Narrow band imaging in endoscopic evaluation of the larynx

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Purpose of review
Narrow band imaging (NBI) is a novel endoscopic technique using filtered wavelengths in order to enhance the microvascular abnormalities associated with the preneoplastic and neoplastic changes of the mucosal lining of the upper aerodigestive tract. The present review is focused on the use of NBI in the management of patients with laryngeal cancer.

Recent findings
The larynx and hypopharynx represent an ideal site for NBI application because their thin, nonkeratinized, stratified squamous epithelium permits optimal visualization of the subtle neoangiogenic changes associated with precancerous and neoplastic diseases, including benign processes like recurrent respiratory papillomatosis. These abnormal vascular patterns have been recently described in great detail and demonstrated to be useful diagnostic tools in different settings of laryngeal cancer management: from preoperative diagnosis and staging to intraoperative evaluation of microsurgical margins and posttreatment follow-up. Particularly intriguing is the capacity of NBI to properly distinguish postactinic changes from persistent/recurrent disease.

Summary
From different institutions in several countries, NBI continues to receive confirmations of its validity as an ancillary diagnostic tool for endoscopic evaluation of oncologic patients. This also holds true for laryngeal and hypopharyngeal neoplastic diseases.

Keywords
cancer, diagnosis, larynx, narrow band imaging, surveillance

INTRODUCTION

Narrow band imaging (NBI) is the last member in the family of the 'biologic endoscopy' techniques, a common umbrella that includes different diagnostic tools, some first described more than 40 years ago (such as toluidine blue staining), whereas others (e.g., autofluorescence and confocal microendoscopy) have been developed more recently [1▪]. Different from standard white light endoscopy, which simply observes the macroscopic appearance of mucosal lesions, biologic endoscopy techniques provide deeper insight into the behaviour of a target lesion (to obtain a so-called 'optical biopsy') and allow visualization of lesions that are not otherwise visible. Even though the gold standard for definition of the nature of a lesion remains histopathologic examination of a formalin-fixed, paraffin-embedded tissue sample, biologic endoscopy attempts to reduce the number of unnecessary biopsies, and minimize the number of false negatives. Moreover, it allows a more comprehensive surveillance of patients at high risk for developing mucosal lesions of the upper aerodigestive tract (UADT) and permits earlier detection of lesions that might be overlooked with classic white light evaluation.

NBI represents a conceptual revolution in the biologic endoscopy field because its main focus is not on evaluation of the neoplasm itself, but on its vascularization. By addressing the neoangiogenic patterns inside and surrounding a target lesion, NBI can effectively overcome most of the limits described for supravital stains and autofluorescence,

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KEY POINTS

- NBI is a novel endoscopic technique that uses filtered light to enhance the neoangiogenic patterns associated with preneoplastic and cancerous mucosal lesions of the UADT.
- The larynx and hypopharynx have a thin, nonkeratinized, stratified squamous epithelium that renders observation by NBI of these microvascular abnormalities easy and reliable.
- Well known patterns of distribution, density and shape of the IPCLs as identified by NBI have been associated with definite histopathologic diagnosis; these have been demonstrated to be useful tools for preoperative, intraoperative and postoperative evaluation of patients affected by laryngeal cancer and, more recently, RRP.

with a significant reduction in the number of false positives. The growing interest among the international scientific community as well as the increasing number of articles confirming its validity in the endoscopic evaluation of head and neck mucosal tumours make NBI a promising tool in the diagnostic work-up and follow-up of laryngeal neoplasms.

The aim of the present review is to summarize the most recent findings regarding NBI in the evaluation of laryngeal cancer patients.

NARROW BAND IMAGING PHYSICAL BASIS AND EQUIPMENT

From a technical point of view, NBI applies narrowband spectrum filters to enhance the visualization of mucosal and submucosal microvascular patterns, based on the principle that light has different depths of penetration depending on its wavelength. NBI filters select, from the whole spectrum of white light, only the blue and green lights (wavelengths of 415 and 540 nm, respectively), corresponding to the peaks of absorption of haemoglobin. These filtered wavelengths penetrate the superficial layers of mucosa, thus highlighting, without the use of dyes, the capillary network and deeper levels by enhancing the submucosal vessels. In this way, small superficial lesions, otherwise missed by conventional white light endoscopy, are revealed by the enhanced contrast with the surrounding tissues due to their increased vascularity and specific neoangiogenic patterns inside and surrounding them.

Passing from white light to NBI mode is easy and fast, with just the switch of a button on the videoendoscope, videocamera or monitor console. This manoeuvre can be repeated several times during the same examination, without significant prolongation of the examination itself. By switching another dedicated button, the endoscopist may also zoom on a specific area, thus performing a magnifying NBI endoscopy.

Apart from transnasal videoendoscopes of different sizes, NBI cameras may also be applied to rigid 0° and angled telescopes in order to evaluate the larynx both under local and general anaesthesia. Additionally, optimal image definition for both conventional white light and NBI endoscopy is achieved using a High Definition Television (HDTV) camera, which gives 1080 lines of resolution, thus allowing a signal definition that is 4.26 times better than standard endoscopy [2]. This has been quite recently made possible also for flexible transnasal videoendoscopes with an outer diameter of 2.6 mm only.

NARROW BAND IMAGING VASCULAR PATTERNS

NBI is aimed at early evaluation of specific neoangiogenic patterns suggestive for premalignant or neoplastic lesions. These are typically considered the presence of well demarcated brownish or darker areas in a context of green–blue appearing normal mucosa, with scattered thick dark spots, increased microvascular density, and winding or earthworm-like vessels in the form of abnormal intraepithelial papillary capillary loops (IPCL). The presence of afferent hypertrophic vessels pointing like a finger towards the lesion itself and branching out in vascular loops adds further elements to this endoscopic scenario [3–7].

In their well designed study, Lin *et al.* [8▪▪] recently demonstrated how 'thick dark spots' within a well demarcated brownish area with proliferation of dilated and abnormal IPCLs, universally considered as an NBI hallmark of epithelial precancerous or neoplastic evolution [9], are not equally observed throughout the entire UADT. In fact, such NBI findings are typical of areas in which a nonkeratinized, thin, stratified squamous epithelium is found. Lin *et al.*, in fact, observed a statistically significant correlation between the NBI diagnosis of Tis-T1 based on the presence of 'thick dark spots' located in anatomical areas with such an epithelium (namely, floor of the mouth, ventral tongue, soft palate, tonsillar pillars, palatine tonsil, base of tongue, posterior oropharyngeal wall, epiglottis, vocal folds, and hypopharynx). Lymphoid hyperplasia may obscure these early endoscopic findings in the palatine tonsil, base of tongue, and nasopharynx especially in case of very superficial intraepithelial lesions. Other UADT sites are covered by keratinized, thick, stratified squamous epithelium (including gingiva, hard palate, vermilion border,

and dorsal surface of the tongue) or nonkeratinized, very thick, stratified squamous epithelium (such as retromolar trigon, labial, and buccal mucosa). In such locations, 'dark spots' may be initially masked by the thickness of the epithelium itself (up to five times thicker than that of nonkeratinized, thin lining).

One of the most comprehensive descriptions of the different NBI vascular patterns that can be observed in the larynx has been recently published by Ni *et al.* [10▪▪]. These authors performed an interesting study on 104 laryngeal lesions (45 benign and 59 malignant), correlating the NBI appearance of the morphological changes of the IPCLs with definitive histopathologic diagnosis. They observed that polyps invariably present IPCLs that are almost invisible (type I pattern), similar to those observed in laryngitis, in which only enlargement of oblique and arborescent vessels is usually detectable (type II). Squamous cell hyperplasia and mild dysplasia can present a benign vascular architecture that may be partially obscured by keratotic plaques (type III). When IPCLs become clearly visible, but with a regular arrangement and low density (type IV), definitive diagnosis can range from squamous cell hyperplasia to mild and moderate dysplasia. In contrast, in type V patterns the IPCLs are significantly dilated, of high density, with speckled features and various shapes (type Va), partially destroyed with an earthworm appearance (type Vb), or associated with necrotic tissue and with an even more bizarre distribution (type Vc). Type V patterns have been associated with invasive carcinoma in 84% of patients, the remainder being mild-to-severe dysplasia. However, types Vb and Vc are associated with a definitive diagnosis of invasive cancer in 100% of cases. In conclusion, the authors found a sensitivity, specificity, positive, negative predictive value and accuracy for NBI in making a correct diagnosis based on such neoangiogenic patterns of 89, 93, 91, 92 and 90%, respectively. These rates were statistically higher than those observed after white light evaluation with respect to sensitivity, negative predictive value and accuracy.

CURRENT LARYNGEAL NARROW BAND IMAGING APPLICATIONS

Watanabe *et al.* [7] first reported that the use of NBI in the assessment of 34 patients suspected of having cancer of the larynx led to early detection of abnormal microvascular changes, and was also useful in distinguishing between low-grade and high-grade dysplasias (with a sensitivity and specificity of 91 and 92%, respectively). Our group recently published an update of the University of Brescia experience concerning NBI results in UADT cancer evaluation, clearly demonstrating how this endoscopic technique can play a number of ancillary functions in laryngeal cancer management: during preoperative diagnostic work-up (in order to get a so-called 'optical biopsy' of an already-visible target, and to evaluate the presence of synchronous head and neck mucosal lesions at an earlier stage than that observable under standard white light); in the intraoperative setting (to better evaluate the superficial peripheral extension of a lesion, refining the planned microsurgical laser resection); during posttreatment follow-up (to precociously detect any persistent/recurrent disease and to allow early detection of metachronous lesions of the UADT) [11▪]. In particular, among 347 patients affected by laryngeal and/or hypopharyngeal squamous cell carcinoma, evaluated by NBI either in the preoperative and intraoperative setting or during posttreatment follow-up, we observed an overall diagnostic gain of 21% true-positive adjunctive information in respect to what was visible by white light standard endoscopy. This was in terms of preoperative or intraoperative tumour category upstaging (33 patients), change in planning of surgical resection due to different evaluation of superficial surgical margins during laser resection (13 patients), synchronous tumours detection (two cases) and, during posttreatment surveillance, early diagnosis of persistences/recurrences (22 patients) and metachronous lesions (four cases) [11▪]. Noteworthy, these results were obtained having HDTV usable only in conjunction to rigid 0° and angled telescopes, whereas NBI flexible transnasal videoendoscopes were at that time only non-HDTV resolution. Even better results can, therefore, be expected by applying the HDTV-NBI 2.6 mm diameter flexible transnasal videoendoscopes currently available.

Interestingly, NBI maintains its high sensitivity and specificity even after radiotherapy or chemoradiation. In another study from our group [12], we demonstrated that, after an adequate learning curve, postactinic changes might be reliably distinguished from persistences/recurrences, leading to a comparable (if not minor) number of false positives to that observed in patients followed-up for surgery alone. In fact, type II, III and IV IPCL patterns according to the classification by Ni *et al.* [10▪▪] may be frequently associated to postradiotherapic inflammation, but are easily distinguished from the type V pattern (pathognomonic of persistence or recurrence). Especially after laryngeal organ preservation protocols, this translates into a minor number of unjustified (and risky) biopsies in the search for recurrent disease. Our results are in agreement with those of Nonaka *et al.* [13] who found

that although IPCLs can be modified by postactinic inflammation, it is generally possible to distinguish these from those of neoplastic lesions based on their poorly defined margins and relatively low density. Therefore, even after radiation or chemoradiation, NBI maintains extremely high values of sensitivity, specificity, positive, negative predictive value and accuracy (100, 98, 92, 100 and 98%, respectively) [12]. Our results are also in agreement with those reported by Lin *et al.* [14] concluding that prior radiotherapy apparently does not affect the detection of recurrent or second tumours in the UADT. These authors also observed a statistically higher accuracy of NBI in respect to white light endoscopy for detection of second tumours in the oropharynx (100 vs. 69%) and hypopharynx (100 vs. 39%), especially when considering precancerous lesions and carcinoma *in situ*, whereas they failed to demonstrate superiority of NBI in oral cavity evaluation.

One of the last applications of NBI in laryngology is for diagnosis and transoral management of recurrent respiratory papillomatosis (RRP) [15,16]. In this context, wart-like lesions of the laryngeal mucosa can be easily identified by NBI, thanks to the specific arrangements of the vessels inside the papilloma. Particularly intriguing are the results presented by Tjon Pian Gi *et al.* [15] who prospectively applied this endoscopic tool in 14 patients affected by RRP, evaluating them first by conventional white light and then by NBI. The latter allowed identification of 13 more lesions than white light, and 85% of them were found to be true positives after excisional biopsy and histopathological examination. Therefore, sensitivity of the RRP diagnostic work-up increased from 80% with white light alone to 97% by adding NBI (such a difference turned out to be statistically significant).

NARROW BAND IMAGING ADVANTAGES AND DISADVANTAGES

NBI, especially when coupled to magnifying endoscopy and HDTV, has definite advantages compared to all other biologic endoscopy techniques. It is easy and fast, does not need adjunctive staining or further preparation of the patient and does not cause any discomfort. It has a superb resolution in terms of details and looks at the microvascular architecture inside and surrounding a given mucosal area more than at the specific morphology of the lesion itself. In this sense, it requires a change of mind in the endoscopist and surgeon who use this tool, which requires specific training and a definite learning curve. Especially at the beginning, NBI can lead to an increased number of unjustified biopsies in false-positive pictures.

Minor limitations, observed in every other endoscopic manoeuvre, are related to mucosal bleeding (which renders the endoscopic field extremely dark, thus losing the information on subtle microvascular patterns), sticky mucus, debris or saliva sometimes covering the mucosal surface of the UADT. Moreover, NBI provides information regarding the superficial, two-dimensional extent of the lesion, and is unable to provide insight into the deep extension of tumour due to limitations in depth of penetration. Not every UADT region is equally suited to examination by NBI in the search for abnormal microvascular patterns. However, the thin, nonkeratinized stratified squamous epithelium covering the vast majority of the larynx and hypopharynx makes these organs the ideal targets of such an endoscopic technique.

CONCLUSION

NBI is gradually emerging as an interesting biologic endoscopy technique for pretreatment and post-treatment evaluation of laryngeal and hypopharyngeal cancers, and in the search for synchronous lesions. Recent applications in other laryngeal diseases like RRP will probably expand its future role in laryngology. Its high diagnostic accuracy, favourable cost-effectiveness ratio and absence of adjunctive discomfort for patients make it an attractive diagnostic tool.

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Conflicts of interest

The authors declare that this manuscript was conceived and written by the cited authors, they do not have to disclose financial information, and they confirm no conflict of interest concerning this manuscript.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 541).

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