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Correlation of narrow-band imaging findings using the Ni and European Laryngeal Society classification systems during in-office flexible laryngoscopy with histopathology

Nupur Kapoor Nerurkar and Asitama Sarkar

Bombay Hospital Voice and Swallowing Centre, Bombay Hospital and Medical Research Centre, Mumbai, India

Abstract

Objective. This study used the European Laryngeal Society (2016) and Ni (2011 and 2019) classifications for narrow-band imaging and correlated the findings with histopathology.
Methods. Retrospective analysis was conducted by retrieving data of patients who underwent micro-laryngoscopy for suspicious glottic lesions. The narrow-band imaging findings were classified using both classification systems. Retrieved histopathology report findings were correlated with narrow-band imaging data.
Results. Using the European Laryngeal Society and Ni classifications, 37 (69.8 per cent) and 35 (66 per cent) patients, respectively, were suspected to have malignant lesions. Upon histopathology, 37 (69.8 per cent) lesions were malignant. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy using the European Laryngeal Society classification were 91.9 per cent, 81.3 per cent, 91.9 per cent, 81.3 per cent and 88.7 per cent, and using the Ni classification were 91.9 per cent, 93.8 per cent, 97.1 per cent, 83.3 per cent and 92.5 per cent, respectively.
Conclusion. The Ni classification had better specificity and accuracy. The European Laryngeal Society classification is simple to use and may serve as a useful screening tool. For optimum results, both European Laryngeal Society and Ni classifications may be used together, in that order.

Main Article

Nupur Nerurkar takes responsibility for the integrity of the content of the paper

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Corresponding author:
Nupur Kapoor Nerurkar;
Email: nupurkapoor@yahoo.com
Fax: 91 22 2208 0871

Introduction

Narrow-band imaging light is broadband white light modified into two narrow-band illumination beams with wavelengths of 415 nm (blue light) and 540 nm (green light). These wavelengths correspond to the wavelength of oxyhaemoglobin absorption, and thus penetrate the mucosa and submucosa to display the superficial and subepithelial capillary networks respectively. Narrow-band imaging is based upon the fact that depth of light penetration depends on light wavelength: the greater the wavelength, the deeper the penetration.[1] When these wavelengths are used in combination, they provide an extremely high contrast image of the tissue surface.[2] Specific neo-angiogenic patterns that are prominently visible using narrow-band imaging may suggest premalignant or neoplastic lesions. Typically, these neo-angiogenic patterns present as well demarcated brownish dots in a context of green–blue appearing normal mucosa, or scattered thick dark spots, increased microvascular density, and earthworm-like vessels in the form of abnormal intra-epithelial papillary capillary loops. Narrow-band imaging endoscopy can facilitate early diagnosis of laryngeal growth lesions by enabling observation of these intra-epithelial papillary capillary loop patterns.[3–5] In identifying laryngeal cancer and its precursor lesions, narrow-band imaging with white light endoscopy has shown significantly higher sensitivity (97 per cent *vs* 79 per cent) and accuracy (97 per cent *vs* 90 per cent) than white light endoscopy alone.[6,7]

In 2011, Ni *et al.* suggested a classification in which vascular features of intra-epithelial papillary capillary loops were classified into five types, which correlated well with the severity of dysplasia of laryngeal lesions as demonstrated by histological examination.[2]

In 2016, the European Laryngological Society proposed a classification for vascular changes of vocal fold lesions, dichotomously dividing vascularity into longitudinal and perpendicular patterns. Longitudinal vascularity, such as ectasia, meandering vessels, and increasing number and density of blood vessels are triggered by mechanical stress on the vocal folds. These changes, when present in two dimensions of length and width of vocal folds, are associated with benign conditions and may be reversible. The perpendicular vascular changes represent dilated intra-epithelial papillary capillary loops.[8] Growth of vessels in the third dimension is regularly associated with carcinogenesis (induced by a virus or other exogenous factors). The spiralling shape with wide- or narrow-angled turning points are important for differential diagnosis, as these alterations are indicators of recurrent respiratory papillomatosis, precancerous or cancerous lesions.[9]

In 2019, Ni *et al.* proposed another classification specific for lesions with leucoplakia, as they found that the sensitivity of the narrow-band imaging diagnosis reduced because of the presence of the white plaque.[10] Leucoplakia is a precancerous lesion, identifiable from histopathological results which range from stages of dysplasia to invasive cancer.[11] Vocal fold leucoplakia may be caused by long-term stimulation factors (smoking, alcohol consumption, excessive use of voice, laryngopharyngeal reflux and human papilloma virus infection).[9,12]

Our study aimed to use the European Laryngeal Society and Ni (2011 and 2019) classification systems available for narrow-band imaging and to correlate the findings with histopathology. We also wanted to understand the possible reasons for false positive and false negative cases. We aspired to use both classification systems in the most optimal manner, to identify, diagnose and plan the management of suspicious vocal folds lesions.

Materials and methods

This retrospective, observational study was performed by retrieving the medical records of all patients treated with microlaryngeal surgery for suspicious growth lesions of vocal folds during a one-year period (March 2021 to March 2022). Patients who had undergone radiotherapy in the past and those known to have recurrent respiratory papillomatosis were excluded from this study.

Evaluation using narrow-band imaging, by in-office flexible laryngoscopy, is performed routinely for suspicious vocal fold lesions at our voice clinic using the Olympus® ENF-V3 video rhino-laryngoscope with the Olympus Visera Elite CLV-S190 light source. Patient narrow-band imaging data are routinely captured and stored in ScopyDoc image management system software (version 7.0.2; Medsynaptic, Pune, India).

All patients included in this study were assigned a random number by a moderator (second author), and their narrow-band imaging photographic data were retrieved and organised into corresponding numbered folders without revealing the patient's identity. These folders were then sent to three different laryngologists. Classification as per both the European Laryngeal Society and Ni grading systems using representative images were performed by the three laryngologists (first author and two acknowledgements) for all 53 lesions, and the specifics of each patient were duly noted.

The histopathology reports of the excised specimens were recovered, and the lesions categorised as benign or malignant. Patients with non-dysplastic lesions (inflammatory, granulomatous lesions) and mild–moderate-grade dysplasia were considered as having benign lesions, while patients with carcinoma in situ and invasive squamous cell carcinoma were considered as having malignant lesions.

The compiled data were entered using MS Excel® 2007 spreadsheet software and analysed using SPSS® version 16 statistical software. Descriptive analysis for numerical data and categorical data were summarised as means with standard deviations, or frequencies with percentages for various parameters respectively. In order to check the validity of narrow-band imaging using the Ni and the European Laryngeal Society classifications during in-office flexible laryngoscopy, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated, with histopathology as the 'gold standard'. We also checked the agreement amongst the three laryngologists who classified the data, using Cohen's kappa statistics to overcome subjective bias.

Results

A total of 53 vocal fold lesions were included in our study. The mean age of the study sample was 60.0 ± 11.9 years (range, 34–86 years) with 29 patients (70.7 per cent) in the age group of 51–70 years. There were 39 (95.1 per cent) males and 2 (4.9 per cent) females.

In our study, there were 47 (88.7 per cent) vocal fold lesions with leucoplakia and 6 (11.3 per cent) without glottic leucoplakia on laryngeal endoscopy. Upon narrow-band imaging examination using the European Laryngeal Society classification, of the 53 lesions, 37 (69.8 per cent) were suspected to be malignant, while 16 (30.2 per cent) were anticipated to be benign glottic lesions. When using the Ni classification (Ni 2011 classification for lesions without leucoplakia, and Ni 2019 classification for lesions with leucoplakia), under narrow-band imaging examination, 35 lesions (66 per cent) were suspected to be malignant, while 18 (34 per cent) were expected to be benign glottic lesions. On histopathology, 37 of all 53 lesions (69.8 per cent) were malignant. The true and false positive and negative cases are illustrated in Figure 1.

Using Cohen's kappa statistics, the overall agreement between the European Laryngeal Society classification system and histopathological findings of lesions was 88.7 per cent, with a simple kappa value of 0.731, showing good agreement, which was statistically significant ($p < 0.001$). In our study, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy for narrow-band imaging to identify vocal fold lesions as benign or malignant using the European Laryngeal Society classification was 91.9 per cent, 81.3 per cent, 91.9 per cent, 81.3 per cent and 88.7 per cent, respectively. The three laryngologists were in moderate agreement with each other when classifying the data using the European Laryngeal Society system, with a kappa value of 0.576.

Using Cohen's kappa statistics, the overall agreement between the Ni classification system and histopathological findings was 92.5 per cent, with a simple kappa value of 0.827, showing excellent agreement, which was statistically

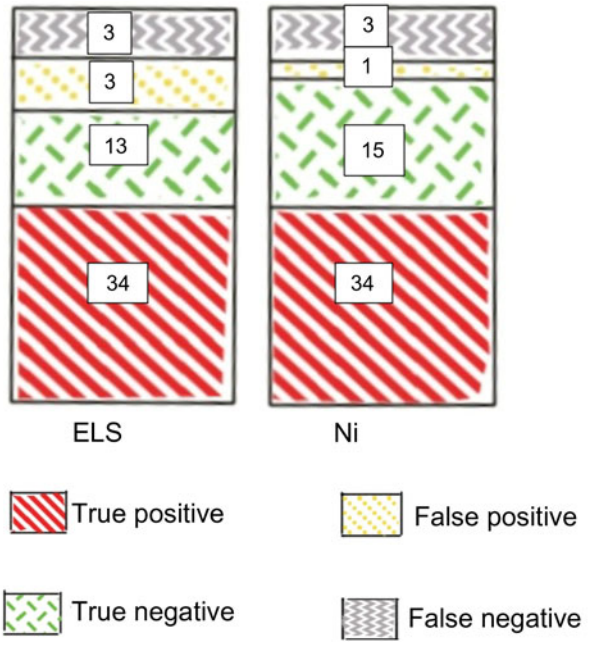

Figure 1. Bar diagram representing true and false positive and negative cases using European Laryngeal Society (ELS) and Ni classification systems, with histopathology as the 'gold standard'.

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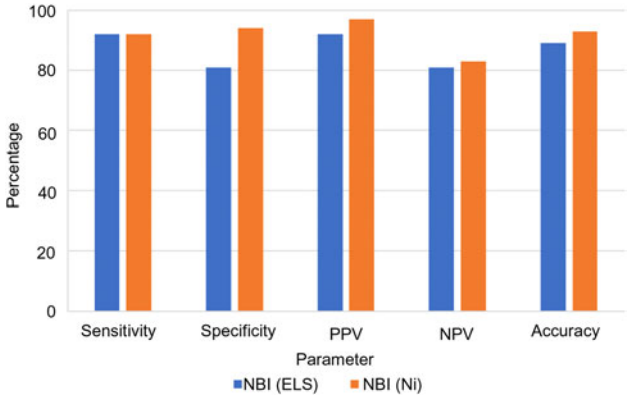

Figure 2. Bar diagram showing comparison of the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of the Ni and European Laryngeal Society (ELS) classification systems in our study. NBI = narrow-band imaging

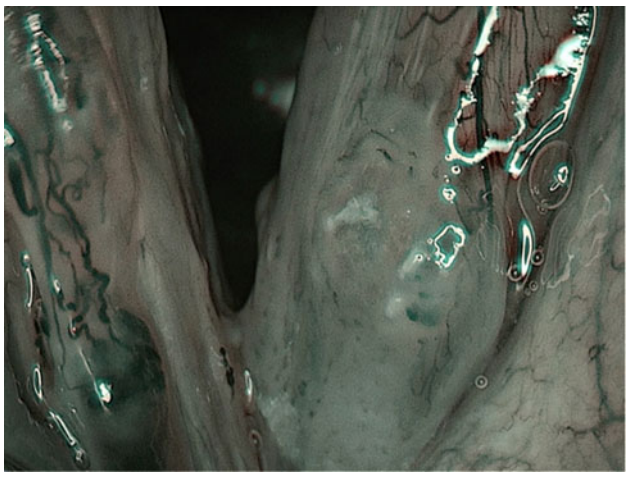

Figure 3. Narrow-band imaging performed on this patient revealed a left vocal fold Ni 2019 classification type III pattern and a European Laryngeal Society classification perpendicular pattern. Histopathology confirmed a left vocal fold polyp, suggesting discordance with the European Laryngeal Society system for the left vocal fold lesion. On the right vocal fold, the vascularity showed a Ni 2011 classification type II pattern and a European Laryngeal Society classification longitudinal pattern. Histopathology confirmed a right vocal fold polyp, which was in concordance with both Ni 2011 classification and the European Laryngeal Society system.

significant ($p < 0.001$). In our study, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy for narrow-band imaging to identify vocal fold lesions as benign or malignant using the Ni classification was 91.9 per cent, 93.8 per cent, 97.1 per cent, 83.3 per cent and 92.5 per cent, respectively (Figure 2). The three laryngologists were in substantial agreement with each other when classifying the data using the Ni system, with a kappa value of 0.692.

Discussion

Mucosal microvascular proliferation and changes are some of the first signs of malignant alteration.[13,14] Narrow-band imaging is beneficial in exploiting the fact that tumours recruit the surrounding blood vessels to support their growth and metabolic requirements.[15] Thus, early recognition of oncologically suspicious vocal fold lesions is a key advantage of narrow-band imaging.

A commonly used classification for suspected glottic lesions (without leucoplakia) by narrow-band imaging is the one proposed by Ni *et al.* in 2011.[2] According to Ni and colleagues, type Va lesions include severe dysplasia (carcinoma in situ); type Vb and Vc lesions represent invasive cancer.[2]

In order to solve problems brought about by the umbrella effect[16] seen in vocal folds covered with leucoplakia, and to improve the consistency between narrow-band imaging and pathological diagnosis, in 2019, Ni *et al.* suggested another classification system for narrow-band imaging findings of vocal fold lesions with leucoplakia.[10] Under the narrow-band imaging endoscope, vocal fold leucoplakia classified as types IV, V and VI is malignant, while leucoplakia classified as types I, II and III is benign. In cases with a type III vascular pattern, the intra-epithelial papillary capillary loops are visible, where the epithelium is not covered by leucoplakia, appearing as small brown spots without distinct margins. Ni 2019 classification type III vascularity, when classified as per the European Laryngeal Society system, would be defined as a perpendicular pattern, which is categorised as malignant. In our study, we had two patients with a Ni 2019 classification type III intra-epithelial papillary capillary loop pattern, who were incorrectly considered as having malignant lesions according to the European Laryngeal Society classification. On histopathology, they were found to have moderate dysplasia and a vocal fold polyp respectively (Figure 3). Both patients were correctly diagnosed as having a benign lesion when using the Ni 2019 classification on narrow-band imaging endoscopy.

In 2016, the European Laryngeal Society proposed a simple and easy-to-use classification of the vascular changes of vocal fold lesions, as visualised on narrow-band imaging endoscopy. It divides vascular patterns into longitudinal and perpendicular types. Endoscopically, the perpendicular pattern is recognised as intra-epithelial papillary capillary loops; the angle of the loops' turning points may either be wide or narrow, likely corresponding to papilloma or malignancy.[8] The exact angle for the turning points of these vascular loops, so as to further sub-classify them as wide or narrow, is not defined.

In 2020, Ahmadzada *et al.* reported the sensitivity, specificity, negative likelihood ratio and positive likelihood ratio of narrow-band imaging in diagnosing laryngeal cancer using the Ni 2011 classification as 95.0 per cent, 83.3 per cent, 0.06 and 5.76, respectively.[17] As per the Ni 2019 classification, the sensitivity, specificity, positive predictive value and negative predictive value for the diagnosis of suspicious lesions with leucoplakia under narrow-band imaging was 82.6 per cent, 92.8 per cent, 73.1 per cent and 95.7 per cent, respectively.[10] In our study, using the Ni classification (2011 classification in cases without glottic leucoplakia and 2019 classification in cases with leucoplakia), we found that the sensitivity, specificity, positive predictive value, negative predictive value and accuracy for narrow-band imaging to identify vocal fold lesions as benign or malignant was 91.9 per cent, 93.8 per cent, 97.1 per cent, 83.3 per cent and 92.5 per cent, respectively. It is likely that the higher specificity found in our study, compared with that of Ahmadzada *et al.*[17] and Ni *et al.*,[10] is because we used both the Ni 2011 and Ni 2019 classifications, as appropriate.

In 2018, Šifrer *et al.* studied 40 patients, and reported the sensitivity, specificity, positive predictive value, negative predictive value and accuracy for narrow-band imaging to predict malignancy using the European Laryngeal Society classification as 100 per cent, 95 per cent, 88 per cent, 100 per cent and 96 per cent, respectively.[18] In 2020, Šifrer *et al.* conducted another study, with a larger sample size of 144 cases, to further

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investigate the effectiveness of the European Laryngeal Society classification. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of the European Laryngeal Society system was 98 per cent, 95 per cent, 88 per cent, 99 per cent and 95 per cent, respectively.[19] The above results suggest that the European Laryngeal Society classification can serve as a useful screening tool.

We found three false negative cases in our results using both the European Laryngeal Society and Ni classifications. On histopathology, two patients were found to have invasive squamous cell carcinoma and one patient had carcinoma in situ. For two of these three patients, the thick leucoplakia layer over the vocal folds probably prevented us from identifying possible underlying intra-epithelial papillary capillary loops because of its 'umbrella effect' (Figure 4).[16] In early glottic cancers with leucoplakia, the partially or fully obscured atypical large brown spots of the intra-epithelial papillary capillary loop may often result in misjudgements as small benign lesions, because of inadequate visualisation to understand the morphology of the intra-epithelial papillary capillary loop, leading to decreased accuracy in diagnosis. In the third patient, we noted that the vascularity looked more like wide-angled meandering blood vessels in two dimensions of vocal folds (benign), rather than narrow-angled squiggly worms in three dimensions, thereby preventing its classification as a perpendicular pattern (malignant), in line with the European Laryngeal Society system (Figure 5). When using the Ni classification for this patient, the vascular pattern was not twisted-earthworm-like, and did not fit into Ni classification types IV, V or VI. A clear-cut definition of meandering vessels as opposed to a 'squiggly worm' pattern would be useful. We propose that an angle of 90 degrees or more be considered as a meandering vessel pattern, though this will require validation by larger case studies.

Figure 4. Narrow-band imaging performed on this patient revealed a bilateral Ni 2019 classification type I pattern and a European Laryngeal Society classification longitudinal pattern. Histopathology revealed right vocal fold carcinoma in situ and left vocal fold mild dysplasia. The thick right vocal fold leucoplakia was probably responsible for hiding the underlying true vascular pattern, which resulted in discordance when using both the Ni and European Laryngeal Society classification systems.

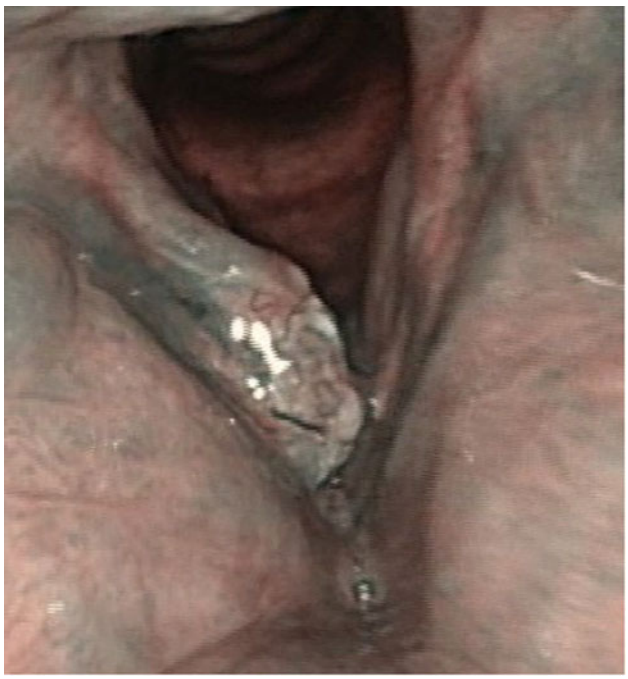

Figure 5. Narrow-band imaging performed on this patient suggested a right-sided Ni 2019 classification type I pattern and a European Laryngeal Society classification longitudinal pattern. Histopathology revealed invasive squamous cell carcinoma, suggesting discordance with both the European Laryngeal Society and Ni classification systems. In this case, the blood vessels appeared more 'meandering' in nature, rather than a 'squiggly worm' pattern, which is probably responsible for the false negative narrow-band imaging report.

- When correlating European Laryngeal Society (2016) and Ni (2011 and 2019) classifications for narrow-band imaging with histopathology, both showed high and equal sensitivity
- European Laryngeal Society classification is simple to use and may serve as a useful screening tool
- The Ni classification system is more complex to use, but the Ni classification type III pattern accurately detected benign lesions even in the presence of intra-epithelial papillary capillary loops
- The Ni classification system had better specificity and accuracy

We had three false positive cases in our study using the European Laryngeal Society system; these lesions were expected to be malignant based on narrow-band imaging examination findings, but were found to be benign on histopathology. Of these three cases, all were false positive when we used the European Laryngeal Society classification, while only one of them was a false positive when we used the Ni system. For the patient who was a false positive using both the classifications, the histological diagnosis was reported as granulomatous inflammation, and the presence of multiple aberrant blood vessels around the leucoplakia gave an impression of intra-epithelial papillary capillary loops on the mucosal surface on narrow-band imaging. For the other two false positive cases, both were false positive only when classified using the European Laryngeal Society system, while the Ni 2019 classification correctly diagnosed the lesions as benign (histopathology reported these as a vocal fold polyp and moderate-grade dysplasia respectively) with a Ni 2019 type 3 pattern. An important precursor of a polyp is varix or capillary ectasia on the vocal fold caused by microtrauma, leading to neo-angiogenesis and

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subsequent microhaemorrhaging in the superficial lamina propria, mimicking the intra-epithelial papillary capillary loop pattern.[20] However, the Ni 2019 classification type 3 category seems to be effective in picking up these patterns that, upon European Laryngeal Society classification, may give a false impression of a perpendicular (malignant) pattern.

The European Laryngeal Society classification is a simple, easy and practical approach using a dichotomous distinction between benign (longitudinal vessels) and malignant (perpendicular) lesions, while the Ni classification provides for a rigid yet detailed classification of the vascular changes. Although the accuracy of the Ni classification (92.5 per cent) in predicting malignant lesions in our study was better than that of the European Laryngeal Society classification (88.7 per cent), we recommend that a combination of both European Laryngeal Society and Ni classifications be used (in that order) by laryngologists, to shorten the learning curve of narrow-band imaging examination and enable effective performance of an 'optical biopsy'.

We acknowledge that the relatively small sample size and retrospective analysis of data are limitations of our study. Larger multi-centric studies are required to further validate our findings.

Conclusion

In our study, which had a level of evidence of 4, both the European Laryngeal Society and Ni classifications showed high and equal sensitivity, while the Ni classification had better specificity and accuracy. The European Laryngeal Society classification is simple to use, especially earlier in the learning curve with the narrow-band imaging system, and is recommended as an initial screening tool by laryngologists. The Ni grading system is more complex to use; however, the Ni (2019) classification type III pattern accurately detected benign lesions even in the presence of intra-epithelial papillary capillary loops that fell in the group of false positives using the European Laryngeal Society classification system. For optimum results, we suggest that both European Laryngeal Society and Ni classification be used together, in that order.

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Competing interests. None declared.

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