

# Comparative evaluation of the diagnostic value of biopsy and NBI endoscopy in patients with cancer of the hypopharynx and larynx

## Authors' Contribution:

A – Study Design  
B – Data Collection  
C – Statistical Analysis  
D – Data Interpretation  
E – Manuscript Preparation  
F – Literature Search  
G – Funds Collection

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## ABSTRACT:

**Introduction:** Novel endoscopic technique – Narrow Band Imaging (NBI) seems to be a promising method for an early detection of neoplastic lesions of the upper aerodigestive tract. Compared to white light endoscopy, NBI improves the visualisation of the mucosal and submucosal microvascular patterns of observed pathologies. The aim of the study was to evaluate the diagnostic value of biopsy and NBI in patients with cancer of the larynx and hypopharynx.

**Material and methods:** The study was conducted in 100 adult subjects hospitalized in the Clinic of Otolaryngology, Laryngological Oncology, Audiology and Phoniatics of Military Medical Academy University Teaching Hospital in Lodz, who were planned for surgical procedures for excision or surgical biopsy of pathological lesions of the hypopharynx or larynx. The following examinations were performed: subjective and objective, otorhinolaryngological, NBI endoscopy and histopathological assessment of suspicious lesions. The microvascular pattern of observed lesions was assessed according to the Ni scale criteria. The next stage of the study was to compare the endoscopic examination results (type of vascular pattern according to the Ni scale) with the histopathological result. The obtained results were subjected to statistical analysis.

**Results:** The sensitivity of NBI endoscopy in detection of malignant neoplasms in patients with hypopharynx and larynx lesions is 90.48%, specificity – 91.14%, positive predictive value – 73.08%, negative predictive value – 97.30%.

**Conclusions:** NBI endoscopy is a modern imaging method, increasing the diagnostic potential of endoscopy in the early detection of malignant lesions within the hypopharynx and larynx.

## KEYWORDS:

hypopharynx carcinoma, larynx carcinoma, NBI

## INTRODUCTION

Head and neck cancers still remain a current issue as well as a diagnostic and therapeutic challenge. More than 850 thousand cancers of this area are diagnosed every year in the world. Most cases, that is over 350 thousand, concern the oral cavity and the lips. Subsequent places of the list are taken by larynx, oropharynx, hypopharynx and salivary glands [1]. In Europe, the incidence rate of head and neck cancer is 10.8 per 100 000 persons [2]. Despite the promotion of a healthy lifestyle, the incidence rate remains at a similar level. In developed countries there is a change of patient profile – an increasing percentage of patients are young people, often in reproductive age [3]. This is caused by a growing number of human papillomavirus (HPV) infections which, according to the latest reports, is the third most frequent cause of neoplastic transformation in the head and neck region, especially in the area of oropharynx [4]. The symptoms of head and neck cancer are uncharacteristic and often of little concern to patients, who may delay medical consultation. Late diagnosis of malignant changes translates into poor prognosis. Early diagnosis of these lesions could change the unfavourable statistics regarding the treatment of head and neck cancer.

One of the most popular diagnostic methods in otolaryngological practice is endoscopic examination. During the examination, the doctor can easily assess the location of the suspicious lesion and its relation to individual anatomical structures. Additional information about the nature of suspicious changes is provided by endoscopy with the use of Narrow Band Imaging (NBI).

It allows to trace the course of vascularisation of the described lesion and its location within the suspected area (e.g., swollen, changed mucosa), and thus determine whether the lesion may be malignant [5]. Traditional endoscopy is useful in the diagnosis of typical, often advanced pathological changes in the mucosa of the oral cavity, throat and larynx, but it shows limitations in relation to superficial, small neoplastic lesions [6]. Endoscopy with the use of Narrow Band Imaging is based on the modification of spectral properties of wave beam with the use of a special filter placed in the optical system. This filter selectively lets through green and blue light acquiring beams with wavelengths of 400–430 nm (targeted 415 nm) and 525–555 nm (targeted 540 nm) [7, 8]. The longer the wavelength, the deeper it will penetrate into the tissues.

The appearance of a suspicious lesion differs depending on whether it is examined in white light or NBI (Fig. 1.). As first, the size of change and its location should be assessed, which can be done during white light endoscopy. After turning on the NBI light we focus only on the analysis of appearance and blood vessels patterns, as well as the visible margin of the lesion [9]. Wavelength of 415 nm penetrates into the capillaries of the mucosa and contrasts them with a brownish colour, while a wavelength of 540 nm penetrates into the vessels of the submucosa and colours them using cyan (grey-blue) colour [10]. Moreover, thanks to the High-Definition Television (HDTV) technology that is provided for cameras of certain endoscopes, we are able to acquire a high resolution image that is about 4 times better compared to standard endoscopy [11].

The appearance of lesions determined in NBI as malignant is described as the presence of well-limited dark areas that contain places of increased neovascularisation with irregular, scattered vessels [12]. It is assumed that the presence of at least one hypertrophic vessel arranging in the shape of small loops or suddenly ending in close vicinity of the suspicious change is an indicator of malignancy [13]. In order to organise those quite subjective images, Ni et al. [14] created a classification of lesions on the basis of examinations conducted on 104 suspicious lesions of the larynx.

- Type I – found mainly in mild lesions (polyps) – incorrect blood vessels are almost unnoticeable;
- Type II – describes the expansion of oblique and arborescent vessels with enlarged diameter; they are easy to notice;
- Type III – hypertrophic epithelial cells partially make it impossible to assess the architecture of vessels;
- Type IV – abnormal intraepithelial capillary loops are easy to notice but are characterised by an organised and regular image with low density. The changes described above include both squamous hyperplasia as well as high- and low-grade dysplasia;
- V type – abnormal intraepithelial capillary loops are visibly expanded, with high density; they are arranged in Va – spotted, various shapes; Vb – partially destroyed ‘worm-like’ vessels; Vc – the surface of the lesion is covered with necrotic tissue and the vessels are irregularly scattered on the tumour surface.

## MATERIALS AND METHODS

Within the period from November 2016 to January 2019 there were qualified 100 people with hypertrophic lesions located in the area of hypopharynx or larynx. They were the patients hospitalised in the Department of Otolaryngology, Laryngological Oncology, Audiology and Phoniatrics of Military Medical Academy University Teaching Hospital in Lodz, who were scheduled for surgical procedures of removal or surgical biopsy of hypertrophic lesions of the hypopharynx or larynx. They expressed voluntary will and written consent to participate in the study.

After obtaining written consent, the following examinations were performed: subjective and physical examination, laryngological examination, endoscopic examination with the use of Narrow Band Imaging (NBI) and histopathological assessment. The endoscopic

examinations were performed in an isolated room equipped with Olympus-branded endoscope, model CV170 and were displayed on NDS ENDOVUE 90K0010 surgical monitor than archived by IRIS programme.

Vascularisation of pathological lesions was evaluated and qualified to specific groups according to the Ni scale criteria (type I–IV as a benign lesion, type V as a malignant lesion).

The next stage of the study was to compare the result of endoscopic examination (obtained type of vascularisation according to the Ni scale) with the result of histopathological assessment.

The acquired results were subjected to statistical analysis.

## STUDY RESULTS

The study was conducted on 100 adult patients with hypertrophic lesions located in the area of hypopharynx or larynx, aged 27 to 91 (mean age was 58.95 years), including 44 women and 56 men.

The mean age in the study group was 56.43 in women and 60.9 in men. The median age in the study group was 59 in women and 62 in men.

The type of vascularisation of lesions according to the Ni scale was as follows: Type I – 20% of cases, Type II – 23%, Type III – 19%, Type IV – 17%, Type Va – 9%, Type Vb – 3%, Type Vc – 9% (Fig. 2.).

The diagnostic values of NBI endoscopy in the detection of malignant neoplasms of hypopharynx and larynx appear as follows:

- Sensitivity – 90.48%,
- Specificity – 91.14%,
- Positive prediction value – 73.08%,
- Negative prediction value – 97.30%,
- The area under the curve – 96.67%.

## DISCUSSION

One of the solutions which will improve prognosis in head and neck cancers is an early diagnosis of lesions suspected of cancerous nature – preferably at the dysplasia stage. There is a need to search for the ideal screening method, which according to literature should be inexpensive, easy to conduct, safe and comfortable for patients, and above all have high sensitivity and specificity [15–16].

Comparing with other diagnostic methods used in otorhinolaryngology practice in the group at high risk of head and neck cancer, it has been assessed that Narrow Band Imaging endoscopy is fast, inexpensive and does not cause complications [17]. These criteria meet some of the requirements of an ideal screening diagnostic method.

During NBI endoscopy we acquire an immediate result which allows to undertake further diagnostic and therapeutic actions. In case of qualification for surgical biopsy, endoscopic examination

enables to localise the most suspected of cancerous process sites. On the other hand, regular follow-up examinations conducted among patients after treatment enable early detection of recurrence and determine the appropriate moment for a subsequent surgical biopsy. Therefore, this method contributes to the reduction of the number of biopsies and false negative histopathological results [18].

Valls-Mateus et al. [19] attempted to answer the question of what is the most difficult according to NBI endoscopy. They assessed the characteristic features for false positive and false negative diagnoses.

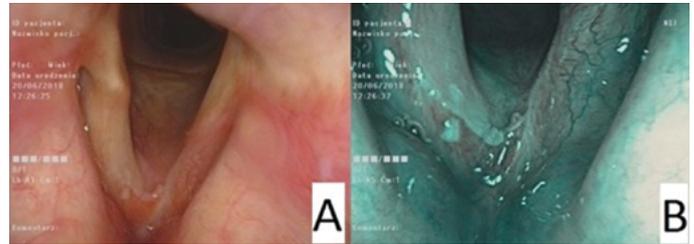
Rare laryngeal cancers do not have their own fixed vascular pattern characteristic for Narrow Band Imaging endoscopy. So far only Nonaka et al. [20] and Valls-Mateus et al. [19] have described sarcoma cases in NBI. It is a raised, well-vascularised lesion, which does not have characteristic capillary loops. In reference to the Ni scale, this description does not meet the criteria of type V (vascularisation confirming the malignant nature) and influences a false negative result.

In this study, undifferentiated squamous cell carcinoma of neuroendocrine origin was a false negative result. This is an extremely rare tumour, accounting for less than 1% of all laryngeal cancers [21]. One description of the appearance of the neuroendocrine tumour seen in NBI is given in the literature, concerning the lesion localised in the intestinal lumen [22] and in the area of the head and neck [19]. The authors have not observed any characteristic vascularisation that confirms the malignant nature of the lesion. These observations show that NBI endoscopy is of limited use in the diagnosis of rare cancers.

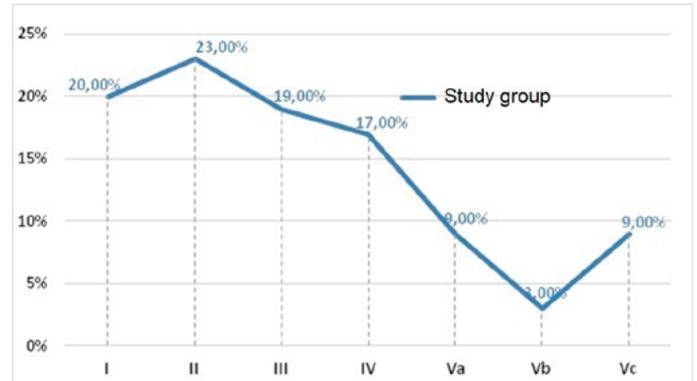
Similar situation concerns lymphoproliferative lesions. These cases concern mainly the gastrointestinal tract [23–25]. In otorhinolaryngology, only Valls-Mateus et al. [19] referred to this issue. According to them, lymphomas of the head and neck do not show any specific vascularisation available in NBI examination when compared to changes located in the gastrointestinal tract.

In this study one person was examined whose history and symptoms indicated the risk of lymphoproliferative process. The lesion visible in the NBI examination was localised in the hypopharynx and was characterised by a suspicious vascularisation similar to type IV according to the Ni scale criteria. However, the histopathological result excluded the malignant nature of the described lesion.

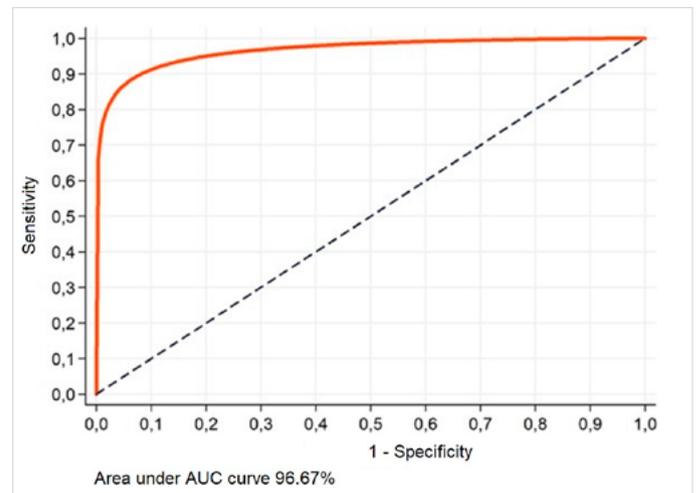
Another often encountered hypertrophic lesion, which is difficult to diagnose with the use of Narrow Band Imaging, are papillomas. The first reports on the use of NBI in the diagnosis of recurrent laryngeal papillomas were described by Tjong Pian Gi et al. [26]. It has been assessed that endoscopy with the use of Narrow Band Imaging is characterised by high sensitivity (97%) and low specificity (28%). This is caused by the fact that capillary loops that are visible during examination are quite similar to the vascularisation of malignant changes. Bertino et al. [27] describe laryngeal papillomas in NBI light as lesions with significantly dilated blood vessels, with high density and visible brown coloured areas of various shape. This description resembles the vascularisation pattern of Va type accord-



**Fig. 1.** Comparison of the image of pathological lesions in the right vocal fold in white light (A) and in NBI light (B). Fig. 1b. shows the clear boundaries of the lesion and its vascularisation. Fig. 1a. shows a pathological lesion, but it is not possible to precisely determine its range.



**Fig. 2.** Percentage distribution of perivascular type by Ni scale in the study group.



**Fig. 3.** Sensitivity and specificity of the application of endoscopy with the use of a narrow beam of NBI light in the detection of malignant neoplastic lesions in the group of subjects with hypertrophic lesions in the larynx and hypopharynx.

ing to the Ni scale criteria. Lukes et al. [28] provided useful information to help distinguish between papilloma and squamous cell carcinoma. They have determined that papillomas consist of papillary structures organised in various shapes which are characterised by a central vascularisation inside each one of them. Additionally, they have observed that the surface of a papilloma is smooth while the surface of squamous cancer is irregular with hyperkeratotic lesions. In order to determine this, a quite precise evaluation is necessary (the endoscope camera must be in close vicinity of the lesion). This is not always possible in patients under local anaesthesia in ambulatory care settings. In the presented study, the histopathological result confirmed the diagnosis of the papilloma in 9 patients. All these patients were qualified to type IV.

The appliance of Narrow Band Imaging endoscopy in patients suspected for recurrence after radiochemotherapy remains a contested issue. Studies published by Piazza et al. [29], Nonaka et al. [30] and Lin et al. [31] prove that NBI is an effective diagnostic method in distinguishing the difference between post-radiation changes and the relapse of a malignant neoplasm. On the other hand, in a study conducted by Zwakenberg et al. [32] 96% of patients have shown type IV or V according to the Ni scale despite the fact that histopathological examination has excluded the malignant nature of changes. The authors explain the acquired results with chronic changes occurring in the mucosa after radiochemotherapy treatment. The assessment of a subtle vascularisation pattern of pathological lesion in NBI is masked by a changed mucosa [33].

Piazza et al. [29] along with Lin et al. [31] have adopted the presence of well-limited brownish areas (similar to the ones occurring in type Va according to the Ni scale) as a criterion of malignance. Zwakenberg et al. [32] claim that twisted vessels with a regular course, low density and blurred border can be considered as the image of normal vascularisation in post-radiation tissues. Zabrodski et al. [33] remind that the macroscopic appearance of the described lesion is also important because the presence of ulcers or necrosis is characteristic for malignant neoplasms. The issue of vascularisation evaluation of pathologies in patients after radiotherapy requires further research. Two patients with hypertrophic laryngeal lesions who underwent surgery followed by radiotherapy were included in the study. During NBI endoscopy they were qualified as type IV according to the Ni scale criteria. These lesions showed abnormal vascularisation in the form of dilated and twisted capillary loops, but without brownish areas characteristic of type Va. Histopathological examination has confirmed the diagnosis of recurrent malignant

neoplasm in both of those patients. The cases described above prove the interpretation difficulties concerning NBI endoscopy in patients after radiotherapy.

In 2018, Zhou et al. [34] published a meta-analysis assessing the value of NBI endoscopy in the diagnosis of cancerous lesions of the head and neck area. Sensitivity is 88.5%, specificity 95.6%, area under the curve AUC 96.94%. Separating only cases of the larynx and hypopharynx, sensitivity equals 92.9% and specificity 97.5%. The results are similar to those obtained in this study (sensitivity – 90.48%, specificity – 91.14%, area under the curve AUC – 96.67%). The endoscope used to perform the examinations in the presented study was equipped with high-definition technology which, in reference to Zhou et al., has a positive influence on the sensitivity and specificity of the examination (91.6% vs 88.6%, 93.8% vs 88.6%).

To sum up, Narrow Band Imaging endoscopy is characterised by high sensitivity and high specificity which oscillate around 90%. The value of the area under the curve exceeding 90% indicates high clinical and practical usefulness of the diagnostic method.

## CONCLUSIONS

1. NBI endoscopy is a modern imaging method, increasing the diagnostic potential of endoscopy in the early detection of malignant lesions within the hypopharynx and larynx;
2. Narrow Band Imaging enables very reliable, safe and economically attractive differentiation of neoplastic, precancerous and inflammatory lesions from normal mucous membrane at various stages of diagnostics.

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