

# Modern diagnostics of early glottic cancer

## Współczesna diagnostyka wczesnego raka głośni

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**ABSTRACT:** This article is a review of literature and a summary of the current guidelines in the diagnosis of hypertrophic vocal folds lesions suspected of malignancy. It gives a detailed overview both of initial diagnosis, as well as the methods of in-depth intraoperative diagnostics and proposals for careful evaluation during post-treatment follow-up examinations.

**KEYWORDS:** diagnosis, dysplasia, endoscopy, glottic cancer

**STRESZCZENIE:** Niniejszy artykuł stanowi przegląd piśmiennictwa i podsumowanie aktualnych wytycznych w diagnostyce zmian przerostowych fałdów głosowych podejrzanych o złośliwy charakter. Szczegółowo omówiono zarówno etap wstępnej diagnostyki, jak również stosowane metody pogłębionej diagnostyki śródoperacyjnej i propozycje wnikliwej oceny w trakcie badań kontrolnych po leczeniu..

**SŁOWA KLUCZOWE:** diagnostyka, dysplazja, endoskopia, rak głośni

### ABBREVIATIONS

**CT** – computed tomography

**ELS** – European Laryngological Society

**HSDI** – high-speed digital imaging

**HSV** – high-speed videolaryngoscopy

**IPCL** – intrapapillary capillary loops

**MR** – magnetic resonance

**NBI** – Narrow Band Imaging

**SPIES** – Storz Professional Image Enhancement System

**VHI** – Voice Handicap Index

**VLS** – Videolaryngostroboscopy

**V-RQOL** – Voice-Related Quality of Life

or completely limit the functions of the vocal organ. For three decades, there has been a lack of improvement in overall survival for patients with advanced laryngeal cancer. Therefore, early detection and treatment of lesions are key to improving the survival rates in patients affected by this disease.

Early glottic carcinoma includes a fairly heterogeneous group of pathological changes of the vocal folds: from carcinoma *in situ* not exceeding the basal membrane, through lesions limited to one vocal fold without impairment of vocal fold mobility (T1a), as well as lesions involving both vocal folds, with or without anterior commissure involvement, without impaired mobility of both vocal folds (T1b) as well as selected lesions, including one additional anatomical structure of the larynx, apart from the vocal fold, without impaired mobility of both vocal folds (T2) (Fig. 1.).

The differential diagnosis of glottic lesions suspected of malignancy includes clinical pictures of chronic hypertrophic laryngitis, leukoplakia, and pachydermia.

Histopathology is the basis in the diagnosis of hypertrophic changes within the glottis. Nevertheless, the development of endoscopic technology now makes it possible to perform a thorough investigation already at the stage of preoperative diagnostics. It is likely that in the near future, due to the results of multidirectional research on the molecular profile of laryngeal cancer, the clinical assessment will be even more precise.

The current histopathological classification of laryngeal hypertrophic lesions includes, according to the latest recommendation

### INTRODUCTION

Among all the cancers of the upper respiratory tract, squamous cell carcinoma of the larynx is the most common. According to data provided by the National Cancer Registry, in 2017 there were over 2,200 new cases of laryngeal cancer diagnosed in Poland, and 1,500 people died of this disease [1]. Global data, presented by the *International Agency for Research on Cancer*, reported over 177,000 cases of laryngeal cancer in 2018 and predict a growing trend in the future [2].

Most invasive cancers develop on the basis of precancerous dysplastic lesions in the laryngeal epithelium due to exposure to irritants such as cigarette smoke and gastroesophageal reflux disease. Treatment of advanced stages of this cancer requires laryngeal resection or a combination of radiotherapy and chemotherapy, which significantly

of the World Health Organization from 2017, the following stages: lesions without dysplasia, low-grade dysplasia, high-grade dysplasia (including carcinoma in situ), invasive cancer [3]. The possibility of differentiating individual stages of histopathological advancement upon clinical evaluation would enable the implementation of targeted and effective treatment dedicated to specific stages. Of particular importance is the possibility of differentiating lesions without dysplasia and low-grade dysplasia, where surgical resection of lesions may be very limited, without significant implications for the function of the vocal folds.

The current progress in visualization methods has made it possible to significantly improve the accuracy of the differential diagnosis of organic laryngeal pathologies as early as the stage of clinical inspection.

This article aims to summarize the literature reviews of various diagnostic methods that are distinguished by a proven effectiveness in diagnosing early-stage laryngeal cancer. Furthermore, this paper highlights various stages in the diagnosis of this type of pathology, which is not limited to a thorough evaluation before the planned treatment, but also includes in-depth intraoperative evaluation and meaningful post-treatment follow-up for early detection of recurrence.

## PREOPERATIVE DIAGNOSTICS

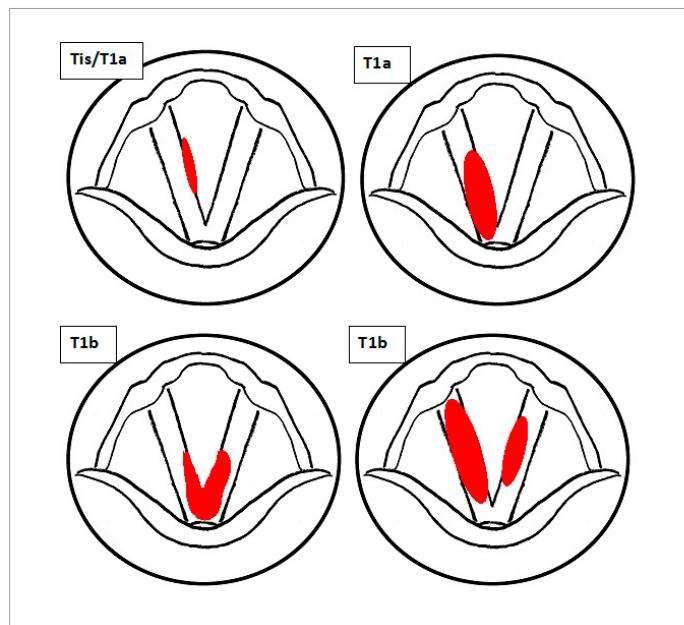
At this stage of clinical evaluation, it is most important for the practitioner to obtain answers regarding:

- the nature of the hypertrophic lesion (no dysplasia or low-grade dysplasia vs. high-grade dysplasia vs. invasive cancer),
- cancer staging (Tis/T1a/T1b/T2/T3),
- prognostic factors,
- voice/quality of life assessment.

Information obtained on the basis of a physical examination is most often very typical for all glottic hypertrophic lesions and therefore has a very low specificity in both differential diagnosis and staging. The patient is usually male in the sixth or seventh decade of life, with hoarseness, and often with a history of hypertrophic changes of the larynx and with chronic tobacco abuse.

Therefore, the standard for conduct in patients with glottic hyperplasia is a physical examination including laryngeal endoscopy. Due to the localization of changes in the vocal folds, apart from the evaluation of the anatomical structures of the larynx, the condition of the mucosa, the extent of pathological changes and the mobility of the vocal folds, it is also legitimate to evaluate the vibration dynamics of the vocal folds in a stroboscopic examination, which should take into account: the presence of mucosal wave, the type of glottic closure, simultaneity and amplitude of vocal fold vibrations.

In videolaryngostroboscopy (VLS) the most important functional parameter for the differential diagnosis of hypertrophic



**Fig. 1.** Examples of T stages for early glottic cancer.

changes in the vocal folds is the assessment of the mucosal wave in the vocal fold with the hypertrophic lesion. Normal vibration activity of the altered vocal fold mucosa is likely to exclude the presence of invasive cancer infiltrating the vocal ligament [4, 5]. The results of the systematic review and meta-analysis concerning the assessment of the diagnostic accuracy of VLS in the differentiation of early glottic cancer showed a high sensitivity of the method (86–100%), but a relatively low specificity in most of the publications included in the analysis (7–93%) [6]. VLS cannot be reliably used to classify the degree of laryngeal dysplasia, while the visualized reduced amplitude of vibration and altered vibration of the mucosal segment affected by the lesion turned out to be significant prognostic factors for recurrence after surgery and progression of dysplasia [7] (Fig. 2.).

Modern methods include high-speed digital imaging – HSDI, or high speed videolaryngoscopy – HSV which, unlike stroboscopic examination, record the actual frequency of vibrations of the vocal folds. The key benefit of these techniques is the ability to record vocal folds vibration in cases of severe dysphonia, including very brief or intermittent mucosal vibrations that may not be detected on VLS. Despite the steadily increasing number of publications on the usefulness of this method, the papers mainly focus on assessing functional changes in the larynx or benign glottic changes.

Based on a list of publications available in the literature by Mehllum et al., who analyze the diagnostic value of a lack of mucosal wave as a predictor of malignant lesion in the vocal fold, HSDI showed comparable sensitivity to VLS (85% and 83%, respectively), but lower specificity (19% and 34%, respectively) [8]. Also, Yamauchi et al., who analyzed the vibratory characteristics of the vocal fold mucosa with leukoplakia and early carcinoma in HSDI, presented results identifying segments without vibrations in 50% of laryngeal cancer and 8.3% of mild leukoplakia, emphasizing that they are comparable with stroboscopic results [9].

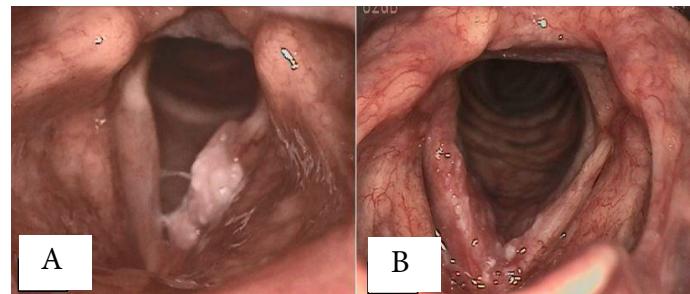
Currently, the recommended methods of diagnostic management in laryngeal hypertrophic changes include image-enhanced endoscopy. The main techniques are:

- *Narrow Band Imaging* (NBI®, Olympus, Tokyo, Japan),
- *Storz Professional Image Enhancement System* (SPIES®, Karl Storz, Tuttlingen, Germany).

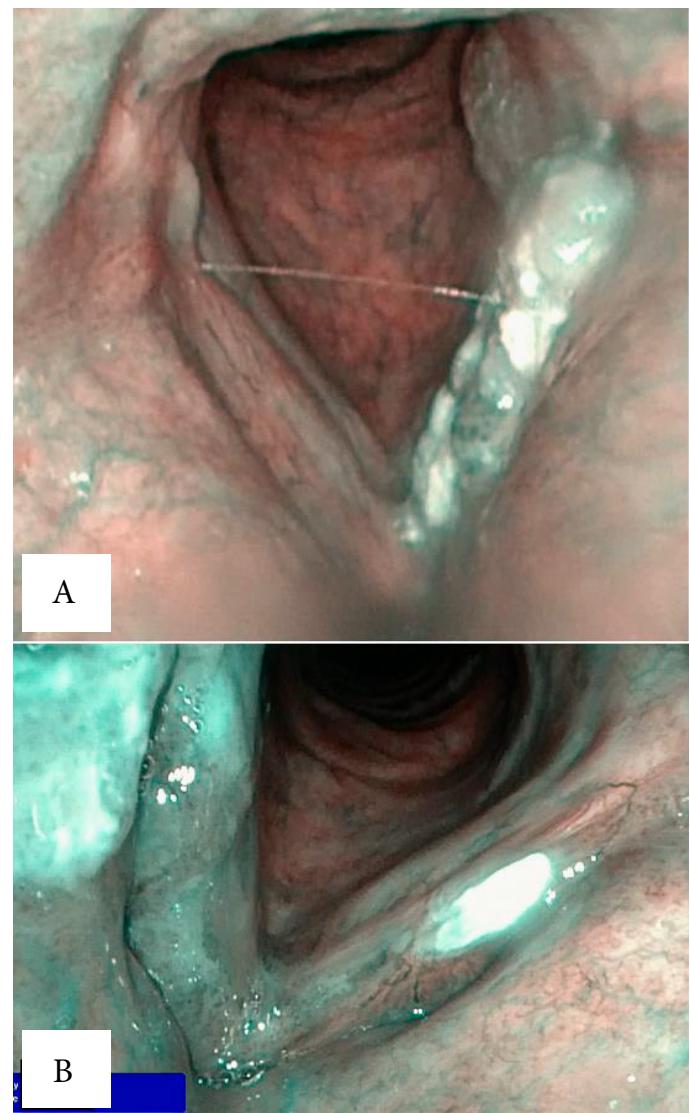
NBI technology uses filters to select the specific wavelengths – green and blue (respectively: 540 nm and 415 nm). These wavelengths correspond to the peak absorbance spectrums of hemoglobin and thus enable the visualization of the mucosal capillary network and the submucosal vessels. In 2011, Ni et al. proposed the classification of NBI vascular patterns in lesions of the laryngeal mucosa [10]. Identification of dilated vessels directing perpendicularly to the surface of the mucosa, referred to in the literature as intrapapillary capillary loops (IPCL), forms a basis for the differentiation of dysplastic and malignant lesions from benign. The available results from a meta-analysis evaluating the usefulness of the NBI in the identification of laryngeal cancer and including 29 publications, showed a significantly higher sensitivity, specificity and accuracy of NBI compared to white light endoscopy in the differential diagnosis of malignant lesions of the laryngeal mucosa [11]. The second most commonly used endoscopic system from Storz uses computer enhancement of color contrast in their imaging. Publications have confirmed the usefulness of the classification by Ni et al. with the assessment of vascular patterns of changes in the laryngeal mucosa also for this endoscopic method [12]. So far, only one study has compared the effectiveness of both methods – NBI and SPIES – in differentiating high-grade dysplasia and invasive laryngeal cancer from benign lesions, and no considerable differences were found for both methods [13] (Fig. 3.).

Enhanced image endoscopy now allows for a highly precise diagnosis of the nature of the hypertrophic glottic changes at the preoperative stage. Considering however both the different localization of lesions within the glottis as well as their extent, it should be noted that these methods do not allow to assess the depth of the infiltration. In certain situations, supplementary information can be obtained from the assessment of the vibratory function of the involved vocal fold [14]. Endoscopic findings revealing the extension to the anterior commissure and/or involvement of the whole width of the vocal fold are an indication for radiological imaging to precisely assess the advancement of the laryngeal lesions. In the case of anterior commissure involvement, radiological assessment includes: the evaluation of the thyroid cartilage infiltration, the preepiglottic space and extralaryngeal structures infiltration, while in the case of lesions covering the whole width of the vocal fold, it is important to assess the periglottic area, the spread into the laryngeal ventricle and to the subglottic region (Fig. 4., 5.).

The recommended method for radiological imaging of the larynx is computed tomography (CT). Some studies have shown that magnetic resonance imaging (MR), due to a higher resolution, is more sensitive than CT in the assessment of invasion in early laryngeal cancer, including the identification of cartilage

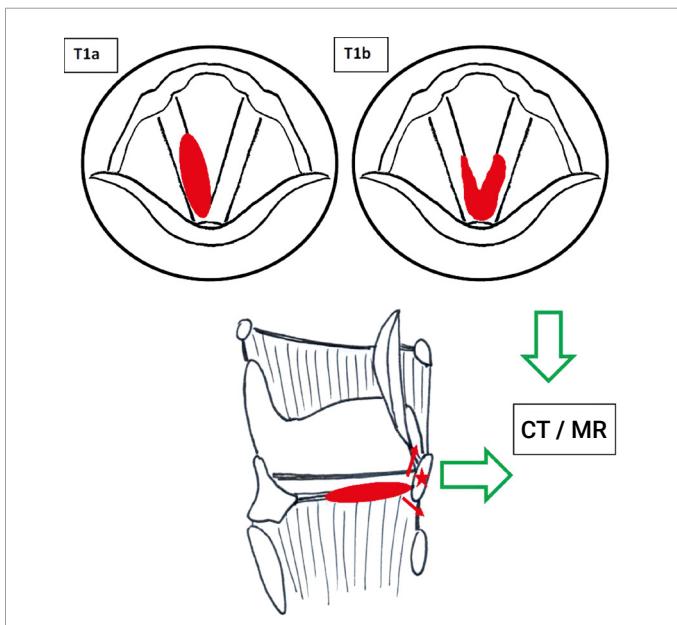


**Fig. 2.** Videolaryngostroboscopic images of early glottic cancer: T in situ of the left vocal fold with present mucosal wave in the segment with the lesion (A) and T1 with involvement of the right vocal fold and the anterior commissure, resulting in a lack of mucosal wave along the entire length of the right vocal fold (B).



**Fig. 3.** Narrow-band imaging in the detection of early glottic cancer: T1 tumor of the left vocal fold (A) and T2 tumor of the right vocal fold with infiltration of the vestibular fold (B); in both cases, a visible pathological pattern of vessels within the lesion with the presence of intrapapillary capillary loops type Va.

infiltration [15]. However, other authors are pointing that the diagnosis of cartilage invasion is overestimated in MR; this could be associated with incorrect assessment of the tumor-associated inflammation, which widens the margins of abnormal tissues [16]. The results of a recent systematic review assessing the usefulness

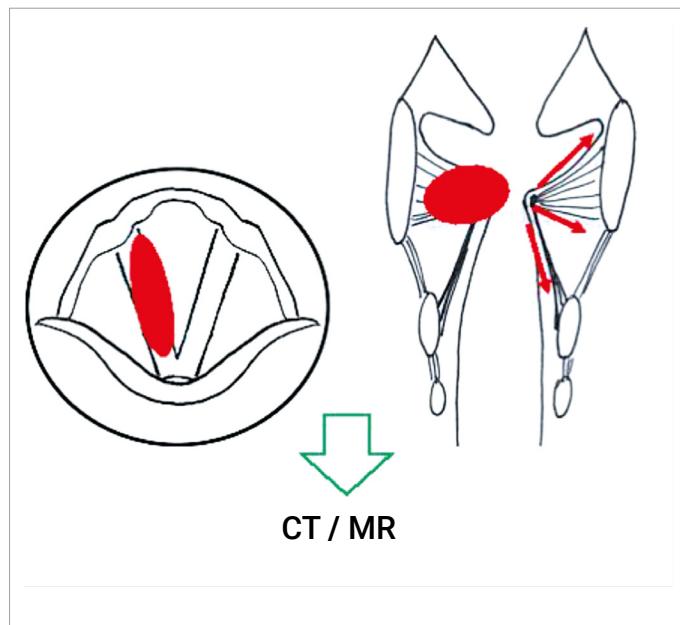


**Fig. 4.** Possible directions for the spread of infiltration in the presence of the laryngeal anterior commissure involvement.

of MR in the diagnosis of early glottic carcinoma show that the available data are heterogeneous, mainly based on the analysis of a small number of patients, and the reported MR protocols appear to be suboptimal for small laryngeal lesions [17]. With modern availability in day-to-day practice of various DICOM browsers, an interesting proposition is a checklist for the systematic assessment of the extent of malignant laryngeal lesions in CT and MR [18]. The authors recommend to use it especially before the planned treatment of intralaryngeal resection of early glottal carcinomas in order to optimize the surgical management strategy. It must be remembered that the European Laryngological Society (ELS) recommends a functional assessment of all patients with voice disorders before and after planned treatment in order to assess the effectiveness of therapy and compare treatment methods. Therefore, patients with early glottic cancer should also undergo a comprehensive voice quality assessment, regardless of the planned radical treatment method. The protocol for such an evaluation should include, in addition to VLS, perceptual assessment of voice, aerodynamic evaluation, acoustic parameters and the self-assessment of voice quality and / or quality of life based on the Voice Handicap Index (VHI) and Voice-Related Quality of Life (V-RQOL) questionnaires [19].

The assessment of the prognostic factors for recurrence-free survival and overall survival in patients with early laryngeal cancer is a vital aspect of diagnosis and may have an impact on the decisions regarding therapeutic management, the extent of therapeutic management and planning follow-up visits after treatment.

An age over 60, infiltration involving the anterior commissure of the larynx, a higher T stage, and low tumor differentiation are statistically significant factors worsening the long-term outcomes



**Fig. 5.** Possible directions of infiltration in lesions involving the whole width of the vocal fold.

[20, 21]. In the present, there are still no reliable tissue, serum or salivary markers that could be used in the screening of patients with hypertrophic changes of the larynx, the differential diagnosis of histopathological advancement or the assessment of the risk of recurrence after treatment.

## INTRAOPERATIVE DIAGNOSTICS

Surgical treatment of early glottic carcinoma is currently performed using methods of endolaryngeal microsurgery with the CO<sub>2</sub> laser. Before starting the resection, it is important to perform another intraoperative evaluation of the advancement of early glottic cancer with an operating microscope and by direct evaluation of the laryngeal tissues in directoscopy.

The accuracy of the assessed stage can be increased by using intraoperative endoscopic evaluation with image enhancement, which enables also a more precise resection planning while maintaining negative margins. In their systematic review of 5 studies, which analyzed the results of 577 patients treated with laser cordectomy, Campo et al. showed a substantial reduction in the percentage of positive margins using intraoperative NBI (28%) compared to white light endoscopy (52%) [22].

In turn, the infusion of saline into the subepithelial space of the vocal fold – *Saline infusion (SI)/Hydrodissection* is recommended for intraoperative assessment of the depth of infiltration of the vocal fold. The identification of the residual subepithelial space and the superficial lamina propria makes it possible to improve the precision of the microsurgical procedure [23].

The comparison of the usefulness of both methods for intraoperative confirmation of the malignancy of the laryngeal lesions showed

a higher sensitivity of image-enhanced endoscopy (58%) compared to saline infusion (32%). Subsequently, the subepithelial dissection had a higher specificity (87%) compared to endoscopic methods (76%) [8].

The evaluation of the radicality of surgical resection during laser microsurgery for laryngeal carcinoma is based on the assessment of margins in the intraoperative histopathological examination or a second microsurgery of the larynx 4–6 weeks after the first procedure (“second look”) in order to check and/or excise the scar in the case of close margin (< 2 mm). Both methods have supporters among researchers working on this topic. However, prospective studies assessing the advantage of one variant over the other are missing. The choice of a specific option depends on: the experience of a given center, organizational possibilities and the scheme of developed procedures.

## FOLLOW-UP AFTER TREATMENT OF EARLY GLOTTIC CANCER

Intralaryngeal resection of early glottic cancer spares the phonatory and respiratory functions of the larynx. The acceptable margin of resection of healthy tissue in this area is 2 mm, which is determined by the histological structure of the glottic region. However, to optimize oncological outcomes, there is a need for frequent and reliable patient follow-up with the use of accurate and precise diagnostic tools that enable early detection of local recurrence. The most frequently proposed schedules

for controls in patients after surgical treatment of early glottic cancer include visits:

- every 4–6 weeks for the 1st year after treatment,
- every 6–8 weeks for the 2nd year after treatment,
- every 3–4 months for the 3rd year after treatment,
- every 6 months for the subsequent years.

Follow-up visits should include endoscopic assessment of the laryngeal mucosa and early detection of suspected recurrent lesions, as well as assessment of the restoration of vocal fold vibration after treatment, hence both VLS and image-enhanced endoscopy are recommended. In accordance with the ELS protocol, patients with early glottic cancer should undergo an assessment of voice quality, most often at 3, 6 and 12 months after treatment.

## CONCLUSION

The aim of modern diagnostics of glottic cancer is a thorough assessment of the histopathological stage of the changes in the vocal fold mucosa and their advancement prior to treatment in order to precisely select the therapeutic method. Taking into consideration the functional aspect of the vocal folds, diagnostic methods in patients with early laryngeal cancer should also include the assessment of voice quality in this group of patients before and after the treatment.

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