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Clinical experience of narrow band imaging (NBI) usage in diagnosis of laryngeal lesions

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
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ABSTRACT:

Introduction: One of the most recent methods used in imaging of the larynx is NBI. NBI allows to detect specific patterns of pathological angiogenesis suggestive of premalignant or neoplastic lesions.

Aim: The aim of the study was to compare imaging of laryngeal lesions in WLE and NBI in relation to histopathological examination.

Material and methods: 333 patients with laryngeal lesions underwent endoscopic evaluation in WLE and NBI. Sensitivity, specificity, PPV, NPV for both methods were calculated. The diagnostic value for WLE and NBI was evaluated for two assumptions: a positive result indicates (1) severe dysplasia and cancer, or (2) only cancer.

Results: Sensitivity, specificity, PPV, NPV for the first assumption were, respectively for white light compared to NBI: 95.4% vs 98.5%; 84.2% vs 98.5%; 79.6% vs 97.7% and 96.6% vs 99.0%. The values for the second assumption were: 97.4% vs 100%; 79.3% vs 93.5%; 72.6% vs 89.4% and 98.2% vs 100.0%. Higher sensitivity was observed for the second assumption, while higher specificity was recorded for the first assumption. Specificity was significantly higher for NBI than for WLE ($p < 0.001$).

Conclusions: NBI allows to detect and differentiate laryngeal lesions, which are invisible in WLE. Endoscopic examination, especially in NBI mode, is non-invasive, repeatable and remains a useful tool in the daily practice and diagnosis of patients with pathological lesions in the larynx.

KEYWORDS: laryngeal cancer, narrow band imaging, premalignant laryngeal lesions, white light endoscopy

ABBREVIATION

NBI – Narrow Band Imaging
NPV – Negative Predictive Value
PPV – Positive Predictive Value
WLE – White Light Endoscopy

INTRODUCTION

Endoscopic examination is commonly used in the diagnosis of laryngeal diseases, which makes it possible to visualize it more accurately and to archive images in comparison to mirror examination. However, currently available diagnostic tools, including endoscopic techniques, are not sufficient to unequivocally assess the observed pathologies of the laryngeal mucosa and to differentiate early neoplastic lesions or the extent of tumor infiltration.

In recent years, WLE may be supplemented with NBI. The NBI technique is based on taking advantage of differences in the light-absorbing properties of blood and mucosa. Thanks to the filters used, only blue and green light are emitted, with a wavelength of 415 and 540 nm, respectively. They coincide with the peak of absorption through hemoglobin, and thus: a wavelength of 415 nm penetrates into the capillaries of the mucosa, making them visible in brown. In contrast, the 540 nm wavelength reaches the submucosal vessels and dyes them in cyan. This allows an accurate assessment of the vascularization of the lesion. Considering the fact that the requirement for tumor growth above 1–2 mm^3 is the creation of its own network of vessels, characterized by chaotic architecture, significantly different in shape and size from normal vessels, this method allows the detection of pathological changes at a very early stage of carcinogenesis [1, 2, 3]. Muto et al. (2005) were the first to employ the NBI technique to assess the pharynx and upper gastrointestinal tract in the follow-up examination of patients after treatment of esophageal cancer [4]. Watanabe et al. began using this method to assess the larynx in 2009 [5]. In recent years, NBI has been used to diagnose changes in the mucosa of the upper aerodigestive tract and reproductive system [4, 5, 6]. In 2011, Ni et al. proposed a classification which, due to the assessment of mucosal vascularization in NBI, enables the prognosis of histological diagnosis of the lesion. Pathologies qualified for

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types I–IV were considered benign, and for types Va-c suspected of tumor growth. On this basis, it is possible to predict early the occurrence of neoplastic transformation within the laryngeal lesion, already at the stage of the clinical examination, and – as a consequence - to plan further treatment [7, 8, 9, 10].

AIM

The aim of the study was to compare the diagnostic value of white light and narrow band endoscopy in the assessment of pathological changes in the laryngeal mucosa in relation to histopathological examination.

MATERIAL AND METHOD

The study included 333 patients diagnosed at the Otolaryngology, Head and Neck Oncology Clinic of the Medical University in Lodz who met the following inclusion criteria: presence of hypertrophic lesion in the larynx, possibility of performing and archiving a full video-endoscopic examination of the larynx in white light and NBI, surgical treatment and obtaining the result of the histopathological examination of the laryngeal lesions. Exclusion criteria were disqualification from laryngoscopy under general anesthesia, lack of possibility to perform endoscopic examination of the larynx, submucosal lesions. Patients who had a malignant tumor other than squamous cell carcinoma in histopathological examination were also eliminated from the study. The study design was approved by the Bioethics Committee at the Medical University in Lodz (consent No. RNN/165/17/EC).

After local anesthesia of the nasal and pharyngeal mucosa with 1% lidocaine, all patients underwent white light endoscopic examination. The observed changes were classified as benign (polyp, Reinke edema, vocal nodules, cysts), suspicious (chronic hypertrophic laryngitis, leukoplakia, erythroplakia, papilloma) and malignant (tuberous or infiltrative lesions clinically, arousing serious suspicion of cancer). This was followed by an examination using NBI, and the identified changes were assigned to types I–V according to the classification of Ni et al. (2011). All patients with pathological changes in WLE and/or NBI examination were qualified for direct laryngoscopy for removal or biopsy of hypertrophic lesions and histopathological verification. The results of the assessment of the nature of the change in the WLE examination were compared with the results of NBI, followed by the results of histopathological tests. The sensitivity, specificity, PPV and NPV of both methods were calculated for the assumptions that the positive result is severe dysplasia and cancer, and only cancer. The results for WLE and NBI were then compared using McNemar's test. To assess the compatibility of WLE and NBI results, as well as endoscopic examination using both methods with histopathological results, Cohen's Kappa coefficients were calculated. Statistica 13.1 software (Statsoft, Tulsa) was used for statistical analysis. P values <0.05 were considered statistically significant.

RESULTS

Comparison of results of evaluation in WLE with the results of histopathological examination are presented in Tab. I.

Of the 175 lesions identified as benign in WLE, the histopathological examination confirmed in most cases the benign nature of the lesion, while in 16 cases histopathological examination showed at least dysplasia, including 6 patients with severe dysplasia or cancer.

In 41 patients, laryngeal lesions were considered suspicious in WLE. In this group, leukoplakia was the most prevalent (N = 19; 46.3%). This pathology is difficult to clearly assess and interpret in clinical examination due to the inability to assess lesions under hyperkeratotic plaque. In 18 (44%) patients, benign lesions (chronic inflammation or hyperplasia) were diagnosed in the histopathological examination, in 10 patients (24.3%) – mild or moderate dysplasia, and in 13 remaining cases (31.7%) – severe dyplasia or cancer.

In 112 out of 117 (95.7%) cases qualified as malignant, squamous cell carcinoma was confirmed in histopathological examination. A further 2 patients were diagnosed with mild and moderate dysplasia. In contrast, the remaining 3 patients had epithelial hyperlasia.

Comparison of the results of assessment in NBI mode with the results of histopathological examination is presented in Tab. II. Of the 173 lesions considered benign in NBI, in most cases (N = 168; 97.1%) histological examination confirmed chronic inflammation or epithelial hyperplasia. However, in 5 patients (2.9%) histopathological examination showed at least dysplasia, including 1 patient with severe dysplasia. It should be noted that in no case classified as benign in NBI was cancer diagnosed by histopathological examination.

In 28 patients, laryngeal lesions were considered suspected in NBI. In 35.7% (10 patients), benign lesions (chronic inflammation or hyperplasia) were diagnosed in histopathological examination, in 60.7% (17 patients) – mild or moderate dysplasia, and in 3.6% (1 patient) – severe dysplasia.

In the group of lesions considered suspicious in NBI, papillary hyperplasia was found in 25%, in which the perpendicular course of vessels was difficult to differentiate with intrapapillary capillary loops within precancerous and cancerous lesions.

In NBI, 132 cases were classified as malignant. Histopathological examination in 129 of these patients confirmed squamous cell carcinoma (97.7%). One patient was diagnosed with moderate dysplasia, the other two with papillary hyperplasia.

The test characteristics for the above assumptions are presented in Tab. III. Sensitivity, PPV and NPV were shown to be higher for NBI compared to WLE for both variants. In addition, in both assumptions a significantly higher NBI specificity was found compared to WLE in the differentiation of pathological changes of the laryngeal mucosa ($p < 0.001$).

The NBI sensitivity and specificity for two assumptions were high. An increase in sensitivity was observed as the group of positive results narrowed. For the variant assuming that the positive result is cancer, 100% sensitivity was achieved. This means that with NBI, no cancer was omitted in the evaluation of the larynx in the study group. On the other hand, a higher specificity (98.5%) of the method

Fig. 1. Images from fiberoscopic examination in white light and NBI (Patient AW, 61 years old). In white light endoscopic examination an uneven edge of the right vocal fold was found. In NBI, apart from the uneven surface of the right vocal fold, planar mucosal lesions with irregular endothelial vessel loops are visible, corresponding to the grade Va according to Ni et al. (2011), covering the right supraglottic area from the level of the vocal fold. Histopathological examination revealed severe dysplasia.

Tab. I. Comparison of the results of the assessment of pathological changes in the laryngeal mucosa in white light with the results of histopathological examination: Kappa with Quadratic Weighting 0.87 (95%CI: 0.84–0.90) (WLE).

		HISTOPATHOLOGY			
		Chronic inflammation/Hyperplasia	Mild dysplasia/Moderate dysplasia	Severe dysplasia or invasive cancer	Overall
WLE	Benign lesions	159	10	6	175 (52,55%)
	Suspicious lesions	18	10	13	41 (12,31%)
	Malignant lesions	3	2	112	117 (35,14%)
	Overall	180 (54,05%)	22 (6,60%)	131 (39,35%)	333 (100%)

was observed when it was assumed that the positive result indicates severe dysplasia and cancer. High usefulness of NBI has been demonstrated compared to white light endoscopy due to visualization of filtered pathological vessels within the laryngeal mucosa (Fig. 1.).

DISCUSSION

The presented results indicate that NBI has greater clinical usefulness than WLE in the diagnosis of cancer and precancerous lesions of the larynx. They are based in the literature, although studies evaluating the importance of NBI in the assessment of the mucosa of the upper aerodigestive tract are difficult to compare with each other. The authors use different protocols to evaluate the mucosa and different classifications of pathological changes. In the authors' own research, the approach proposed by Cosway et al. was used, who recommend a preliminary assessment of the mucosal surface in white light mode on the downward pass of the flexible fiberscope [11]. Subsequently, on the upward pass of the endoscope, the mucosa should be assessed in NBI mode. They suggest switching to NBI mode when a change in WLE is identified, and respectively to WLE mode if pathology is found when assessed in NBI. This technique allows the assessment of changes in both WLE and NBI.

The use of different imaging classifications evaluating morphology of mucosal capillaries with NBI is controversial. The criteria, which are most commonly used are those set by Ni et al. (I–IV – benign, Va–c – malignant). Their usefulness has been supported, among others, by Bertino et al. (2015) and Kraft et al. (2016) [8, 9]. On the other hand, the scale according to Ni et al. is considered to be complicated, with a time-consuming and subjective analysis. Therefore, attempts are being made to create new classifications that are easier in everyday practice; however, their usefulness has not yet been confirmed by more extensive research [7, 12, 13]. In the authors' own work, the classification according to Ni et al. (2011) and the division of lesions of the larynx into 3 groups following Vilaseca et al. (2017) have been employed: I–III – benign, IV – suspicious, Va–Vc – malignant.

Usually, the recognition of benign lesions is not difficult in clinical evaluation both with the use of WLE and NBI. Similarly, the diagnosis of tuberous or infiltrative changes suggesting a serious suspicion of cancer usually raises no doubt. The most significant differences relate to changes classified as suspicious in own research and assessed as leukoplakia and papillomas. Some authors classify them as benign [10, 14] and others as suspected of exhibiting cancerous growth [8, 9, 15]. In the present study, both leukoplakia and adult-type papillomas were incorporated in the group of suspected lesions due to the inclusion of these clinical conditions as precancerous lesions, according to the WHO classification [16]. The above approach is confirmed by the results of the authors' research, in which, in the group of lesions of the laryngeal mucosa considered suspected in WLE (N = 41), 46.3% were cases of leukoplakia (N = 19). Due to the inability to assess the vessels under the hyperkeratotic plaque, this pathology is a change difficult to unambiguously assess and interpret also in a clinical study using NBI. Appropriate

Tab. II. Comparison of the results of the assessment of pathological changes in the larynx mucosa in NBI with the results of histopathological examination: Kappa with Quadratic Weighting 0.95 (95%CI: 0.94–0.97).

		HISTOPATHOLOGY			
		Chronic inflammation/Hyperplasia	Mild dysplasia/Moderate dysplasia	Severe dysplasia or invasive cancer	Overall
NBI Scale acc. to Ni et al. (2011)	Benign lesions (I–III)	168	4	1	173 (51,95%)
	Suspicious lesions (IV)	10	17	1	28 (8,41%)
	Malignant lesions (V)	2	1	129	132 (39,64%)
	Overall	180 (54,05%)	22 (6,60%)	131 (39,35%)	333 (100%)

Tab. III. Sensitivity, specificity, PPV, NPV in the assessment of pathological changes in the larynx in white light and NBI, respectively for two assumptions, that the positive result indicates: (1) severe dysplasia and cancer, and (2) only cancer, in the studied group of patients (N = 333).

	ASSUMPTION 1		ASSUMPTION 2	
	WLE	NBI	WLE	NBI
Sensitivity	95.4%	98.5%	97.4%,	100%
Specificity	84.2%	98.5%	79.3%	93.5%
PPV	79.6%	97.7%	72.6 %	89.4%
NPV	96.6%	99,0%	98.2%	100 %

qualification for papillary hyperplasia creates similar diagnostic difficulties. In the present study, papillomas were found in histological examination in 25% of the group of lesions considered suspicious in NBI; perpendicular vasculature is often observed in papillomas, which is difficult to differentiate from endothelial vascular loops within precancerous and neoplastic lesions. Often, these changes may be incorrectly classified as cancerous growth.

In the present study, the pathological changes in the laryngeal mucosa were adopted in histopathological terms, in accordance with the 2005 WHO histological classification [17]. Various classifications of histopathological studies are provided in the literature. Bertino et al. (2015) classified severe dysplasia, carcinoma in situ and cancer as cancerous lesions [8]. In turn, they considered mild to moderate dysplasia as precancerous lesions. Kraft et al. (2015) and Vilaseca et al. (2017) considered moderate, severe dysplasia and cancer to be positive results, which is consistent with the assumptions of the new unified 2017 WHO histological classification of laryngeal changes [9, 16, 18, 19]. Ni et al. (2011) divided the changes of the laryngeal mucosa into three groups: a) malignant (carcinoma in situ, invasive cancer), b) precancerous (squamous hyperplasia, mild, moderate or severe dysplasia) and c) benign (polyps and chronic laryngitis) [10].

Statistical analysis of the examined group of patients showed higher sensitivity and significantly higher specificity of NBI in differentiating benign and malignant lesions compared to WLE. This is supported by studies of Vilaseca et al. [19] who found that for cancer, moderate and severe dysplasia sensitivity and specificity were: 90%, 49% in WLE and 90%, 78% in NBI. Kraft et al. (2015) recorded sensitivity and specificity for WLE 79%, 95% and 97%, 96% for NBI [9]. Bertino et al. (2015) obtained results similar to own results for NBI sensitivity and specificity (97.4%, 84.6%, respectively) [8]. In their study, the sensitivity of WLE was 98.7% while the specificity was surprisingly low – 3.3%. The authors explain this by the fact that they considered any leukoplakia, erythroplakia as well as hypertrophic and ulcerative lesions to be malignant. As a consequence, the percentage of false positive results was as high as 35.5%. For this reason, in the present study the clinical division of mucosal lesions into three groups, isolating a group of suspicious lesions, was employed. In this group, we included pathologies with a clinically ambiguous character and these causing the greatest diagnostic difficulties, i.e. most often leukoplakia and papillomas; in histopathological examination, severe dysplasia or cancer was diagnosed in about ⅓ of cases in this group. Particularly important is the fact that due to the use of NBI, the group of suspicious lesions decreased by about 30% (41 suspected cases in WLE vs 28 in NBI). It follows that narrow band imaging makes it possible to clarify the clinical picture of the pathological change of the larynx mucosa as well as allows to draw conclusions about the histopathological nature with higher probability, and as a consequence – qualify for appropriate therapeutic management.

In the present research, for the purpose of in-depth statistical analysis, two assumptions were made differing in the definition of a positive result. Higher NBI sensitivity (100%) was found for the assumption in which only cancer was a positive result. This means that with NBI no cancer was missed. Assuming that severe dysplasia and cancer are positive results, both sensitivity and specificity have reached a very high level of 98.5%. This is evidence of the possibility for almost faultless isolation of benign lesions, with the use of narrow band imaging endoscopy. It follows that NBI allows the exclusion of healthy patients from further diagnostics, and thus constitutes a good screening method. Therefore, changes that do not raise suspicion of tumor growth in NBI can be monitored without qualifying patients for unnecessary surgical procedures during which they could be exposed to additional damage to the laryngeal structures.

CONCLUSIONS

1. NBI allows the recognition of pathological changes in the larynx, which are non-visible in white light;

2. Higher sensitivity and statistically significantly higher specificity of the NBI assessment compared to white light endoscopy in differentiating benign and neoplastic changes of the larynx was revealed;

3. Endoscopic examination, especially enhanced with the NBI technique, is a non-invasive, repeatable method and remains a highly useful tool in the daily diagnosis of patients with pathological laryngeal lesions. However, the histopathological assessment remains the deciding examination.

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