLI and WLI followed by NBI. From this perspective, we could conclude that adding NBI to the WLI examination markedly improved the diagnostic accuracy of gastric SDLs compared with magnifying WLI alone.

This study may have other limitations in that the two modalities were compared by using magnifying endoscopy. The current global standard is to use nonmagnifying WLI. Therefore, as the next step, we should investigate whether magnifying NBI is superior to the conventional nonmagnifying WLI. We are now conducting a multicenter, randomized, controlled trial to compare magnifying NBI with nonmagnifying WLI (UMIN Clinical Trials Registry ID C000001072).

In summary, we demonstrated that adding NBI to the WLI examination is essential for making an accurate diagnosis of gastric SDLs compared with magnifying WLI alone and demonstrated the high reliability of DL and IMVP as diagnostic criteria for gastric SDLs. The excellent diagnostic capacity of magnifying NBI should allow the diagnosis of most SDLs without the need for a biopsy, which should decrease the number of unnecessary biopsy specimens. In addition, magnifying NBI should enhance the early detection of gastric cancer, which should facilitate endoscopic treatments such as EMR and endoscopic submucosal dissection. Magnifying NBI will also benefit the patient because its examination time is no longer than that of magnifying WLI despite its excellent performance.

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Esophagus (2009) 6:249–252
DOI 10.1007/s10388-009-0204-1

CASE REPORT

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Multiple early-stage malignant melanoma of the esophagus with long follow-up period after endoscopic treatment: report of a case

Received: November 13, 2008 / Accepted: August 6, 2009

Abstract Primary malignant melanoma of the esophagus (PMME) is a rare disease. Most patients are diagnosed at an advanced stage and few at an early stage. We report a patient with multiple early-stage PMME (tumor invasion was limited to the mucosa, and no lymph node metastasis was detected). Despite initial endoscopic treatment followed by systemic chemotherapy, frequent multiple metachronous lesions occurred. These lesions were all flat type, and disease control of the primary site was achieved only by repeated endoscopic treatment. Liver metastasis developed 7 years after the first diagnosis of this disease; however, the patient has been doing well with stable disease for 1 year after single transarterial chemoembolization.

Key words Primary malignant melanoma of the esophagus · Early stage · Endoscopic mucosal resection

Introduction

Primary malignant melanoma of the esophagus (PMME) accounts for 0.1%–0.2% of all malignant disease of the esophagus. Ninety-five percent of all melanomas are found in the derma, and only 0.5% are localized in the esophagus [1]. The prognosis of PMME is unfavorable because most patients are in the advanced stage at diagnosis and rapidly develop lymph node and distant metastases. Six cases of early-stage PMME have been reported in five papers [2–6]. Only one of these cases was treated curatively by endoscopic mucosal resection (EMR) [3]. We now report on a rare case of multiple early-stage PMME, which has been controlled for 8 years by the combination of systemic chemotherapy and repeated endoscopic treatment.

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Case report

A 75-year-old, previously healthy man underwent an esophagogastroduodenoscopy (EGD) for screening. Three black-pigmented flat lesions were detected in the middle and lower thoracic esophagus (Fig. 1), and biopsy specimens revealed features of malignant melanoma. The patient refused esophagectomy, and EMR was tried in August 2001. The resected specimen revealed that the tumor had invaded the lamina propria (Fig. 2) with no lymphatic or venous invasion and that the horizontal margin was positive. The patient again refused esophagectomy and was followed up closely in the outpatient clinic.

Five months after the first EMR, a recurrence was suspected near the EMR scar. The patient was referred to our hospital. As an alternative treatment to the esophagectomy, six courses of systemic chemotherapy comprising dacarbazine (100 mg/body on day 1, 200 mg/body on days 2–5), nimustine hydrochloride (100 mg/body on day 1), and vincristine (1 mg/body on day 1) were scheduled every 4 weeks. However, he was forced to discontinue the treatment after four courses of chemotherapy because of severe thrombocytopenia. He then underwent an EGD every 2 or 3 months, and small black-pigmented spots resembling lentigo were detected frequently (Fig. 3). A biopsy specimen revealed the typical histological pattern of melanoma, suggesting metachronous multiple lesions. Because no lymph nodes were involved and no distant metastasis developed, endoscopic treatment including EMR (six times for nine lesions) and tumor ablation using argon plasma coagulation (three times for seven lesions) or bipolar coagulation probe (four times for six lesions) were performed until June 2009. Pathological diagnosis of all EMR specimens was in situ or microinvasive PMME with no lymphatic or venous invasion. Tumor cells were positive for melan A and HMB45 immunohistochemically. A typical case of microinvasive PMME is shown in Fig. 4A,B. Three specimens of nine resected lesions by EMR showed clearly that the black-pigmented area was only part of the whole tumor, and the horizontal margin was positive. A typical

horizontal margin-positive case of PMME is shown in Fig. 5.

Seven years after the first diagnosis of PMME, multiple liver tumors (in S4, S6, and S8) were detected by screening abdominal computed tomography (CT) in December 2007 (Fig. 6A). To make a definite diagnosis, a liver needle biopsy was performed in April 2008. The needle biopsy specimens revealed the same histological pattern of PMME (Fig. 6B) and were positive for melan A and HMB45. Then, liver metastasis was confirmed. The primary lesion was well controlled, and no other distant metastasis was observed. Because the patient was too old to reintroduce systemic chemotherapy and the dynamic CT image suggested a hypervascular liver tumor, transarterial chemoembolization (TACE) was performed. After a single TACE session, the metastatic liver lesion was stable, and he was in good condition as of June 2009. The clinical course of this case is summarized in Fig. 7.

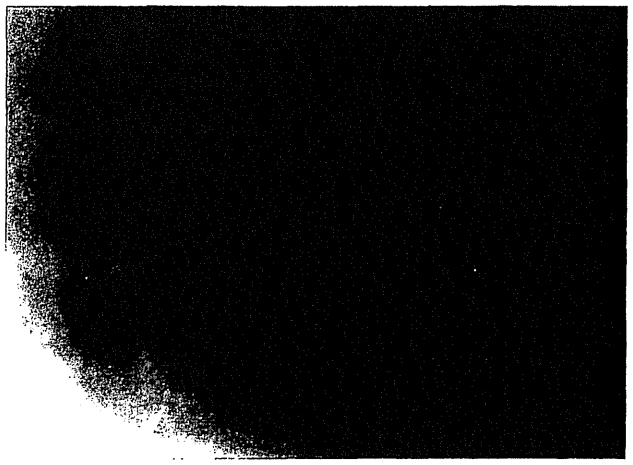


Fig. 1. Esophagogastroduodenoscopy showed a black pigmented flat lesion in the lower esophagus

Discussion

The following diagnostic histological criteria for PMME have been suggested by Allen and Spitz [7]: (1) a typical histological pattern of melanoma and the presence of melanin granules within the tumor cells, (2) origin in an area of junctional change within the squamous epithelium, and (3) junctional activity with melanotic cells in the adjacent epithelium. Melanoma cells were positive immunohistochemically for melan A, HMB45, and S-100 protein. These stains are useful for diagnosing amelanotic melano-

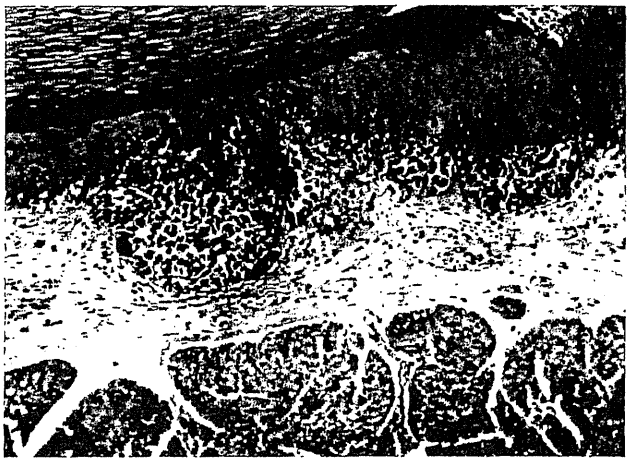


Fig. 2. A specimen of endoscopic mucosal resection revealed that the melanoma cells had invaded the lamina propria

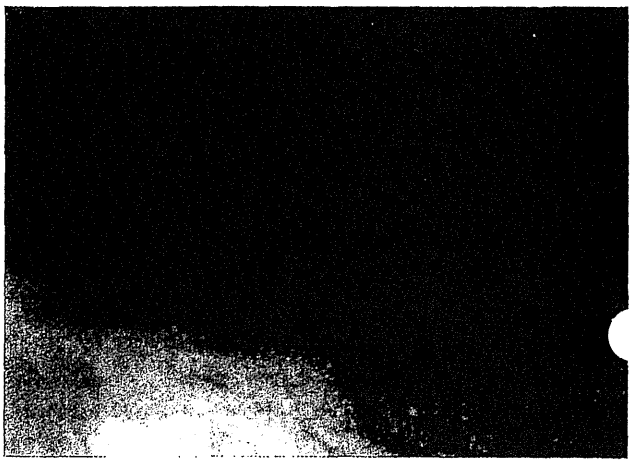
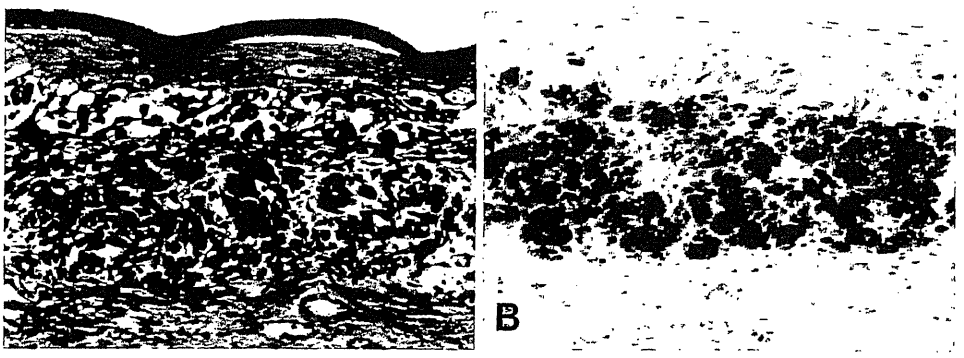


Fig. 3. Small black-pigmented spots resembling lentigo were detected frequently after the initial endoscopic treatment

Fig. 4. A specimen of endoscopic mucosal resection revealed the typical histology pattern of micro-invasive primary malignant melanoma of the esophagus (PMME) (**A**) and was positive for melan A (**B**), immunohistochemically. A chromogenic reaction was developed using alkaline phosphatase



mas in which the tumor cells show no evident melanin granules [8].

The prognosis of PMME is extremely poor because of its rapid metastatic spread via the lymphatic and blood vessels. Early death from widespread metastases is the usual clinical course. The average overall survival is only 10–13 months, and only one-third of all patients survive for longer than 1 year after diagnosis [1]. Surgical resection is considered the best method for treating PMME [9–12]. Smaller satellite nodules may present around the main tumor, and wider margins of resection are required for treating PMME than with other esophageal tumors. However, even if only the patients who have undergone radical esophageal resection are analyzed, the 5-year survival rate is less than 5% [13,14]. Therapeutic options such as radiotherapy, chemotherapy, and immunotherapy provide limited benefits, even when used in conjunction with surgery.

Endoscopically, PMME lesions appear as intraluminal, polypoid, and (usually, but not necessarily) pigmented, irregular masses, which might also be ulcerated. However, only one of six reported cases of early-stage PMME was the polypoid type [5], and the other five cases were all the flat type [2–4,6]. In contrast, no report is available about the flat-type submucosal invasive PMME. In our patients, many satellite lesions occurred in separate areas, and all lesions were the flat type. In almost 90% of patients, the lesions occur in the middle or distal one-third of the esophagus, usually as a solitary tumor, but multiple lesions have been reported in 12% of patients [13,15]. To our knowledge, ours is the first report of multiple early-stage PMME.

Especially in cases of the flat-type PMME, it is difficult to accurately define the tumor area macroscopically. Because the melanoma cells originated from the basal/deeper layers of the epithelium, it is likely that the size of the black-pigmented area depends on the number and density of the melanoma cells and does not reflect the true size of the tumor. Narrow-band imaging and/or magnifying endoscopy [16] was not useful for accurately determining the tumor area in our patient (Fig. 8A–C).

Endoscopic treatment for PMME should be considered for diagnostic purposes [17] and for treatment purposes

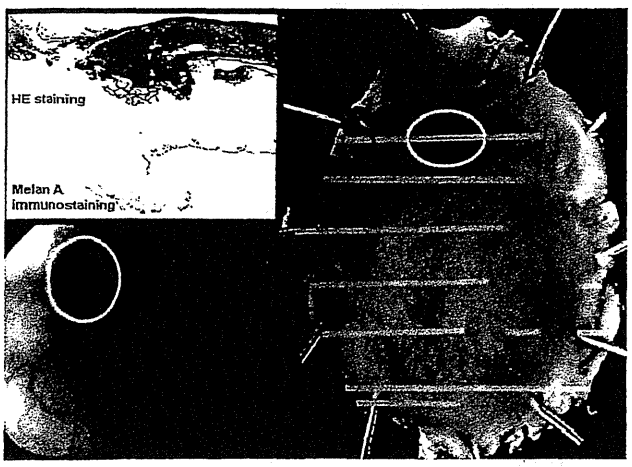


Fig. 5. A specimen of endoscopic mucosal resection showed clearly that the black-pigmented area is only part of the whole tumor, and the horizontal margin was positive. *Yellow lines* indicate the histological distribution of microinvasive PMME. *HE*, hematoxylin and eosin staining

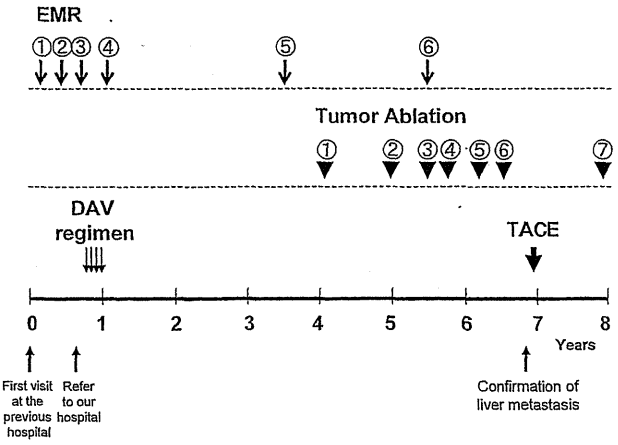


Fig. 7. Clinical course of this case. Local control of multiple early-stage PMME was achieved mainly by endoscopic treatment [six episodes of endoscopic mucosal resection (*EMR*) for 9 lesions and seven episodes of tumor ablation therapy with argon plasma coagulation or bipolar coagulation probe for 13 lesions]. *TACE*, transarterial chemoembolization; *DAV*, dacarbazine, nimustine hydrochloride, and vincristine

Fig. 6. **A** Seven years after the first diagnosis, multiple liver tumors were detected by screening abdominal computed tomography (*arrowheads* in S6). **B** A needle biopsy specimen from the liver tumor revealed the typical histological pattern of malignant melanoma

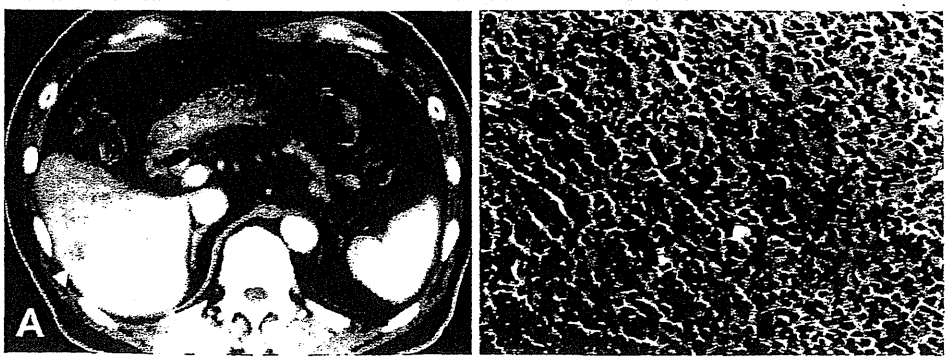


Fig. 8. Narrow-band imaging (**A**), magnifying endoscopy (**B**), and magnifying endoscopy with narrow-band imaging (**C**) were not useful for determining the tumor area accurately

only in limited cases [3,18–20]. Early-stage PMME can be removed technically by endoscopic treatment; however, indications for local therapy for this disease are still controversial because of the inaccurate diagnosis of the tumor area and uncertain tumor behavior. Further accumulation of cases of this rare disease is required.

Acknowledgments We greatly thank Drs. Akihiko Yoshizawa and Takaki Sakurai (Laboratory of Diagnostic Pathology, Kyoto University Hospital) for the pathological diagnosis and fruitful discussion. We also thank Drs. Toshihiro Kusaka, Hisato Kawakami (Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University), and Koushi Kinoshita (Min-I-Ren Chuoh Hospital, Kyoto) for patient management and endoscopic treatment.

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Jpn J Clin Oncol 2009;39(10)686–689
doi:10.1093/jjco/hyp078

Clinical Trial Note

A Phase II Trial of Combined Treatment of Endoscopic Mucosal Resection and Chemoradiotherapy for Clinical Stage I Esophageal Carcinoma: Japan Clinical Oncology Group Study JCOG0508

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Received December 23, 2008; accepted June 7, 2009; published online August 24, 2009

Standard treatment for clinical stage I esophageal cancer with submucosal invasion (T1b) has been surgical resection. We conducted a Phase II trial to evaluate the efficacy and the safety of combined treatment of endoscopic mucosal resection (EMR) and chemoradiotherapy for clinical stage I (T1b) esophageal cancer. Patients diagnosed as having clinical stage I (T1b) esophageal cancer which is considered to be resectable by EMR are eligible. When pathological examination of the EMR specimen confirms T1b tumor with negative or positive resection margin, the patient undergoes chemoradiotherapy. The study continues until 82 patients with T1b tumor with negative resection margin are enrolled from 20 institutions. The primary endpoint is 3-year overall survival (OS) in pT1b cases with negative resection margin. The secondary endpoints are 3-year OS and progression-free survival in all eligible cases, OS in pT1a-MM cases with margin-negative, complications of EMR and adverse events of chemoradiotherapy. The data from this trial will be expected to provide a non-surgical treatment option to the patients with clinical stage I (T1b) esophageal cancer.

Key words: superficial esophageal cancer – endoscopic mucosal resection – chemoradiotherapy

INTRODUCTION

According to the Japanese Classification of Esophageal Cancer by the Japan Esophageal Society, T1 esophageal tumors defined by the TNM system (6th edition) is further divided into T1a (mucosal) and T1b (submucosal) tumors by the Japanese Classification of Esophageal Cancer (1). Endoscopic mucosal resection (EMR) is usually indicated for T1a tumor, whereas the standard treatment for T1b tumors has been a surgical resection with adequate lymph node dissection in Japan because of the high incidence of lymph node metastasis (~40%) (2). However, surgical resection often deteriorates patient's general condition. Some patients with clinical T1b esophageal cancer are over-treated by surgery with a result of pathological T1a tumor, because the accuracy of diagnosis of T1b esophageal cancer is not high.

Recent advance in techniques of EMR including endoscopic submucosal dissection (ESD) enables us to remove the clinical T1b tumor and gives us accurate diagnosis of depth of invasion. However, the patients with T1b are at risk of lymph node metastasis (3) and therefore EMR alone cannot be considered as curative.

Chemoradiotherapy is one of the effective modalities for both early and advanced esophageal tumors. Since chemoradiotherapy is less toxic than surgical resection, the usefulness has been tested in several clinical trials (4,5). In Japan,

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a Phase II trial (JCOG9708) was conducted to evaluate the efficacy and the safety of concurrent chemoradiotherapy using 5-fluoraouracil (5-FU) plus cisplatin (CDDP) for T1 tumors (6). However, 22% of patients showed minor relapses that needed to be removed by endoscopic treatment. We have therefore conducted a pilot study of EMR followed by chemoradiotherapy and have reported promising results (7). Thus, the Japan Clinical Oncology Group initiated this multi-institutional Phase II trial (JCOG0508) to evaluate the efficacy and the safety of combined treatment of EMR and chemoradiotherapy for clinical stage I (cT1bN0) esophageal cancer.

The Protocol Review Committee of JCOG approved the protocol in October 2006 and the study was activated in December 2006.

JCOG0508 PROTOCOL

Purpose

The aim of this study is to evaluate the efficacy and the safety of combined treatment of EMR and chemoradiotherapy for clinical stage I (T1b) esophageal cancer.

Study Setting

The study is a multi-institutional (20 centers), single-arm Phase II trial.

Resources

This study is supported by the Grants-in-Aid for Cancer Research (17S-3, 17S-5, 20S-3, 20S-6) and Health and Labour Sciences Research Grant for Clinical Cancer Research (17-12) from the Ministry of Health, Labour and Welfare, Japan.

Endpoints

The primary endpoint is 3-year overall survival (OS) in pT1b cases with negative resection margin (comment 4). The secondary endpoints are 3-year OS and progression-free survival (PFS) in all eligible cases, OS in pT1a-MM (muscularis mucosa) cases with negative resection margin, complications of EMR and adverse events of chemoradiotherapy.

In this trial, resection margin is diagnosed from endoscopic findings immediately after mucosal resection for horizontal margin and from pathological findings for vertical margin. OS is defined as the time from registration to death from any cause, and it is censored at the last contact day for living patient. PFS is defined as the time from registration to either the first event of progression or death from any cause, and it is censored at the latest day when patient is alive without progression.

Inclusion Criteria

Patients are included in this trial if they meet all of the following criteria: (i) histologically proven squamous cell carcinoma of the esophagus by endoscopic biopsy, (ii) tumors located within the thoracic esophagus, (iii) depth of tumor invasion is diagnosed as T1b by endoscopy and endoscopic ultrasonography, (iv) the number of multiple intra-esophageal tumors is less than three, and the depths of invasion of them are diagnosed as cT1a-EP (carcinoma *in situ*) or cT1a-LPM (tumor invades lamina propria mucosa), (v) clinically node-negative (cN0) and no metastasis to other organs (cM0), (vi) size of main tumor is $\leq$5 cm, and circularity of esophageal lumen is less than three-fourths, (vii) no ulcerative lesion in the tumors, (viii) no intra-esophageal metastasis, (ix) no prior treatment of chemotherapy or radiation therapy against any other malignancies, except for previous curative EMR for pT1 esophageal cancer, (x) aged between 20 and 75 years old, (xi) performance status of 0 or 1, (xii) sufficient organ functions and (xiii) written informed consent.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria: (i) iodine allergy, (ii) enable to discontinue anticoagulant or antiplatelet medications, (iii) synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ*, (iv) pregnant or breast-feeding women, (v) severe mental disease, (vi) systemic administration of corticosteroids, (vii) HBs antigen positive, (viii) active bacterial or fungous infection, (ix) concurrent unstable angina or myocardial infarction within 3 months before registration, (x) unstable hypertension, (xi) diabetes mellitus, uncontrolled or controlled with insulin, or (xii) interstitial pneumonia, lung fibrosis or severe emphysema.

Registration

After confirming the inclusion/exclusion criteria by telephoning or faxing the JCOG Data Center, the patients are registered into this JCOG0508 trial.

Quality Control of EMR

Twenty institutions among the Gastrointestinal Oncology Study Group of the JCOG participate in this trial. All participating physicians have agreed to the technical details for EMR. For quality control of EMR technique and endoscopic diagnosis, we perform central review of the photographs in all patients at the semi-annual investigators meeting. Regarding an ESD procedure, we permit it only for expert physicians who have significant experiences in ESD and EMR, and they are registered by the primary investigator (M.M.). The minimum request for ESD permission is the experience of EMR $\geq$ 50 and ESD $\geq$ 10 for esophageal