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The Role of Narrow Band Imaging in Head and Neck Cancers

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Abstract Early diagnosis of malignant tumors in the head and neck region is very difficult. Therefore, endoscopic systems with narrow band imaging (NBI), which enhances image contrast, have an important clinical value in detecting superficial mucosal lesions. In particular, highlighting of the intraepithelial microvasculature helps determine the nature of the lesion. This new image-enhanced technology already has proven effective in the early diagnosis of head and neck squamous cell carcinoma, including laryngeal, hypopharyngeal, oropharyngeal, nasopharyngeal, and oral cancers, as well as of unknown primary cervical lymph node metastasis. NBI laryngoscopy can be applied easily in clinical practice and has become a valuable tool in diagnosing head and neck cancers early, providing the option of minimally invasive treatment such as endoscopic or partial surgical resection.

Keywords Head and neck cancers · Narrow band imaging · Laryngoscopy · Early diagnosis

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Introduction

The most common histologic type of malignant head and neck tumor is squamous cell carcinoma. However, early diagnosis of primary tumors in this region is very difficult, with most patients receiving the diagnosis at an advanced stage of disease, when prognosis is poor. Radiologic examination such as CT and MRI can detect only larger lesions. Thus, endoscopy is the primary examination method for the early diagnosis of upper aerodigestive tract carcinomas. However, conventional white light (WL) endoscopy is limited in both resolution and contrast, which may lead to misdiagnosis of superficial mucosal cancer and precancerous lesions, even by experienced endoscopists. To resolve these issues, new endoscopic imaging technologies were developed, the most mature and representative of which is narrow band imaging (NBI; Olympus Medical Systems Corporation, Tokyo, Japan). NBI is a novel optical technology that allows better visualization of superficial mucosal lesions, which combined with the electronic laryngoscope demonstrates important clinical value in head and neck cancers (Fig. 1). Compared with conventional WL endoscopy, NBI endoscopy can reveal small and superficial mucosal lesions that might otherwise be missed; therefore, it has proven to be a useful diagnostic tool for the early detection of head and neck squamous cell carcinoma [1, 2].

The Basis of NBI Endoscopy and Visualization of the Mucosal Vasculature

NBI is an innovative optical image enhancement technology that highlights microsurface patterns and microvascular morphologies on the mucosal surface. It is easy to set up and operate, and the user can switch rapidly from conventional WL to the NBI system simply by pressing a button on the

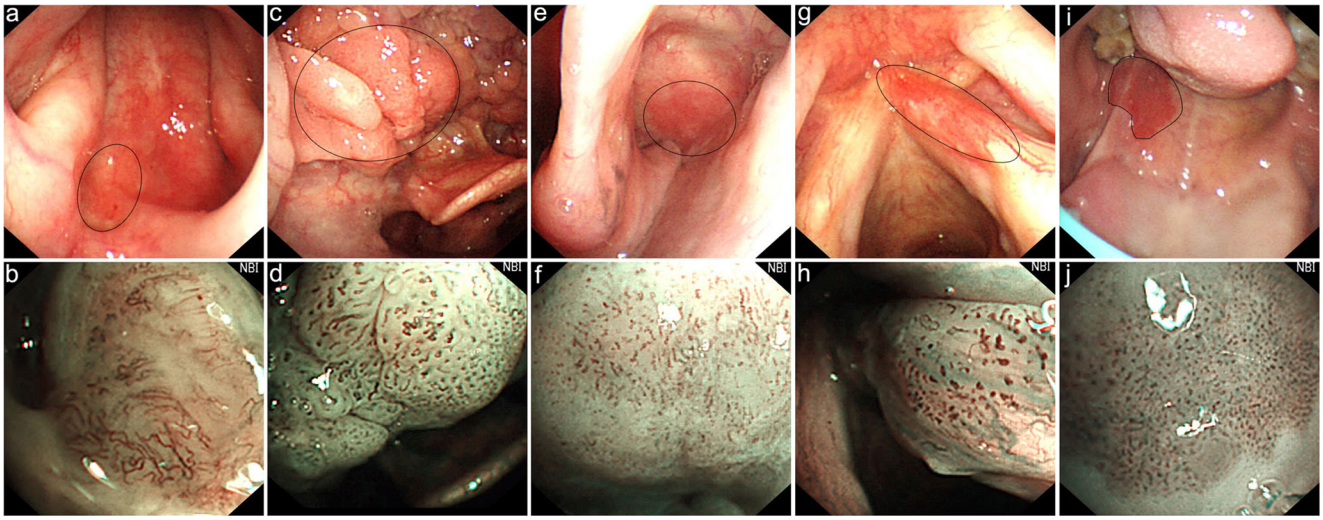

Fig. 1 Superficial early cancers in the head and neck region detected by NBI endoscopy. **a** The nasopharynx appeared smooth and slightly red under WL endoscopy. **b** Brownish snake-like, winding microvessels to the left of Rosenmüller's fossa were detected by NBI endoscopy. Histopathology of the biopsy specimen revealed nonkeratinizing undifferentiated nasopharyngeal carcinoma. **c** The left base of the tongue was thick and slightly red under WL endoscopy. **d** Brownish dots or tadpole-like microvessels were observed on the mucosa with NBI. Histopathology showed squamous cell carcinoma. **e** The right pyriform sinus was smooth and had a slightly red area under WL endoscopy. **f** Brownish dots were identified under NBI. Histopathology revealed squamous cell carcinoma in situ. **g** The right vocal cord was smooth and reddish under WL endoscopy. **h** Brownish dots were identified under NBI. Histopathology revealed squamous cell carcinoma in situ. **i** The left retromolar area was reddish under WL endoscopy. **j** A clearly demarcated brownish area and scattered brown dots were well visualized with NBI endoscopy. Histopathology showed squamous cell carcinoma in situ

videoendoscope. This imaging system works by exploiting the specific characteristics of the electromagnetic spectrum of light [3, 4•]. Whereas conventional electronic endoscopy systems have a xenon lamp and rotation disk with three broadband optical filters spanning the entire spectrum of the visible wavelength (~400–800 nm), NBI uses only two spectral regions: one blue, 400–430 nm (centered at 415 nm), and one green, 525–555 nm (centered at 540 nm). This technology was developed specifically for highlighting the vasculature. The color of the mucosa is determined primarily by hemoglobin, which strongly absorbs short blue and green wavelengths but does not absorb red wavelengths. Consequently, the blue filter in the NBI system is designed to correspond to the peak absorption spectrum of hemoglobin to emphasize the contrast of the capillary bed and intrapapillary capillary loop pattern in the superficial mucosa by making them appear brown. Meanwhile, thicker blood vessels in the deeper mucosa and submucosa are enhanced by the green light centered at 540 nm and appear cyan. The reflection then is captured by a charge-coupled device (CCD), and an image processor creates a composite pseudocolor image, which is displayed on a monitor. Thus, NBI can enhance mucosal contrast without the use of dyes, making superficial mucosal lesions easily identifiable. For this reason, NBI endoscopy also is known as "optical chromoendoscopy" [5].

Not only can NBI endoscopy reveal small superficial lesions of the mucosal surface by contrast enhancement, it also can help determine the nature of the lesions by allowing visualization of the mucosal microvascular architecture, which is essential in identifying lesion types in head and neck cancers. This ability might significantly improve the endoscopic lesion detection rate and diagnostic accuracy, offering important clinical applications. Under NBI endoscopy, mucosal microvascular patterns of the squamous epithelium exhibit typical features [6••]. On close observation of the mucosal surface, capillaries on the superficial layer of the mucosa are displayed clearly under NBI. Superficial blood vessels of the squamous epithelium mucosa are derived from the submucosal vein with at least three levels of ramification [7]. The first is branching vessels, which extend to the horizontal plane and lie immediately above the lamina muscularis mucosae. These vessels make up the mucosal vascular network and further divide into smaller, obliquely running vessels. At the end of these oblique vessels is the intraepithelial papillary capillary loop (IPCL), located below the epithelial basement membrane. On normal observation of the epithelium, the IPCL is barely recognizable, but under NBI combined with a magnifying endoscope, it can be visualized clearly as brown dots. IPCL changes may be tracked starting from an inflammatory mucosa, then progressing from low to high dysplasia and finally to cancer. In normal epithelium, the IPCL is observed as a smooth-running, small-diameter capillary. When squamous cell carcinoma develops in situ, the IPCL exhibits the following four pattern changes: dilatation, meandering, caliber change, and nonuniformity. This pattern

classification corresponds well to the underlying histologic changes in the squamous epithelium [8••].

In December 1999, the first clinical NBI pictures were taken. Then in 2001, Sano et al. [9] reported the first clinical use of NBI in the gastrointestinal tract, allowing them to make detailed observations of changes in the mucosal surface texture and underlying vasculature. Subsequently, NBI endoscopy was demonstrated to be effective in detecting neoplastic and dysplastic lesions in the gastrointestinal tract, upper aerodigestive tract, bronchial tree, and urogenital tract [10–13]. Currently, NBI is a useful and effective tool for detecting small superficial malignant lesions during routine endoscopic examination.

Microvessel Characteristics and Current Applications of NBI Endoscopy in Head and Neck Cancers

Laryngeal Carcinoma

NBI endoscopy is very effective in diagnosing laryngeal lesions and can detect early-stage laryngeal cancer and precancerous lesions. Watanabe et al. [14] and Piazza et al. [15] reported the typical characteristics of laryngeal carcinoma under NBI endoscope: any well-demarcated brownish area with thick dark spots and/or winding vessels is considered a malignancy. The sensitivity and specificity of NBI for diagnosing laryngeal cancer compared with histopathologic results are both greater than 90 %. We found that the IPCL patterns in laryngeal mucosal epithelium exhibit dynamic changes during the transition from the precancerous to the malignant stage and identified five types of laryngeal lesions according to the microvessel characteristics of the IPCL [16••]. In type I lesions, the IPCL is almost invisible, although oblique and arborescent vessels of small diameter may be seen clearly. This type usually represents normal mucosa or polyps. In type II lesions, the IPCL also is nearly invisible, but the diameter of the oblique and arborescent vessels is larger than in type I. This presentation usually indicates inflammation, particularly after radiotherapy. In type III lesions, the IPCL is obscured by a white mucosal patch, usually suggesting leukoplakia. In type IV lesions, the IPCL is visible, with a relatively regular arrangement and low density, as scattered, small, dark brown dots. This type usually represents mild or moderate dysplasia. Type V lesions are divided into three subtypes: Va, Vb, and Vc. In type Va, the IPCL is significantly dilated and very dense and appears clearly as large brownish dots. It usually represents severe dysplasia or carcinoma in situ. In type Vb, the IPCL is dilated and elongated significantly and presents as snake-, earthworm-, tadpole-, or branch-like morphologies. This presentation usually suggests progression to invasive cancer. In type Vc, the neoplasia is covered with necrotic tissue and the IPCL is destroyed, presenting as brownish speckles or tortuous shapes with uneven density scattered on the tumor surface, which usually indicates advanced laryngeal cancer. Based on this classification system, types I to IV lesions are considered benign, whereas type V lesions are malignant. When IPCL types were considered in diagnosing laryngeal lesions, the resulting accuracy was 90.4 %, significantly better than that of WL endoscopy (76.9 %, $P=0.028$). The specificity and sensitivity in diagnosing laryngeal cancer were 88.9 and 93.2 %, respectively. The sensitivity was significantly greater than that of WL endoscopy (68.9 %, $P=0.020$), whereas the specificity showed no significant difference (89.8 %, $P=0.509$). The type Va designation was the most accurate in the early diagnosis of laryngeal carcinoma; the sensitivity and specificity of Va in diagnosing severe dysplasia and carcinoma in situ were 100 and 79.5 %, respectively. Recently, Bertino et al. [17] and Kraft et al. [18] verified these laryngeal IPCL types, obtaining similar results. Further, during follow-up examination after surgery or radiotherapy, the emergence of clear brownish dots (IPCL Va) or snake-shaped microvessels (IPCL Vb) often indicates local recurrence. Thus, identifying IPCL types under NBI endoscopy not only adds important value in diagnosing laryngeal lesions but also contributes effectively to the early detection of postoperative recurrent lesions [19].

Oropharyngeal and Hypopharyngeal Carcinoma

The oropharyngeal and hypopharyngeal mucosa is covered with stratified squamous epithelium, and changes in its microvascular morphology during carcinogenesis are similar to those of laryngeal and esophageal carcinoma. As such, the diagnostic IPCL types also may be used to refer to laryngeal or esophageal lesions; however, type III lesions in laryngeal cancer are less visible because of the absence of leukoplakia in the hypopharynx. In mild or moderate dysplasia of the hypopharynx, the IPCL presents as relatively small, sparse dots under NBI endoscopy, and the lesion boundaries are unclear. With progression to severe dysplasia or carcinoma in situ, clear brownish dots are seen on the mucosal surface and the lesion boundaries appear more refined than they do under WL. Upon tumor invasion into the submucosa, the IPCL morphology changes from brown dots to more torturous lines resembling snakes or earthworms. Finally, in the late stages of malignancy, the tumor surface often is accompanied by necrosis and the microvasculature of the mucosal surface is deformed, even disappearing in some cases as it is covered by necrotic tissues. On areas with thick lymphoid tissue, such as the base of tongue and tonsil, IPCL morphology sometimes is influenced by follicular hyperplasia, in which case, the IPCL may not appear as brownish dots or twisted and dilated microvessels on the tumor surface.

Muto et al. [20••] used NBI combined with magnifying endoscopy to screen 320 cases of esophageal carcinoma and to detect the morbidity of synchronous superficial cancer in the esophagus and the head and neck region. Their results show that superficial oropharyngeal or hypopharyngeal carcinoma was present in 8 % of esophageal cancer patients (26/320). The IPCL characteristics considered in diagnosing superficial squamous cell carcinomas by NBI were a well-demarcated brownish area and an irregular microvascular pattern. A randomized controlled study then showed that NBI detected superficial cancer more frequently than WL imaging in the head and neck region (100 vs 8 %, $P<0.001$). The sensitivity of NBI for diagnosing superficial cancer in the head and neck region also was significantly greater than that of WL imaging (100 vs 7.7 %, $P<0.001$), although there was no significant difference in specificity between the two techniques (78.6 vs 95.5 %, $P=0.28$). Yoshimura et al. [21] summarized the endoscopic features of oropharyngeal and hypopharyngeal superficial carcinoma under conventional WL and NBI endoscopy. They found that redness was the common characteristic of pharyngeal superficial carcinoma on conventional WL endoscopy. On nonmagnified NBI endoscopy, the superficial lesions exhibited a well-demarcated brownish area, which on magnified NBI endoscopy appeared as an intervascular brownish epithelium and abnormal microvessels exhibiting dilation, proliferation, and irregularities. The redness of lesions on conventional WL endoscopy had 72 % sensitivity, 59 % specificity, and 62 % accuracy in diagnosing superficial carcinoma in the oropharynx and hypopharynx. If the intervascular brownish epithelium and microvascular irregularities on magnified NBI endoscopy were taken into account in addition to lesion redness, the diagnostic yield was 52 % for sensitivity, 92 % for specificity, and 82 % for accuracy. NBI endoscopy therefore can detect superficial pharyngeal cancer, and these lesions may be treated endoscopically with successful clinical outcomes [22, 23]. Satake et al. [24] reported the long-term outcome of 176 patients who had superficial pharyngeal squamous cell carcinoma treated by transoral organ-preserving pharyngeal endoscopic resection. The overall survival rate at 5 years was 84.5 %, disease-specific survival at 5 years was 100 %, and pharyngeal function was preserved in all patients.

Nasopharyngeal Carcinoma

The nasopharyngeal mucosa is covered by respiratory pseudostratified ciliated columnar epithelium. Nasopharyngeal carcinoma (NPC) is characterized by a poorly differentiated or undifferentiated presentation. It differs from nonnasopharyngeal head and neck squamous cell carcinomas in several ways, including its association with the Epstein–Barr virus (EBV), increased radio- and chemosensitivity, and greater propensity for lymph node metastases [25]. Wang et al. [26] first proposed the NBI types of nasopharyngeal lesions. Based on patterns appearing on NBI, they divided the lesions into five categories. Type I lesions are brownish spots, type II have an irregular microvascular pattern (IMVP), type III have light crests, type IV have side difference, and type V have either an IMVP or side difference. Using the NBI type V pattern in diagnosing NPC showed 97.1 % sensitivity, 93.3 % specificity, 91.7 % positive predictive value, 97.7 % negative predictive value, and 94.9 % accuracy. Wen et al. [27•] classified the appearance of nasopharyngeal microvessels on NBI into four types. Type I vessels 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 and earthworm-like, with a very irregular diameter and vessel course. Based on this classification, 96.4 % of lesions (53 of 55) with type IV IPCL were confirmed as carcinoma. The sensitivity of NBI was significantly greater than that of WL endoscopy in NPC screening (93.9 vs 71.2 %, $P=0.001$), but there was no significant difference in specificity (94.1 vs 95.4 %, $P=0.52$). We found that when NPC lesions were superficial and in the early stage, type IV microvessels also appeared, suggesting that NBI might be useful in the early detection of NPC. Additionally, we found that the appearance of superficial microvessels detected by NBI endoscopy was associated with the radiosensitivity of NPC. There was a positive correlation between the microvessels on the tumor surface detected by NBI and tumor regression following radiotherapy. Therefore, NBI endoscopy might be used to predict radiosensitivity and aid in the personalized treatment of NPC.

Oral Carcinoma

The oral mucosa is covered with stratified squamous epithelium prone to keratinization and epithelial thickening, which affects the microvascular exposure on the mucosal surface. Takano et al. [28] provided the first IPCL classification of oral mucosa. They developed their classification of oral squamous epithelium by dividing the NBI findings into type I (normal mucosa, regular brown dots), type II (IPCL pattern dilation and crossing), type III (IPCL pattern elongation and meandering), and type IV (IPCL pattern destruction and angiogenesis). Shibahara et al. [29] investigated the potential role of this classification system in diagnosing early oral cancer and other oral diseases. They recruited 121 patients into their study and used magnified NBI endoscopy for screening. Their results showed that in most cases, healthy mucosa and oral mucosal diseases were classified as type I or II, whereas most oral cancers were classified as type III or IV. Sensitivity and specificity for identifying oral cancer were estimated at 92.3 and 88.2 %, respectively. Yang et al. [30•] investigated the

accuracy of the three established NBI diagnostic patterns in detecting high-grade dysplasia, carcinoma in situ, and carcinoma in oral leukoplakia: NBI criterion I, brownish spots and demarcation line with irregular microvascular patterns; NBI criterion II, well-demarcated brownish area with thick dark spots and/or winding vessels; and NBI criterion III, IPCL type III (IPCL pattern elongation and meandering) and type IV (IPCL pattern destruction and angiogenesis). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of endoscopy by NBI criterion III for detecting pathologic malignances in oral leukoplakia were 84.62, 94.56, 74.32, 97.06, and 93.0 %, respectively. The malignancy detection rate was significantly higher with NBI criterion III than with the other two criteria ($P < 0.001$). Twisted, elongated, and destructive IPCL patterns on NBI are indicators of malignancy in oral erythroplakia [31].

Unknown Cervical Lymph Node Metastasis From an Unknown Primary

Cervical lymph node metastases from unknown primary tumors are rare, constituting only about 2 % of all new head and neck cancers. However, the management of these patients remains a major challenge in oncology [32]. We investigated the value of NBI endoscopy in detecting unknown primary tumor sites due to cervical lymph node metastases of squamous cell carcinoma [33]. Our study enrolled 53 patients with cervical lymph node metastasis of squamous cell carcinoma in which the primary tumor site was not detected by routine CT, MRI, and laryngoscopy. The results, however, showed that NBI examination detected the primary tumor site in 47 % of the patients (25/53), which was better than routine radiology and endoscopy ($P < 0.001$). Hayashi et al. [34] used magnified NBI endoscopy to screen 46 patients with cervical lymph node metastasis from an unknown primary and detected the primary tumor in the hypopharynx and oropharynx region in 16 patients (35 %). WL endoscopy, on the other hand, could not reveal the presence of any lesions. The characteristics of these occult primary tumors were small or superficial, including a well-demarcated brownish area or an irregular microvascular pattern on NBI, which are typical features of superficial squamous cell carcinomas in the head and neck region. These types of lesions can be missed easily by CT or MRI, or even fluorodeoxyglucose–positron emission tomography/CT (FDG-PET/CT) scanning because of their limited resolution and insufficient FDG uptake [35, 36]. NBI endoscopy may provide better visualization of epithelial capillary morphologies and increase the ability to detect possible primary cancer in patients with cervical lymph node metastasis from an unknown primary.

Clinical Problems and Perspectives Regarding NBI in Head and Neck Cancers

NBI endoscopy is used mainly to visualize the pit pattern and microvascular architecture of the surface layers of the mucosa,

Table 1 The values of NBI in head and neck cancers compared with WL endoscopy

Site	First author/year	Study design	No. of patients/ lesions	Diagnostic criteria of NBI	NBI endoscopy		WL endoscopy	
					Sens (%)	Spec (%)	Sens (%)	Spec (%)
Laryngeal carcinoma	Watanabe/2009 [14]	Prospective	34/35	Brown spots	91.3	91.6	/	/
	Piazza/2010 [15]	Prospective	279/279	Dark spots and/or winding vessels	98	90	33	95
	Ni/2011 [16••]	Prospective	85/104	Type V pattern of IPCL	88.9	93.2	68.9	89.8
	Bertino/2015 [17]	Retrospective	217/248	Type V pattern of IPCL	97.4	84.6	98.7	3.3
	Kraft/2014 [18]	Prospective	205/205	Type V pattern of IPCL	97	96	79	95
Oropharyngeal and hypopharyngeal superficial carcinoma	Muto/2010 [20••]	Randomized	320/320	Brownish area and microvascular irregularities	100	78.6	7.7	95.5
	Yoshimura/2011 [21]	Prospective	335/445	Brownish area and microvascular irregularities	52	92	72	59
Nasopharyngeal carcinoma	Wang/2011 [26]	Prospective	79/79	Type V pattern of IPCL	97.1	93.3	64.7	91.1
	Wen/2012 [27•]	Prospective	211/285	Type IV pattern of IPCL	93.9	94.1	71.2	95.4
Oral carcinoma	Shibahara/2014 [29]	Prospective	121/121	Types III and V pattern of IPCL	92.3	88.2	/	/
	Yang/2014 [30•]	Retrospective	414/414	Types III and V pattern of IPCL	84.62	94.56	/	/

Sens sensitivity, *Spec* specificity, *IPCL* intraepithelial papillary capillary loop

which requires high-grade resolution for endoscopic imaging. Digestive NBI endoscopy (gastroscopy or colonoscopy) often uses the magnification function of high-definition endoscopes. Magnified NBI endoscopy can obtain more detailed information on the pathologically altered mucosa and enable more accurate imaging for tissue characterization, differentiation, and diagnosis [37]. However, an electronic laryngoscope requires insertion of a very thin tube, which decreases the number of pixels and limits the spatial resolution of the image. Moreover, no NBI laryngoscope has sufficient magnification to be used to observe the nasopharyngolarynx. Therefore, the microvascular morphologies of the mucosal surface cannot be visualized clearly as in gastrointestinal endoscopy. At the same time, the clinical application of NBI endoscopy requires specific training and a defined learning curve. Particularly at the beginning of its use, NBI may lead to an increased number of unjustified biopsies due to false positive pictures [38]. Although IPCL features are closely related to lesion severity and are highly accurate when evaluated by experienced endoscopists, they still cannot replace histopathologic analysis. For the mucosal microvascular morphologies to be displayed clearly, the lesion surface must be cleansed by washing or suction and the videoendoscope must be close to the lesion without touching it. Improving the accuracy of NBI in diagnosing lesions is a long-term process. A high-definition laryngoscope with a magnification function must be developed, and the IPCL characteristics of different lesions in the head and neck region as detected by NBI endoscopy require further exploration and elucidation. To achieve these goals, the experience gained applying NBI endoscopy to the gastrointestinal tract might be used to formulate reliable diagnostic criteria for the accurate diagnosis of head and neck cancers. The diagnostic criteria of IPCL patterns are important in determining lesion properties and detecting potential malignancy; they can be used further to determine the depth of invasion, thereby aiding the development of endoscopic minimally invasive treatments for head and neck cancers.

Conclusions

The early detection and early treatment of malignant tumors of the head and neck are important clinically; therefore, NBI endoscopy is a promising development (Table 1). Unlike conventional WL, NBI highlights both the mucosal surface and the underlying microvascular by using only two narrow wavebands of light. This technology enables endoscopists to obtain more detailed information about the pathologically altered mucosa and is effective in the early diagnosis of upper aerodigestive tract diseases. NBI endoscopy as applied to assessing benign and malignant lesions of the nasopharyngolarynx relies mainly on the IPCL morphologies on the mucosal surface. Early hypopharyngeal and laryngeal carcinomas show typical IPCL characteristics: clear brownish dots seen on the mucosal surface. The base of tongue, tonsil, and nasopharynx are rich in lymphoid tissue, sometimes hindering the exposure of the superficial microvascular. The specific diagnostic criteria of IPCL patterns in the head neck region must be investigated further and improved.

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Compliance with Ethical Standards

Conflict of Interest Xiao-Guang Ni and Gui-Qi Wang declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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