Narrowband Imaging for Early Detection of Malignant Tumors and Radiation Effect After Treatment of Head and Neck Cancer

Yen-Chun Lin, MD; Akihito Watanabe, MD; Wen-Cheng Chen, MD; Kam-Fai Lee, MD; I-Lin Lee, MD; Wen-Hung Wang, MD

Objectives: To determine the value of narrowband imaging (NBI) screening for the early detection of head and neck squamous cell carcinoma (HNSCC) in patients who have received treatment and to assess the impact of radiotherapy on detection rates.

Design: Cross-sectional study.

Setting: Tertiary referral center.

Patients: From July 1, 2007, through February 28, 2008, a total of 206 patients with HNSCC underwent rhinolarynx videendoscopic screening performed using conventional white-light and NBI systems during their routine postoperative sessions.

Main Outcome Measure: The rate of detecting malignant tumors, depending on the anatomical site and stage of cancer and the history of radiotherapy after primary treatment.

Results: We identified 68 lesions by endoscopy in conventional white-light and/or NBI mode. Of these, 62 were histopathologically confirmed to be cancerous. The rates of detecting cancerous lesions by white-light and NBI modes were 100% and 97% for oral lesions, 69% and 100% for oropharyngeal lesions (P = .02), and 39% and 100% for hypopharyngeal lesions (P = .001), respectively. No difference was found between the 2 modes with regard to the detection of visible T1 to T4 tumors. However, NBI mode was significantly better than white-light mode for the detection of carcinoma in situ (P < .001).

Conclusion: We found that NBI-assisted endoscopy is highly useful for the detection of precancerous lesions in the oropharyngeal and hypopharyngeal mucosa and is not affected by a history of radiotherapy in patients with HNSCC.

copy can be identified on the basis of their neoangiogenic vasculature pattern by using blue light in NBI.

The NBI system was first used by Gono et al, and it enabled successful detection of superficial, precancerous mucosal lesions over the esophagus. Hence, this system was believed to be superior to conventional white-light endoscopy for the detection of superficial mucosal lesions. Yoshida et al reported that NBI improved the overall accuracy in detecting the extent of invasion of superficial esophageal carcinomas. Muto et al recognized the usefulness of the NBI system in a study in which they used a gastrointestinal endoscope to detect superficial lesions at sites on the head and neck mucosa. Watanabe et al were the first to use NBI-assisted rhinolaryngoscopy to detect cancerous lesions in the head and neck of patients with esophageal cancer. They documented that the NBI system might cause an improvement in the sensitivity of the detection of HNSCC in patients with esophageal cancer (an approximately 2-fold improvement over the conventional method). Furthermore, Watanabe et al claimed that NBI-assisted endoscopy significantly improves the diagnostic accuracy, sensitivity, and negative predictive value for HNSCC detection in patients with esophageal cancer. A literature search revealed that a few case series have documented the effectiveness of NBI in detecting early superficial mucosal precancerous lesions in the head and neck region, including the pharynx and the floor of the mouth. However, the usefulness of NBI in large-scale screening of patients with HNSCC after primary treatment has not been reported thus far, to our knowledge. Most of these patients would have received radiotherapy.

It is known that radiotherapy can lead to acute and late mucosal reactions and that radiation mucositis is a complex process that involves all the tissues and cellular elements of the mucosa. During follow-up examination in some cases, it is difficult to clinically distinguish reactive lesions that result from the effects of treatment, especially postradiation mucosal changes, from true recurrent lesions. It is unknown whether the radiation effect could obscure the observation of tissue fluorescence. The objectives of this study were to determine the usefulness of NBI screening for the detection of malignant tumors, depending on the anatomical site and stage of cancer during the postoperative period, and to investigate whether a history of radiotherapy affects the detection of lesions by NBI.

Methods

Study Participants

The present study was a cross-sectional study conducted at a tertiary referral center. From July 1, 2007, through February 28, 2008, a total of 206 patients with HNSCC (195 men and 11 women; mean [SD] age, 56.9 [11.8] years) underwent rhinolaryngoscopy and transnasal endoscopy using both the conventional white-light and NBI systems. All the patients were receiving treatment of their primary cancer. The screening was undertaken during their routine postoperative sessions. The mean (SD) postoperative time was 27.5 (34.8) months (range, 6-40 months), and no difference was found among different anatomical sites (Table 1).

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Patients, No. (%)</th>
</tr>
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<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>56.9 (11.8)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>195 (94.7)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (5.3)</td>
</tr>
<tr>
<td>Prior radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>141 (68.4)</td>
</tr>
<tr>
<td>No</td>
<td>65 (31.6)</td>
</tr>
<tr>
<td>Histologic diagnosis (n=68)</td>
<td></td>
</tr>
<tr>
<td>Squamous hyperplasia</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Mild dysplasia</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>13 (19.1)</td>
</tr>
<tr>
<td>Invasive cancer</td>
<td>49 (72.1)</td>
</tr>
</tbody>
</table>

*Data are presented as number (percentage) of patients unless otherwise indicated. Percentages may not total 100% owing to rounding. *A total of 62 cancerous lesions were detected in 59 patients.

The demographic data and endoscopic characteristics are given in Table 1. The study was approved by the ethics committee of Chang Gung Memorial Hospital, and written informed consent was obtained from all the patients before the endoscopic examinations and tumor excision.

NBI Equipment and Procedure

The NBI system was equipped with a videoscope (ENF-V2 rhinolarynx videoscope; Olympus Medical Systems, Tokyo, Japan), a light source (CLV-160B; Olympus Medical Systems), and a central video system (CV-160B; Olympus Medical Systems). A button on the control section of the videoscope enabled switching between conventional and NBI views. All endoscopic examinations were performed by 1 of the 2 experienced otolaryngologists (Y.-C.L. or W.-H.W.) in the outpatient clinic. The patients were examined while in the seated position. Before the endoscopic procedure, the nasal cavity of each patient was anesthetized with a 4% lidocaine hydrochloride spray. The oral cavity and oropharynx were examined by direct visualization and palpation and subsequently by transoral endoscopy in NBI mode. In the oropharynx, hypopharynx, and larynx, we performed transnasal endoscopy, first in the white-light mode and then using the NBI system.

The criteria for diagnosing a cancerous lesion with conventional white-light endoscopic imaging included the presence of demarcated red lesions, white lesions, elevated lesions, and ulcerative lesions. The criterion for classifying a lesion as malignant using the NBI system was the presence of a well-demarcated brownish area with scattered brown spots...
Patients with lesions that were deemed noncancerous by these diagnostic methods did not undergo any additional examinations or biopsy. On the other hand, patients diagnosed as having abnormal lesions underwent biopsy or lesion resection. With regard to the lesions over the oral cavity, oropharynx, larynx, or hypopharynx, excision was performed by transoral laser microsurgery for oral cavity and oropharyngeal lesions or by endoscopic mucosal resection for hypopharyngeal lesions. The resected lesion specimens were stained with hematoxylin-eosin for histopathologic examination. All the specimens were reviewed by a single pathologist (K.-F.L.), who was masked to the endoscopic findings.

STATISTICAL ANALYSIS

The results are presented as mean (SD) for continuous variables and as percentages for categorical variables. Statistical differences were compared by applying the Fisher exact test for dichotomous variables. \( P < .05 \) was set to indicate statistical significance for nonparametric data analyzed by a 1-tailed test.

Statistical analyses were conducted using a statistical software package (SPSS statistical software, version 12; SPSS Inc, Chicago, Illinois).

RESULTS

All 206 patients tolerated the videoendoscopic examinations well. A total of 68 lesions were defined as suggestive of cancer on the basis of the results of endoscopy with either method. Specimens obtained from the 68 lesions were histopathologically examined, and 62 of these were confirmed to be cancerous (at least as carcinoma in situ). The 6 lesions that were confirmed to be noncancerous on the basis of histopathologic analyses were located in the oral cavity (\( n = 4 \)) and the arytenoid tissue (\( n = 2 \)). A and C, White-light endoscopy; B and D, narrowband imaging (NBI) endoscopy. Two false-positive small superficial lesions were seen at the left (B) and right (D) arytenoids in NBI mode. In these 2 patients, the time since radiation therapy was approximately the same (29 and 34 months after radiotherapy). The histopathologic examination revealed mild dysplasia.
light view, which proved to be verrucous carcinoma by histologic examination. This patient belongs to the false-negative group, which consisted of 1 lesion by NBI mode and 13 lesions by white-light mode. These 13 lesions were confirmed to be carcinoma in situ by histopathologic examination (Figure 1).

The 62 cancerous lesions, found in 39 patients, were located over the oral cavity (n=33), oropharynx (n=16), and hypopharynx (n=13) (Table 2). No lesions were found over the larynx. The diagnostic accuracy of endoscopy performed in white-light and NBI modes was 100% and 97% for lesions in the oral cavity, 69% and 100% for those in the oropharynx (P= .02), and 39% and 100% for those in the hypopharynx (P= .001), respectively.

Of the 62 cancerous lesions, 49 (79%) were detected with conventional white-light endoscopy, and all of them were classified as visible tumors (T1-T4). The remaining 13 lesions that were not detected by conventional white-light endoscopy were histopathologically diagnosed as carcinoma in situ (T0) and could only be detected in NBI mode (Table 3). These 13 superficial T0 lesions were over the oropharynx (n= 5) and hypopharynx (n=8). No difference was found between the 2 modes with regard to the detection of visible T1 to T4 tumors. However, NBI mode was significantly superior to white-light mode for the detection of precancerous lesions in the oropharyngeal and hypopharyngeal mucosa.

Of 206 patients, 141 had received radiotherapy before the examination and 65 had not. We compared the rates of detection of the cancerous lesions by NBI only in patients who had previously received radiotherapy with the detection rates in those who had not. No differences were found in the rates of detection of lesions in the oropharyngeal or hypopharyngeal mucosa (P=.65 and .41, respectively; Table 4). Prior radiotherapy does not appear to affect the detection of lesions by NBI.

Histologic examination was not performed for patients whose lesions were deemed noncancerous after endoscopy by both methods. None of these patients developed squamous cell carcinomas in the area examined during the follow-up period (mean duration, 15.8 months; range, 12-18 months).

### Table 2. Comparison of the Detection Rates of Standard Endoscopy and NBI Depending on the Cancer Sites (62 Cancerous Foci in 39 Patients)

<table>
<thead>
<tr>
<th>Site of Cancerous Lesions</th>
<th>No. of Patients</th>
<th>No. (%) of Foci Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>33</td>
<td>33 (100)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>16</td>
<td>11 (69)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>13</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Larynx</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total No. of Foci</td>
<td>62</td>
<td>49 (79)</td>
</tr>
</tbody>
</table>

### Table 3. Comparison of the Detection Rates of Standard Endoscopy and NBI Depending on the Cancer Stage (62 Cancerous Foci in 39 Patients)

<table>
<thead>
<tr>
<th>Cancer Stage</th>
<th>No. of Patients</th>
<th>No. (%) of Foci Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visible cancers (T1-T4)</td>
<td>49</td>
<td>49 (100)</td>
</tr>
<tr>
<td>Carcinoma in situ (T0)</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Total No. of Foci</td>
<td>62</td>
<td>49 (79)</td>
</tr>
</tbody>
</table>

### Table 4. Comparison of the Detection Rates of NBI Depending on Prior Radiotherapy Status

<table>
<thead>
<tr>
<th>Radiotherapy Site</th>
<th>No. of Patients</th>
<th>No. (%) of Foci Detected by NBI Only per No. of Foci at Subsites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>33</td>
<td>0/20 (0)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>16</td>
<td>3/10 (30)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>13</td>
<td>3/8 (50)</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>6/36 (17)</td>
</tr>
</tbody>
</table>

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**Abbreviations:** NBI, narrowband imaging.  
aFisher exact test.
To date, visual examination and palpation have remained the criterion standard techniques for the identification of mucosal lesions of the head and neck.10,11 The criteria for identifying a lesion as precancerous include loss of surface integrity and changes in the texture, color, and contour patterns of the mucosal surface. A comprehensive examination of the head, neck, and primary lesion site during routine checkups is crucial. The reported feasibility of conventional oral examinations for detecting oral cancer has varied among previous studies. A meta-analysis performed by Downer et al18 revealed that these techniques had an overall sensitivity of 85% (95% confidence interval, 73%-92%) and a specificity of 97% (93%-98%). Although conventional physical examination may be useful for identifying oral lesions, it is not as effective for identifying other potentially premalignant lesions.19

A variety of commercially available diagnostic tools and adjunctive techniques, such as toluidine blue staining,20-22 tissue chemiluminescence,16,23 and autofluorescence,24,25 assist the screening of premalignant lesions in both healthy and high-risk individuals. Toluidine blue staining is the most widely used and established adjunctive technique. The reported overall sensitivity of this technique ranges from 77% to 100%, and the specificity ranges from 31% to 100%.10,22 Onofre et al20 found that all visible carcinomas and only 50% of dysplasias stained positively, as did 35% of the benign lesions. Furthermore, the clinical application of this technique is difficult because (1) dye application is time-consuming, (2) application of the dye over the pharyngeal mucosa is difficult, and (3) the results can be ambiguous in cases of equivocal staining.

In this study, our data revealed that NBI was effective in detecting mucosal lesions in the pharyngeal wall, but it seemed to add no additional value to the detection of lesions in the oral cavity (Table 2). Moreover, the false-positive lesions diagnosed in NBI mode were mostly in the oral cavity (4 of 6). We propose the following possible reasons for these findings. First, because of the complex anatomy of the oral cavity, it is difficult to properly expose the mucosa or epithelium to be examined by flexible endoscopic examination. On the contrary, conventional visual inspection with sufficient light and manual tissue traction provides a good visual field that is far superior to that observed in the endoscopic view. Second, the nature and appearance of the oral cavity mucosa varies at different subsites. The typical demarcated brownish area with scattered spots that is often observed in NBI mode was hardly seen on the tongue surface. Third, although we clearly identified the oral cavity lesions as typical brownish spots, which suggested dilated neovascularization, histopathologic examinations indicated the lesions to be squamous hyperplasias. Additional molecular-level analyses of the false-positive lesions (Figure 2) are required to determine the role of angiogenesis in precancerous lesions. One false-negative verrucous carcinoma lesion was detected using NBI mode. This hyperkeratotic lesion had either an atypical neoangiogenic vasculature pattern or an absolutely different pattern. In addition, the control of ambient light is a limitation of NBI performed for the detection of oral lesions. Room light may confound the sensitivity of the imaging and observation when performing 415-nm NBI to detect oral lesions. Further studies are required to confirm the effect of light settings on the detection rates of lesions in the oral cavity by using NBI mode. The 2 false-positive lesions identified in the arytenoid tissue and diagnosed as mild dysplasia probably had a neoangiogenetic vasculature pattern, which was detected by NBI early at the dysplastic stage, and these lesions are at risk of cancer in the future. Therefore, NBI screening was justified because an early resection performed on the basis of data obtained using NBI might prevent further carcinogenesis.

This study has some limitations. First, diagnostic bias may be present in the form of interobserver variability in image interpretation because 2 physicians performed both examinations using conventional white-light and NBI methods. At least 2 or 3 physicians who are masked to the results should independently perform an endoscopic examination to reduce this diagnostic bias. Second, patients whose lesions were deemed noncancerous by endoscopic observation did not undergo biopsy. The routine use of confirmatory biopsy to provide a diagnostic criterion standard in the patients whose lesions screen negative has been deemed inappropriate and ethically questionable. Instead, in this study, we used a “soft standard”; that is, the patients whose lesions were deemed noncancerous by both diagnostic methods did not develop visible tumors in the area examined during the follow-up period (median duration, 15.8 months; range, 12-18 months). However, larger studies with prolonged follow-up examinations are required to detect false-negative lesions and to determine the specificity of NBI more accurately.

This is the first study, to our knowledge, to document the utility of NBI screening as an adjunctive technique to conventional visual inspection, palpation, and white-light endoscopy for patients with HNSCC who have received treatment. A significantly greater number of superficial pharyngeal mucosal lesions were identified in patients with HNSCC by using NBI mode rather than white-light mode. Narrowband imaging significantly improves the detection of carcinoma in situ lesions in the pharyngeal mucosa during postoperative follow-up. Although radiation could induce mucosal injury that involves all the tissues and cellular elements of the mucosa,14,15 our data revealed that it could not alter the angiogenic process in the precancerous stage.

In conclusion, NBI significantly improves the rates of detection of precancerous lesions of the oropharyngeal and hypopharyngeal mucosa, and its results are not affected by a history of radiotherapy. Furthermore, NBI is a highly useful adjunctive technique during postoperative follow-up. We strongly suggest that NBI be used for routine surveillance of the pharyngeal mucosa in patients with HNSCC.

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REFERENCES


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