HNO 2017 · 65 (Suppl 1):S5–S12
DOI 10.1007/s00106-016-0284-x
Published online: 23 November 2016

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Narrow band imaging for early diagnosis of epithelial dysplasia and microinvasive tumors in the upper aerodigestive tract

Background

Endoscopy of the upper aerodigestive tract has advanced significantly over the past two decades thanks to various innovations. The development of chip-on-the-tip endoscopy and digitalization have played a considerable innovative role. Improvements also have been made in the imaging resolution and the definition of endoscopic images. Here, the introduction of 4K endoscopy (with four times higher resolution) will set new standards in the future. Flexible endoscopy in particular is now taking a leading role in the diagnosis of tumors in the upper aerodigestive tract, thanks to the small diameter of the endoscope and the significant improvements in the chips.

Endoscopic imaging procedures, such as "narrow band imaging" (NBI), autofluorescence, optical coherence tomography, endomicroscopy, etc., provide highly detailed information on the pathological changes during the endoscopic diagnostic procedure. With the developments made in endoscopy, the ambition of "optical biopsy" is almost within our grasp. This allows for accurate assessment of the lesion without a biopsy.

The German version of this article can be found under DOI 10.1007/s00106-015-0108-4.

Endoscopic imaging differentiates between horizontal and vertical techniques. While the horizontal technique primarily assesses the surface of the lesion, vertical imaging focuses on the pathological changes in the tissue (e. g., optical coherence tomography and endosonography).

» "Narrow Band Imaging" is a horizontal endoscopic imaging technique

"Narrow Band Imaging" (NBI) is among the horizontal endoscopic techniques that use filtered narrow band light to allow for a better contrast and thereby imaging of the surface changes in the region of the epithelium, the subepithelium, and the vessels. It therefore also has vertical potential thanks to the particularly good imaging of the perpendicular vascular changes [1]. In combination with high-definition (HD) or 4K technology, NBI is an imaging procedure that is very well suited to detecting precancerous and cancerous changes in the vocal folds. NBI can therefore be used as a noninvasive diagnostic imaging procedure in both outpatient and inpatient settings.

Requirements

NBI is an imaging procedure for endoscopic diagnosis that reduces light to two narrow wavelength bands in the blue and green light spectra, to improve the visibility of certain details on the mucosal surface. The technical equipment consists of a xenon light source with a special NBI filter.

In NBI mode, white light (WL) is filtered into two narrow emitted wave lengths of 400–430 nm (central wavelengths at 415 nm) and from 525 to 555 nm (central wavelengths at 540 nm). As hemoglobin is absorbed at these wavelengths, the blood vessels appear very dark and are contrasted against the surrounding tissue. This allows the vessels to be more clearly defined and for other surface structures to be detected.

Both wavelengths have their own special characteristic. The 415-nm wavelength represents blue light and penetrates approximately 300 µm into the illuminated tissue. With normal mucosal membranes, the light ray reaches the connective tissue with the network of capillary vessels directly beneath the epithelium. Owing to the corresponding absorption of the hemoglobin spectrum, the capillaries appear contrasted in the endoscopic image (**Fig. 1**).

The green light has a longer wavelength of 540 nm. This can penetrate

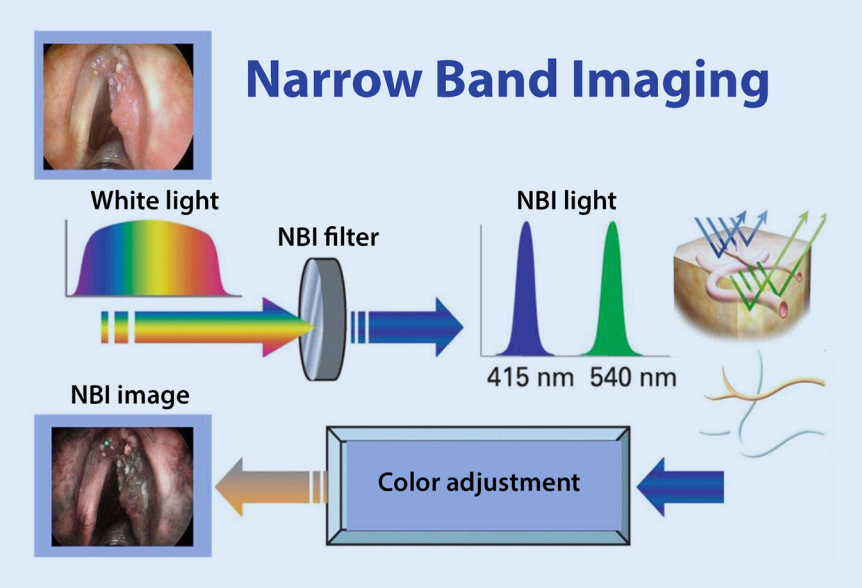

Fig. 1 ▲ "Narrow band imaging" (*NBI*). Development of the NBI image (figure courtesy of Olympus)

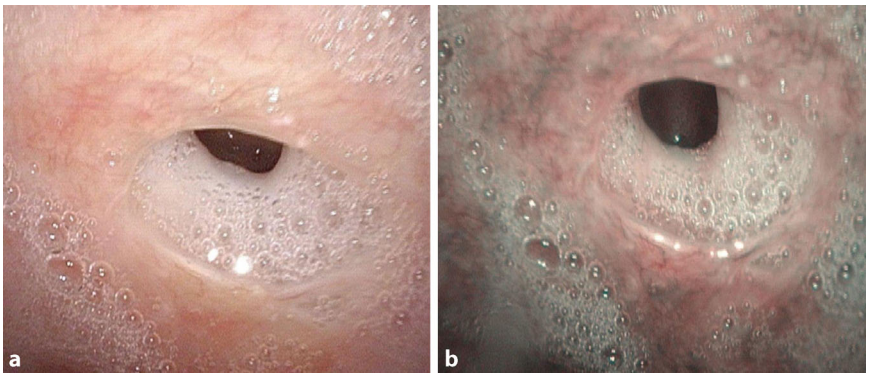

Fig. 2 ▲ Tracheoesophageal fistula in the anastomosis region of gastric pull-up following resection and radiation of an esophageal carcinoma. No tumor-associated vascular changes in the **a** white light or in the **b** NBI mode during tracheoscopy can be detected. Typical longitudinal vascular changes accompanying the scar are visible.

deeper into the connective tissue and thereby provide better visualization of the arterioles and venules in this tissue. The intraepithelial papillary capillary loops (otherwise known as IPCL, loops, or dots) that are specific for both precancerous and cancerous lesions to the vocal cords can be better detected with this technique. This was described as early as 2003 by Shibuya [2] in the area of bronchoscopy.

A 4K or HD camera in combination with a rigid endoscope (0–120°) and/or a flexible video-endoscope (30–90 cm in length and max. 4 mm in diameter) with chip-on-the-tip-technology and a video system are used in NBI endoscopy. The use of a contact endoscope is necessary to magnify the region-of-interest with a specially designed endoscope, which can be applied during panendoscopy or microlaryngoscopy [1, 3].

Use in ENT

In 2004, Muto et al. [4] introduced NBI for endoscopy of the upper aerodigestive tract. At that time, this imaging technique was already being used in gastroenterology [4–7] and pneumology ([2]; ◘ **Fig. 2**).

NBI improves the visibility of epithelial and subepithelial microvascular structures and lesions. Small lesions in particular are much easier to detect and assess compared to WL.

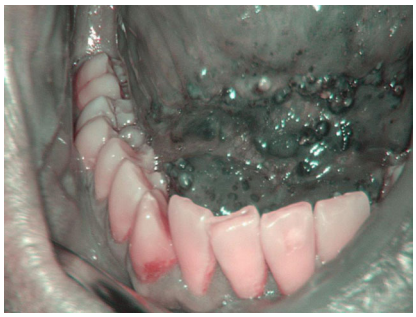

Fig. 3 ▲ HPV-associated mucosal changes with papillary capillary loops in the floor of the mouth. *Red color* indicates dental plaque

Vascular changes, epithelial thickening, and the associated developments of leukoplakia can be detected at an early precancerous stage.

» Small lesions are much more easily detected with NBI compared to white light

NBI allows keratotic lesions to be optimally assessed owing to their shape, their surface structure, and their location in the region, as detailed information can be gleaned about the character of the lesion. This leads to a reliable intraoperative assessment of surgical margins. If the surgical margin is free from blood after the tumor resection, e. g., as it is following laser treatment, it can be assessed again in the patient and extracorporeally in the specimen. Subepithelial vessels can also be better contrasted and a more differentiated evaluation of their form and paths can be made. Differential diagnostic decisions can thereby be optimized.

In the case of carcinomas of the oral cavity and oropharynx (◘ **Figs. 3 and 4**), Piazza reports the following rates for sensitivity, specificity, positive and negative predictive value, and accuracy of HDTV and WL endoscopy: 51, 100, 100, 87, and 68%, respectively. In HDTV technology combined with NBI technology, the values are, by contrast, 96, 100, 100, 93, and 97%, respectively [8].

Kraft et al. [9] showed that in the detection of laryngeal carcinomas (◘ **Figs. 5a–f, 6 and 7**) and their precursor lesions, NBI in combination with WL

endoscopy had a significantly higher sensitivity of 97% vs. 79% and an accuracy of 97% vs. 90% compared with WL alone. In contrast, the specificity was virtually the same for both imaging techniques at 96% vs. 95%.

Takano et al. [10] examined the aforementioned IPCL patterns in precancerous and cancerous lesions of the oral cavity with NBI endoscopy, and confirmed the specific IPCL types and their changes as the tumor develops. Chu et al. [11] stress the high efficacy, especially in the early detection of oral squamous cell carcinomas. Therefore, in the patient group examined by means of NBI the authors found a higher incidence (18 vs. 9%, $p = 0.037$) and a less advanced stage (4 vs. 37%, $p = 0.0005$) of secondary tumors than in the group without NBI use. Fewer patients also required postoperative adjuvant therapy (12 vs. 50%, $p = 0.0005$).

Wang et al. explored the benefits of the technique for the examination of carcinomas of the nose and nasopharynx [12]. Nasal and nasopharyngeal endoscopy in combination with NBI is a fast, convenient, and highly reliable screening method for at-risk patients. Ho et al. [13] report that NBI is able to differentiate between malignant and benign tumors within the scope of nasopharyngoscopy (**Fig. 8**). The sensitivity, specificity, and positive predictive and negative predictive value of NBI in the nasopharynx were 78.0%, 95.5%, 97.0%, and 70.0%, respectively.

Combination with other procedures

In an outpatient setting, NBI can easily be carried out in the same examination using normal WL endoscopy. The user can switch between WL and NBI mode at the press of a button on the camera head, without changing the position of the endoscope in the patient. This enables direct comparison and provides the user with a detailed examination of the structures of interest, so that an impression can be made by combining various imaging results.

Compared with rigid endoscopy, the combination with flexible endoscopy allows for a more detailed and comprehensive examination of the entire aerodigestive tract in a single examination, with close organ proximity and simultaneous documentation.

Compact endoscopy is another effective and practical combination, i. e., the intraoperative coordinated application of NBI and contact endoscopy [3, 14]. Contact endoscopy is a minimally invasive optical technique in which a special, rigid endoscope is applied directly with light pressure to the mucosal membranes. At 60–150 times magnification (**Fig. 9**), high-resolution images of the examined area can be shown in real time and in vivo. The cellular structure and the vessels can also be assessed in detail with contact endoscopy [15]. In combination with NBI, a unique detailed view of the vascular structure is achieved, where changes are an important aspect of the differential diagnosis in the examination of potential degeneration processes.

» Compact endoscopy encompasses Narrow Band Imaging and contact endoscopy

The consideration of intraoperative surgical margins in tumor surgery plays an important role in both local and locoregional follow-up [16]. Contact endoscopy is therefore particularly suited to the examination of malignant changes [17] and the assessment of their surgical margins.

The significant reduction in the superficially positive surgical margins dramatically reduces the number of patients at risk of relapse. Garofolo et al. [18] therefore highlight the importance of complete tumor removal during primary surgery by creating free surgical margins in healthy tissue. This is ensured with the preoperative and intraoperative use of HDTV and NBI. Piazza [19] also highlights the greater diagnostic accuracy and the avoidance of tissue manipulation and staining.

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Abstract

The various stages of tumor growth are characterized by typical epithelial, vascular, and secondary connective tissue changes. Narrow Band Imaging (NBI) endoscopy is a minimally invasive imaging technique that presents vascular structures in particular at a higher contrast than white light endoscopy alone. In combination with high-resolution image recording and reproduction (high-definition television, HDTV; ultra-high definition, 4K), progress has been made in otolaryngological differential diagnostics, both pre- and intraoperatively. This progress represents an important step toward a so-called optical biopsy. Flexible endoscopy in combination with NBI allows for a detailed assessment of areas of the upper aerodigestive tract that are difficult to assess by rigid endoscopy. Papillomas along with precancerous and cancerous lesions are characterized by epithelial and connective tissue changes as well as by typical perpendicular vascular changes. Systematic use of NBI is recommended in the differential diagnosis of malignant lesions of the upper aerodigestive tract. NBI also offers a significant improvement in the pre- and intraoperative assessment of superficial resection margins. In particular, the combination of NBI and contact endoscopy (compact endoscopy) facilitates excellent therapeutic decisions during tumor surgery. Intraoperative determination of resection margins at an unprecedented precision is possible. In addition, assessment of the form and extent of the perpendicular vessel loops stimulated by epithelial signaling enables differential diagnostic decisions to be made, approximating our goal of an optical biopsy.

Keywords

Endoscopy · Precancerous and Cancerous Lesions · Narrow Band Imaging · Vascular lesions · Compact endoscopy · Optical biopsy

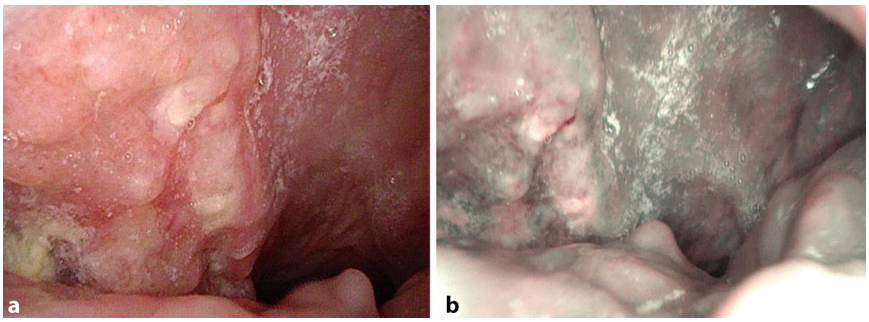

Fig. 4 ▲ Right-sided oropharyngeal carcinoma. Vascular types and marginal epithelial thickening clearly visible. **a** white light (WL), **b** NBI

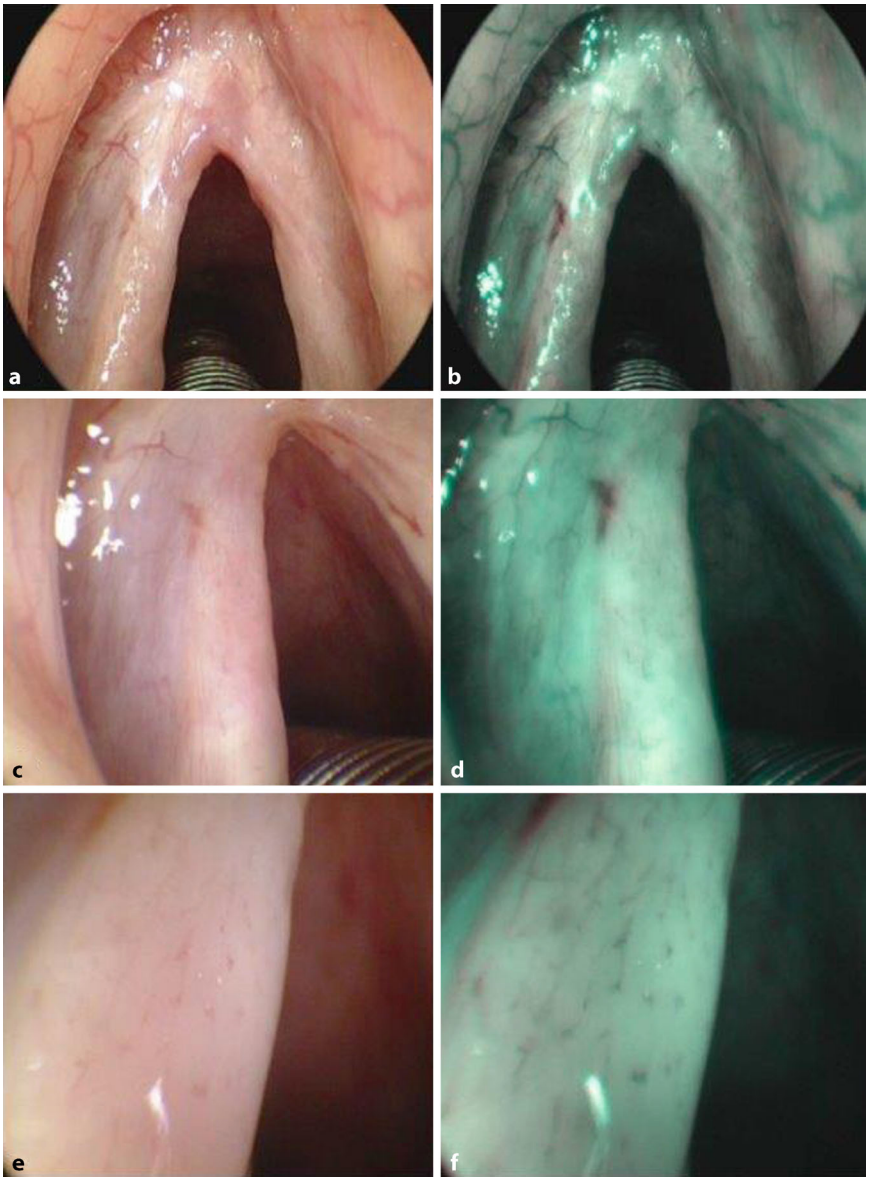

Fig. 5 ▲ Recurrence of a carcinoma in situ in the left vocal fold in, e. g., bilateral cordectomy type I. Increasingly large and with greater resolution of the vocal cord *from top to bottom*. Irregular capillary loops, still symmetrically arranged. **a**,**c**,**e** WL, **b**,**d**,**f** NBI

Epithelial, vascular, and connective tissue changes

New endoscopic methods and techniques have improved the endoscopic diagnosis of epithelial lesions in the region of the upper aerodigestive tract.

Thin, nonkeratinizing squamous cells initially allow for a good endoscopic visibility of the fine vascular lesions during the development of precancerous or cancerous lesions.

During the NBI endoscopy, an epithelial defect or ulceration can generally be clearly delineated by the bright red color change from the regular green color of the surrounding tissue with epithelial coverage. In the NBI examination, an epithelial thickening is primarily evident in the dark green appearance compared with the pink–green color in the normal epithelium. This development is continued with the development of what is known as leukoplakia, which contains the fluorophore keratin that thus lights up bright white in remittent light. The color of the leukoplakia, as the name itself suggests, means that the lesions tend to look whiter, and these therefore camouflage the underlying vessels with what is known as the "umbrella effect." The leukoplakia in itself is only a term used to describe the epithelial changes from hyperkeratosis to squamous cell carcinoma.

When leukoplakia starts to develop, it is still transparent and has sharp and regular margins. It develops concentrically in a round or oval form and generally has a homogeneous, smooth surface.

As it becomes cancerous, these epithelial changes take on a more irregular form and have irregular margins. The surface is also inhomogeneous and patchy in areas. With carcinoma in situ and in microinvasive carcinomas, the leukoplakia has a patchy appearance and is often combined with atypical vascular changes. From here, epithelial stimuli (epithelial signaling) are sent from the basal cell layer of the multilayer nonkeratinized squamous epithelium to the underlying connective tissue and vascular network. The increased metabolic activity of the tumor cell group in the region of the basal epithelial cells and the local hypoxia and hypoglycemia lead to an

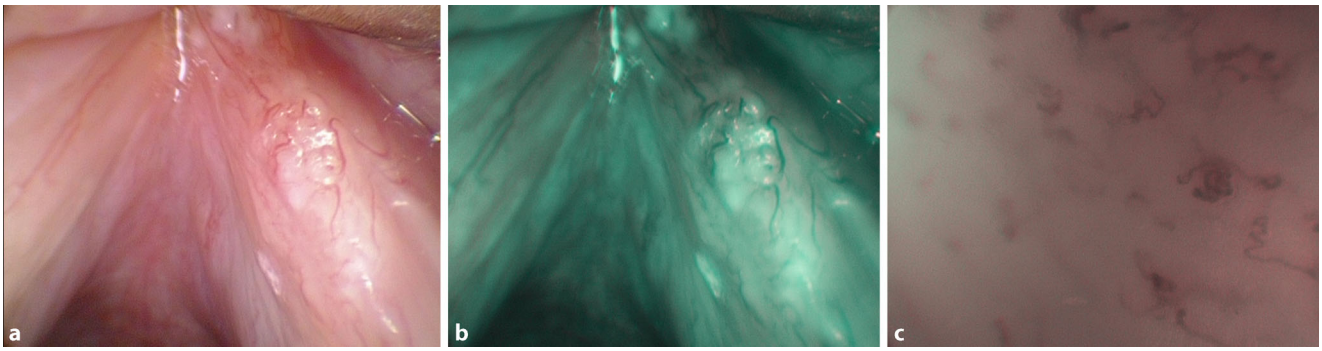

Fig. 6 ▲ Right-sided T1a vocal cord carcinoma. **a** WL, **b** NBI, **c** contact endoscopy with NBI

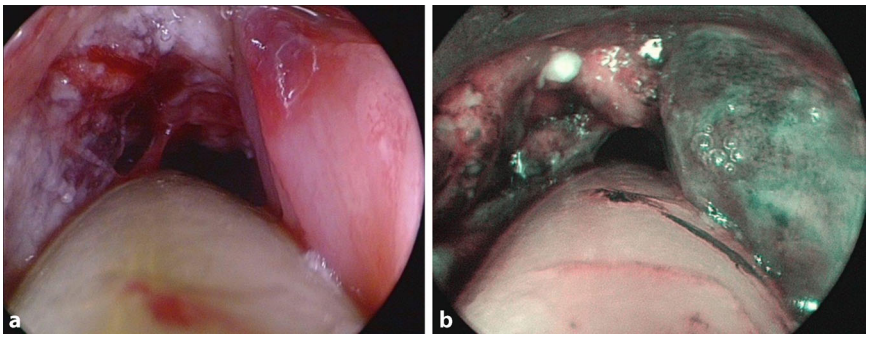

Fig. 7 ▲ pT4 laryngeal carcinoma. Left vocal cord ulcerated and irregular shaped, right vocal cord with edematous thickening. **a** WL, **b** NBI

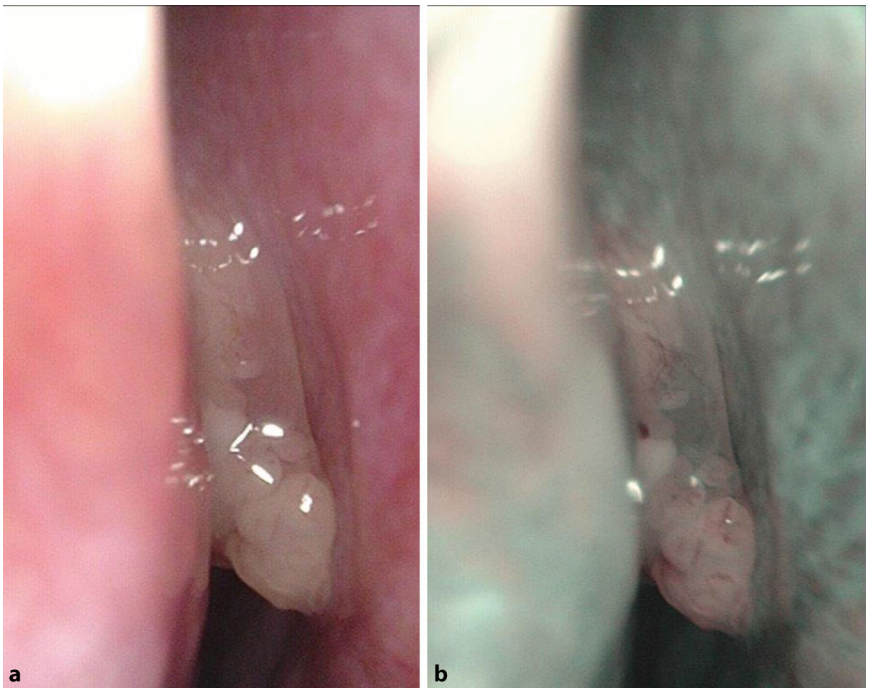

Fig. 8 ▲ Inverted papilloma clamped between the middle turbinate concha and the septum in the right main nasal cavity. Capillary loops in the NBI image are more clearly evident. **a** WL, **b** NBI

increased release of "vascular endothelial growth factor"(VEGF), of hypoxia-induced factors (HIF), and interleukin [1]. As a result of these signals, capillary loops form in combination with the connective tissue in the direction of the stimulus.

There are two different groups of vascular changes: longitudinal and perpendicular. While longitudinal vascular changes are primarily a response to mechanical stress, with the aforementioned stimuli of the epithelium, perpendicular vascular lesions can develop as a result of continued hypoxia, mechanical, chemical, or other external stress factors.

Kumagai et al. [20] found that characteristic vascular changes provide information on the infiltration depth of tumors. These can be especially clearly imaged with NBI.

Ni et al. [21] used WL and NBI images to apply the IPCL model to categorize vascular changes in the esophagus in the classification of precancerous and cancerous lesions in the vocal cords. The IPCL classification has mainly been used to date for endoscopic diagnosis in gastroenterology [22, 23]. The IPCL classification, however, has several drawbacks, which means it cannot be easily applied to all regions of the upper aerodigestive tract. For example, the term "papillary loops" is used incorrectly, as the regular larynx does not necessary have papillary capillary loops. They can, however, be regularly found in the oral cavity and in the pharynx in healthy mucosal membranes (**Fig. 10**).

Perpendicular vascular changes are characterized by the development of IPCL [24]. These typical changes can be very well identified in the case of recur-

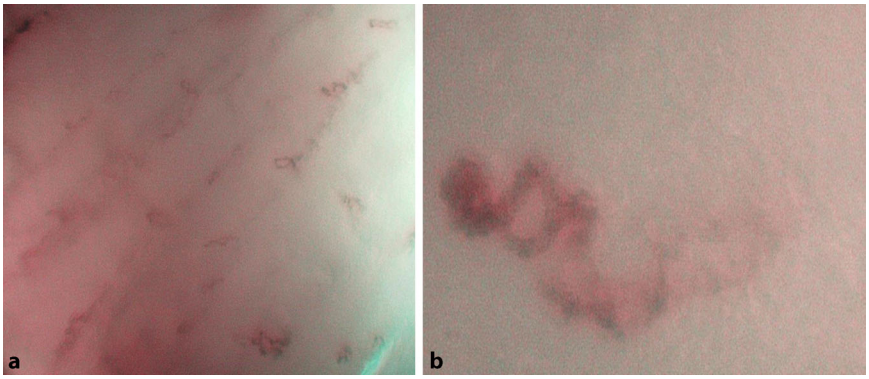

Fig. 9 ▲ Recurrence of a carcinoma in situ of the left vocal cord following bilateral cordectomy. Atypical capillary loops in the compact endoscopy. **a** 60:1 magnification, **b** 150:1 magnification

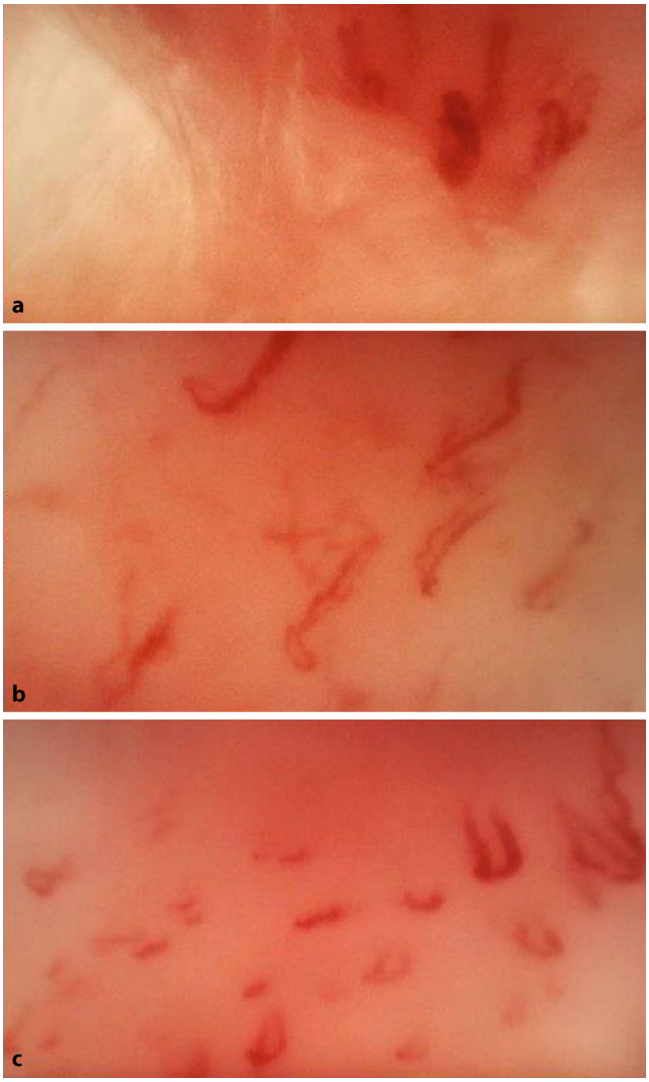

Fig. 10 ◀ NBI and contact endoscopy on the top of the tongue. Regular capillary loops (150:1 magnification). **a,b** Regularly arranged, longitudinal capillary loops in the upper lip (150:1 magnification). **c** Symmetrically arranged capillary loops of the hard palate (150:1 magnification). **b, c** No visible epithelial thickening

rent respiratory papillomatosis (RRP), especially with NBI. [25].

With RRP, the capillary loops can be confirmed as embedded in the typical three-dimensional warty structure by means of endoscopy. They represent the cusp of the vascular loop below the epithelium, which rises from the deeper layers of the mucosal membrane. Unlike precancerous lesions, these capillary loops are symmetrical and point-like. Not only the vessels, however, but also the surrounding tissue is changed by the epithelial stimulus. Typical warty changes develop with RRP. These features, like the central capillary loop in each morula-like bulge, generally help to differentiate the papilloma from more severe dysplasia or a squamous cell carcinoma.

The capillary loops develop irregularly as the cancer develops

Squamous cell carcinomas can also be caused by high-risk HPV infections [26]. Both Lukes et al. [27] and Tjon Pian Gi et al. [25] highlight that changes in the IPCL and the epithelial surface are essential for the differential diagnosis of endoscopic imaging of recurrent respiratory papillomatosis (**Fig. 11**). As it very clearly shows the vascular structure, NBI allows possible degeneration processes of RRP to be detected early.

When the epithelium becomes dysplastic, leukoplakia has an increasingly irregular form and distention. Longitudinal vascular changes, such as ectasias, also develop into perpendicular vascular changes. Capillary loops, too, can be endoscopically detected in the periphery of leukoplakia changes, appearing as small adjacent points. These points also represent the cusps of the capillary loops under the epithelium. Initially, the loops still appear in a regular symmetrical arrangement. As the cancer develops, the vascular loops and the epithelial changes become completely irregular. The irregular tumor surface and the form are caused by vascular malnutrition secondary to chaotic neoangiogenesis.

Outlook

NBI is a practical and effective imaging technique in the upper aerodigestive tract, especially in combination with HD- and 4K-Imaging. NBI is particularly suitable for the early diagnosis of papillomas as well as precancerous and cancerous lesions [19, 21, 28], as the typical trio of features of epithelial tumors – namely, vascular, epithelial, and connective tissue changes – can be especially well imaged with NBI and lead to a clear differential

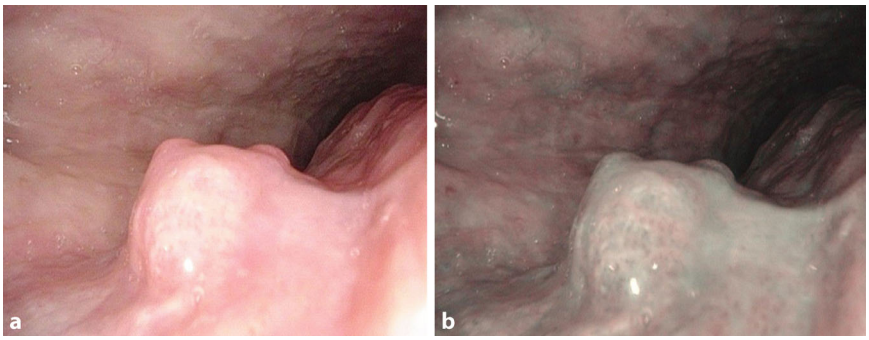

Fig. 11 ▲ Papilloma on the back of the velum. **a** WL, **b** NBI

diagnosis. Vascular changes are playing an increasing and significant role in endoscopic diagnosis of lesions of the upper aerodigestive tract.

The combined intraoperative use of contact endoscopy and NBI (compact endoscopy) in HD quality in particular allows for an extraordinarily differentiated view of the horizontal and vertical vascular changes to the upper aerodigestive tract.

NBI, as an efficient endoscopic imaging procedure in the context of both flexible and rigid endoscopy, thereby presents an important technological stage toward optical biopsy.

Conclusion for clinical practice

- **NBI can be a practical option in the diagnosis and therapy of pathological changes in the upper aerodigestive tract.**
- **Smaller lesions in particular, generally characterized by vascular changes, can be detected much earlier than with WL.**
- **Contact endoscopy allows for an excellent assessment of capillary loops.**
- **NBI can also be used intraoperatively in the context of papilloma or tumor surgery to detect superficial surgical margins.**

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Funding. The supplement containing this article is not sponsored by industry.

Compliance with ethical guidelines

Conflict of interest. C. Arens, C. Betz, M. Kraft, and S. Voigt-Zimmermann declare that they have no competing interests.

This article does not contain any studies with human participants or animals performed by any of the authors.

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