Narrow-Band Imaging

A Novel Screening Tool for Early Nasopharyngeal Carcinoma

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Objective: To compare the real-time diagnostic accuracy of conventional white-light imaging (WLI) endoscopy with that of narrow-band imaging (NBI) endoscopy in patients at high risk for nasopharyngeal carcinoma (NPC).

Design: Prospective study.

Setting: A university tertiary care center.

Patients: From July 28 through October 27, 2009, a total of 211 consecutive patients at high risk for NPC were enrolled. A high-performance endoscopic system equipped with WLI and NBI modes was used for a detailed examination of the nasopharynx during the same endoscopy.

Main Outcome Measures: Diagnostic efficacies of WLI and NBI were compared with pathologic findings. Lesions were classified according to the detailed morphologic epithelial microvessel observations during NBI.

Results: A total of 285 lesions were detected, including 66 cancerous lesions. The sensitivity and negative predictive values of NBI in NPC screening were significantly higher than those of WLI (93.9% vs 71.2%, \(P = .001\); and 98.1% vs 91.7%, \(P = .003\); respectively); specificity and positive predictive value were not significantly different. During NBI, the presence of superficial, distorted, irregularly shaped microvessels indicated malignant lesions; 53 of 55 lesions (96.4%) with type IV intrapapillary capillary loops were confirmed on histologic testing as malignant. The false-negative and false-positive rates for NBI were 4.5% and 3.6%, respectively.

Conclusions: Narrow-band imaging endoscopy is a promising tool to differentiate nonmalignant from malignant nasopharyngeal lesions on the basis of the morphologic findings of mucosal capillary vessels in vivo. In addition, NBI may increase the diagnostic value of endoscopy in populations at high risk for NPC.


ASOPHARYNGEAL CARCINOMA (NPC) occurs at a high frequency in southern China, northern Africa, and Alaska. Chinese people living in the Guangdong province are especially prone to NPC, with a reported incidence of 30 cases per 100,000. Endoscopic examination and biopsy are the main methods used for detection and diagnosis of early NPC, and radiotherapy is the standard treatment. In early NPC, treatment outcomes are satisfactory: the successful control rate of T1 and T2 category tumors ranges from 75% to 90%.\(^1\)

Narrow-band imaging (NBI; Olympus Medical System Corp) is an endoscopic technique that uses narrow-band spectrum optical filters to enhance the visualization of epithelial and subepithelial microvascular patterns. The principle of NBI is based on the fact that the penetration depth of light depends on its wavelength. Narrow-band imaging filters select blue and green light with wavelengths of 415 and 540 nm, respectively, corresponding to the hemoglobin absorption peaks. Light at these wavelengths can penetrate the epithelium, thus highlighting the capillary network, and also penetrate deeper tissues, enhancing visualization of the subepithelial vessels. Therefore, NBI can identify superficial mucosal lesions that may be missed by standard white-light imaging (WLI) endoscopy and further guide biopsy, providing a novel approach to improve the pathologic detection rate and early diagnostic rate of the lesions. The aim of this prospective study was to determine the clinical value of NBI endoscopy in the screening of nasopharyngeal lesions.
Figure 1. Classification of superficial nasopharyngeal vessels in narrow-band imaging. A, Type I: short, thin, and sparse. B, Type II: moderate length and diameter, regularly reticulate. C, Type III: bifurcated, dilated, elongated, and mildly irregular. D, Type IV: earthworm-like distortion with a very irregular diameter or vessel course.

METHODS

PARTICIPANTS

This prospective study was conducted at the outpatient department of otolaryngology at the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, People’s Republic of China, from July 2009 to October 2009. During this period, 510 patients with risk factors for NPC received conventional WLI and NBI during the same endoscopic examination. The risk factors included any of the following: Cantonese ethnicity, NPC family history, Epstein-Barr virus detection, any symptom of nasal obstruction, sense of peculiar smell, blood-stained nasal discharge, epistaxis, ear fullness, tinnitus, hearing loss, diplopia, headache, or cervical mass. Patients with dermatomyositis were also included. In total, 211 consecutive patients with nasopharyngeal lesions were recruited for the study (133 men, 78 women; mean age, 38 years). The exclusion criterion was refusal to sign the informed consent statement. The Institutional Research Committee of the First Affiliated Hospital of Sun Yat-sen University approved the study, and written informed consent was obtained from all patients.

EQUIPMENT AND PROCEDURE

The system used for endoscopy (Visera OTV-S7 PRO; Olympus Medical Systems Corp) is equipped with the light source (CLV-S40; Olympus Medical Systems Corp), video system center (CV-160B; Olympus Medical Systems Corp), and rigid endoscopes (A508; Olympus Medical Systems Corp). Switching between the conventional WLI mode and NBI mode can be achieved conveniently by pressing a button on the light source or the control section of the endoscope.

All procedures were performed by 2 experienced and similarly trained endoscopists (Y.-H. Wen or W.-P. Wen). After nasal mucosal decongestion using a topical solution containing epinephrine, 3%, and tetracaine, 2%, patients were examined in a supine position. The endoscope was introduced through the nasal passage to observe, in sequence, the posterior nostril, superior and posterior walls of the nasopharynx, torus tubarius, pharyngeal opening of the auditory tube, and Rosenmüller recess. The imaging light mode was set to conventional WLI and subsequently switched to NBI during the procedure, and representative images were collected in both modes. All examinations were recorded and stored. All lesions, detected by either WLI or NBI, were biopsied.

WLI AND NBI DIAGNOSIS CRITERIA AND NBI NASOPHARYNGEAL MICROVESSEL CLASSIFICATION

According to the literature, we divided the appearance of nasopharyngeal microvessels examined with NBI into 4 types (Figure 1). Type I are short, thin, and sparse and are located in the space among the lymphoid follicles; Type II have moderate length and diameter and are regularly reticulate; Type III have vascular bifurcations and are dilated, elongated, and mildly irregular; and type IV are distorted in an earthworm-like appearance, with a very irregular diameter and vessel course.

The WLI mode was used to examine lesions with a protruding uneven surface, ulceration, or adherence of white membranous secretion that were endoscopically suspected to be malignant. Cysts, adenoids, and lymphoid hyperplasia were endoscopically thought to be benign. During the NBI mode, lesions exhibiting a well-demarcated brownish area with or without irregular type III or IV microvascular patterns were endoscopically suspected to be malignant. Otherwise, lesions were considered to be benign, including those with type I to II microvessels or lesions with type III microvessels without a well-demarcated brownish area. The endoscopic diagnosis and location of the mucosal lesions were recorded. The efficacy of real-time on-site diagnosis was evaluated because accurate diagnosis made in this manner is clinically more important than retrospective evaluation using stored data.

PATHOLOGIC EVALUATION

Specimens for biopsy were obtained from all lesions after endoscopic evaluation with both modes of imaging. Pathologic evaluation was performed by 2 experienced pathologists who were blinded to the corresponding endoscopic assessment. The final pathologic diagnosis was made by agreement of the pathologists.
STATISTICAL ANALYSIS

All statistical analyses were performed using commercial software (SPSS, version 13.0; SPSS Inc). Results are presented as numbers (percentages) for categorical variables. Statistical differences were compared using the Fisher exact test. Using the histopathologic characteristics as the reference standard, the sensitivity, specificity, positive predictive value, and negative predictive value of conventional WLI and NBI were compared using the \( \chi^2 \) test; \( P < 0.05 \) was considered statistically significant.

RESULTS

PATIENT DEMOGRAPHICS AND CHARACTERISTICS

Two hundred eleven patients with nasopharyngeal lesions were enrolled in the study; demographic characteristics are reported in Table 1. With pathologic testing, NPC was diagnosed in 43 of the 211 patients and lesions were identified as being nonmalignant in 168 patients. In total, 285 nasopharyngeal lesions from 211 patients were evaluated, of which 214 lesions (75.1%) were defined on pathologic testing as inflammatory hyperplasia (including cysts); 3 lesions (1.1%), as atypical hyperplasia; 2 lesions (0.7%), as papilloma; and 66 lesions (23.2%), as cancer. Detailed information on the diagnoses is summarized in Table 2.

Representative WLI and NBI images of nasopharyngeal lesions are shown in Figure 2. By enhancing visualization of the microvascular pattern, screening of characteristic changes in the intrapapillary capillary loops (IPCLs) of mucosal lesions was easier using NBI vs WLI, especially in atypical flat lesions (Figure 3).

DETECTION OF NPC BY WLI AND NBI

Of the 66 cancer lesions diagnosed on pathologic testing, 62 were detected by NBI and only 47 were detected by WLI. The detection sensitivity of NBI for NPC was significantly higher than that of WLI (93.9% vs 71.2%; \( \chi^2 = 11.847; P = .001 \)). The specificity of NPC detection using NBI (206 of 219 [94.1%]) was not significantly different from that of WLI (209 of 219 [95.4%]; \( \chi^2 = 0.413; P = .52 \)). The positive predictive values for NBI (62 of 75 [82.7%]) and WLI (47 of 57 [82.5%]) were not significantly different (\( \chi^2 = 0.001; P = .98 \)). The negative predictive value of NBI (206 of 210 [98.1%]) was significantly higher than that of WLI (209 of 228 [91.7%]; \( \chi^2 = 9.08; P = .003 \)).

RELATIONSHIP BETWEEN NASOPHARYNGEAL MICROVASCULAR TYPE OBSERVED BY NBI AND PATHOLOGIC DIAGNOSIS

Normal nasopharyngeal superficial vessels can be clearly identified with NBI, manifesting as type I and II microvessels, with submucosal vessels observed as green and arborescent branches appearing brown. The arborescent vessels are a crossed network and produce smaller branches. Intrapapillary capillaries arising from the fourth branch of the arborescent vessels enter the epithelial papillae and form IPCLs, which are located under the epithelial basement membrane. Usually, IPCLs are thin and almost invisible; however, morphologic changes in IPCLs are observed in mucosal lesions. In inflammatory hyperplasia, most microvessels appeared as short, thin, and sparse (type I). Microvessels on or around cysts were mostly type II, with a regular weblike distribution or slightly dilated. With the NBI mode, malignant lesions characteristically appeared as well-demarcated brownish areas, with thick dark spots and/or winding vessels. As lesions progressed, IPCLs became more dilated, elongated, irregular, or twisted into a convoluted wormlike appearance (types III and IV, Figure 2). A more irregular IPCL appearance indicated a greater possibility of malignancy. Dilated and mildly irregular type III IPCLs with well-demarcated brownish spots were considered malignant, and slightly dilated and mildly irregular IPCLs without well-demarcated brownish spots were considered benign. Of the lesions with type IV IPCLs, 96.4% of them (53 of 55) were confirmed as carcinoma (Table 2), with the remain-
der (3.6%) confirmed as papilloma or atypical hyperplasia. Only 4.5% of malignant lesions (3 of 66) did not display type III or type IV IPCL changes when examined in the NBI mode.

COMMENT

Nasopharyngeal carcinoma is a nonlymphomatous, squamous cell carcinoma that occurs in the epithelial lining of the nasopharynx.3 Accurate diagnosis by endoscopy and therapy of early-stage neoplasias may increase the curability and reduce the morbidity associated with radiotherapy. Epstein-Barr virus detection plays an important role in NPC screening; however, up to 20% of early NPC cases have negative Epstein-Barr virus serum markers.5 Early-stage NPC can be located in hidden positions or commonly has a macroscopic appearance of superficial inflammation, which can be easily overlooked or misdiagnosed. The sensitivity of conventional endoscopy with a white-light system is inadequate for screening of superficial cancers or precancerous lesions.

The NBI technique, based on traditional nasal endoscopy, can highlight the epithelial capillary network and allow visualization of the deeper subepithelial vessels. With use of NBI, superficial mucosal lesions, which may be missed by standard WLI endoscopy, can be identified easily by their neoangiogenic pattern.6 During NBI, IPCLs in the superficial mucosa appear brown and submucosal vessels appear green.7 Previous studies3 have shown that the structure and organization of blood vessels are dynamic and undergo considerable changes during the progression from neoplasia to invasive cancer as the microvascular network becomes dilated, elongated, distorted, or replaced by neotumor vasculature. Narrowband imaging has demonstrated excellent diagnostic accuracy in the differentiation of a variety of cancerous and noncancerous lesions. Since its emergence, NBI has been applied mainly in the detection of gastrointestinal disease and malignancy.7,8 In recent years, there have been several reports9,10 on the use of NBI in the diagnosis of head and neck malignant tumors, especially in laryngeal carcinoma. The NBI endoscopy system has the same magnification and structure enhancement as WLI endoscopy and can connect to rigid endoscopes, allowing NBI to be applied to other medical fields. To the best of our knowledge, few prospective studies have applied NBI endoscopy in the detection or screening of NPC.11,12

The differentiation between malignant and nonmalignant lesions is the key objective of NPC screening. The NBI filter system is designed for the peak absorption spectrum of hemoglobin to emphasize mucosal surface capillary vessels. Because NBI markedly improves the contrast of the superficial layer capillary pattern, it is easier to detect small or early malignant lesions, therefore increasing the diagnostic sensitivity and accuracy. In the present study, the sensitivity and negative predictive value of NBI endoscopy in the diagnosis of NPC were significantly higher than that of WLI endoscopy (93.9% vs 71.2%, \( P < .001 \); and 98.1% vs 91.7%, \( P = .003 \)); however, the specificity and positive predictive values of the 2 techniques were not significantly different. These findings are similar to those in the studies of Kara et al13 and Ni et al,10 who reported on sensitivity (94% and 93.2%, respectively), specificity (76% and 90.8%), positive predictive value (64% and 90.7%), and negative predictive value (98% vs 93.2%).

In this study, enhancement of vascular patterns by NBI simplified screening of characteristic changes of IPCL pattern or mucosal lesions, especially in some atypical flat lesions (Figure 3). Thus, selective biopsy guided by NBI may improve the pathologic detection rate, reducing the

Figure 2. Nasopharyngeal lesions observed with white-light imaging (WLI; left column) and narrow-band imaging (NBI; right column). A and B, Lymphoplasia. C and D, Cyst. E and F, Pathologically diagnosed atypical hyperplasia in left recess of Rosenmüller, considered benign during WLI and malignant during NBI; specimens from 2 biopsies performed during follow-up were diagnosed on pathologic testing as inflammatory hyperplasia. G and H, Right recess of Rosenmüller papilloma. I and J, Undifferentiated nonkeratinizing carcinoma on posterosuperior wall of the nasopharynx.
chances of oversampling, missed diagnosis, and misdiagnosis. Selective biopsy may also be useful in residual or recurrent cancer detection after surgical intervention or radiotherapy.

The NBI system is limited by some factors, such as visual obstruction by secretions and an overall darker image. Secretions appear dark green and glisten during NBI, which can interfere with screening. Additionally, because of the darker image, the endoscope may have to be placed very close to the mucosal surface, which can lead to contact bleeding and significant interference with the observations. In some patients in this study, a thick keratin layer covered the target area; therefore, during screening of high-risk patients, observation of the surrounding mucosa may help identify characteristic IPCL pattern changes. In some cases, slight suction of the loose keratin layer assisted the NBI observation.

In our study, several malignant lesions (4.5%) did not show characteristic IPCL pattern changes and were misdiagnosed as benign lesions by NBI. One false-positive case, which was observed as scattered brown spots with type IV IPCLs, was determined to be malignant during NBI (Figure 2H) and then was pathologically diagnosed as papilloma. Difficulty in differentiation of papillomas presenting with scattered brown spots and malignant lesions may be one limitation of the NBI technique.

Prior research involving the esophagus indicates that, in the normal mucosa, submucosal vessels that pierce the muscle layer are connected to the arborescent vascular network. Intrapapillary capillaries arising from the fourth branch of the arborescent vessels enter the epithelial papillae and form IPCLs, which are generally thin and almost invisible. Morphologic changes in IPCLs occur in malignant lesions. In mucosal cancer (m1), IPCLs are dilated and elongated, and the number and density of arborescent vessels in the lamina propria mucosae and tela submucosa increase. These changes are similar to those observed in inflammation. As cancer invades deeper into the mucosa (m2), the papillae stretch further and IPCLs become more dilated and elongated. Close to the lamina propria mucosae (m3), the IPCL structure starts to collapse and the surface of the vessels becomes rough. When tumors progress to submucosal invasion (sm), IPCLs are not present, and the preexisting vasculature is replaced by neotumor vasculature, which is leaky and has a distorted, irregularly shaped fragile structure. Based on these reports and the Kumagai et al vascular classification, the present study divided nasopharyngeal microvessels into 4 types. In the NBI mode, most microvessels in NPC appeared as type III or IV, and 96.4% of the lesions with type IV IPCLs were diagnosed as malignant. Observation of the characteristic changes observed in IPCLs in NPC lesions using NBI could accurately guide biopsy, which may reduce the number of unnecessary biopsies, improve the diagnosis efficacy, shorten the time to final diagnosis, and reduce cost. Because most researchers have used their own terms for vessel classification and there is no unified classification criteria for microvessels during NBI observation, a recognized vascular classification standard is required to promote the application of NBI.

In conclusion, increasing numbers of physicians have adopted NBI endoscopy since the emergence of the technique, most often during gastrointestinal examinations, including detection of Barrett esophagus and the early diagnosis of gastrointestinal cancer. Narrow-band imaging endoscopy is useful for the early diagnosis of cancerous lesions, improving diagnostic accuracy, and preventing missed diagnosis or misdiagnosis because of the enhanced visualization of epithelial and subepithelial microvascular patterns. Recently, some researchers have applied NBI to screen patients for head and neck cancers, mainly laryngeal and oropharyngeal cancers. The present study used NBI for screening and detection of NPC. The sensitivity and negative predictive values of NBI in the diagnosis of NPC were significantly higher than those of WLI, which indicates that NBI has a satisfactory practical value and potential for a broad range of applica-

Figure 3. Flat nasopharyngeal lesion in the left recess of Rosenmüller. A, During white-light imaging, no obvious lesion was detected. B, During narrow-band imaging (NBI), dilated, distorted, irregular, and earthworm-like intrapapillary capillary loops were observed. The NBI-guided biopsy specimen was confirmed on pathologic testing as undifferentiated nonkeratinizing carcinoma.
Further research on NBI endoscopy is required, especially in the field of otorhinolaryngology, including large-scale, double-blind, randomized controlled trials to compare NBI, WLI, and pathologic diagnosis.

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