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Effect of a training course on the diagnosis of vocal fold leukoplakia by narrow-band imaging

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Abstract

Objective. To investigate the value of narrow-band imaging training for differentiating between benign and malignant vocal fold leukoplakia.

Method. Thirty cases of vocal fold leukoplakia were selected.

Results. Narrow-band imaging endoscopy training had a significant positive effect on the specificity of the differential diagnosis of vocal fold leukoplakia. In addition, the consistency of diagnostic typing of vocal fold leukoplakia by narrow-band imaging improved to 'moderate agreement' following the combination of types I and II and the combination of types IV, V and VI in the typing of vocal fold leukoplakia.

Conclusion. The narrow-band imaging training course may improve the ability of laryngologists to diagnose vocal fold leukoplakia. The new endoscopic diagnostic classification by narrow-band imaging needs to be further simplified to facilitate clinical application.

Main Article

Dr X-G Ni takes responsibility for the integrity of the content of the paper

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Introduction

Vocal fold leukoplakia is a type of white plaque that covers the surface of vocal folds and exists in different pathological forms. The degree of dysplasia in the different types of vocal fold leukoplakia is a key determinant in malignancy transformation.[1,2] In addition, each pathological type of the disease responds differently to various treatment types.[3] Therefore, accurate diagnosis of the pathological type of vocal fold leukoplakia is significant in the formulation of treatment procedures.

Laryngoscopy is a widely used examination method for the diagnosis of vocal fold leukoplakia. However, given the high similarity in manifestation of different pathological types of vocal fold leukoplakia, it is difficult to accurately evaluate the degree of dysplasia in vocal fold leukoplakia and to determine whether there is cancerisation by routine laryngoscopy.[4] This often results in over- or under-treatment due to misdiagnosis.

Narrow-band imaging is an optical image enhancement technique with the ability to highlight the surface structure and microvascular morphology of mucosal surfaces. Moreover, when combined with electronic endoscopy, narrow-band imaging greatly improves the detection of early cancer on the mucosal surface.[5] The application of narrow-band imaging endoscopy in head and neck tumours has recently been on the rise, and has significantly improved early diagnosis and differential diagnosis of malignant tumours in these regions. Narrow-band imaging endoscopy clearly highlights the microvascular morphology (intra-epithelial papillary capillary loops) on the mucosal surface.[6,7]

According to the intra-epithelial papillary capillary loop morphology on the surface of vocal mucosa, we had previously proposed an endoscopic diagnostic classification based on narrow-band imaging of laryngeal lesions, and vocal fold leukoplakia was defined as type III.[8] However, we found that in clinical application, it is difficult to accurately identify the benign and malignant forms of vocal fold leukoplakia by single typing because of their complexities. Therefore, we have further subdivided the diagnostic classification of vocal fold leukoplakia under narrow-band imaging endoscopy, and propose a new diagnostic classification of vocal fold leukoplakia by narrow-band imaging comprising types I–VI.[9] Preliminary studies have shown that the new classification method is significant in the differential diagnosis of benign and malignant vocal fold leukoplakia.

The current study investigated the application of the new narrow-band imaging classification in laryngoscopy, and evaluated the impact of a training course on the ability of laryngologists to diagnose benign and malignant vocal fold leukoplakia. Further, we evaluated the consistency in nature and typing judgement of vocal fold leukoplakia by laryngologists before and after the narrow-band imaging training course.

Materials and methods

Patients

Patients who had complained of hoarseness at the Department of Endoscopy of the Cancer Hospital, Chinese Academy of Medical Science, Beijing, between January 2015 and January 2017, were selected, and those with white patches on the surface of their vocal folds were included in the study.

The patients' nose, pharynx and larynx were examined by electronic endoscopy using a narrow-band imaging observation mode. However, patients with cauliflower-like or ulcerative tumours on the surface of the vocal fold, vocal fold polyps, vocal fold cysts, Reinke's oedema of the vocal folds or papillomas of vocal folds were excluded.

All examinations and image screenings were performed, using an Olympus Evis Lucera 260 system incorporating a BF-260 video-bronchoscope (Olympus Medical Systems, Tokyo, Japan), by one experienced laryngologist, who did not participate in any other subsequent tests. Before observation in narrow-band imaging mode, vocal fold leukoplakia was first observed in white light imaging mode, and representative images and video clips were collected and saved. A biopsy of the vocal fold leukoplakia was then performed. All patients had a definite pathological diagnosis. All the patients had signed informed consent forms before being examined.

Research participants and research design

In order to examine the convenience of this diagnostic classification in clinical application, we invited 20 professional laryngologists to design a special narrow-band imaging training course for the diagnosis of vocal fold leukoplakia.

We conducted an assessment of 20 laryngologists, focusing on the differential diagnosis for benign and malignant vocal fold leukoplakia cases under white light imaging and narrow-band imaging modes. Basic medical information, pathology and other imaging data of subsequent tests performed on patients were not revealed to the laryngologists, who were also not allowed to have discussions during the test. The assessment was designed to include a pre-training test, narrow-band imaging training and a post-training test, with histopathological diagnosis taken as the 'gold standard' for final diagnosis. According to the World Health Organization classification,[10] vocal fold leukoplakia can be divided into two categories: (1) malignant leukoplakia – severe atypical hyperplasia, carcinoma in situ and squamous cell carcinoma; and (2) benign leukoplakia – inflammation, simple hyperplasia, mild atypical hyperplasia and moderate atypical hyperplasia.

The test comprised 30 cases of vocal fold leukoplakia. The participating laryngologists were asked to classify each case as either benign or malignant. First, the endoscopic images in the white light imaging mode were displayed. Based on the appearance of the leukoplakia in the white light imaging mode, the lesions were classified as benign or malignant. The answers were written on an answer card and retrieved immediately. Endoscopic images of white light imaging plus narrow-band imaging of the 30 cases of leukoplakia were then shown. According to the narrow-band imaging endoscopy image, vocal fold leukoplakia was re-evaluated and the answers retrieved.

Subsequently, narrow-band imaging training was carried out, which mainly covered the following aspects: (1) the basic principles of narrow-band imaging technology; (2) the Ni classification of laryngeal lesions under narrow-band imaging endoscopy;[8] and (3) a new classification of vocal leukoplakia based on narrow-band imaging endoscopy (types I–VI) (Figure 1). The images used during training were different to those used in the test.

The post-training test was conducted immediately after narrow-band imaging training. The participants were questioned about the narrow-band imaging classification of vocal fold leukoplakia, and asked to classify the vocal fold leukoplakia as benign or malignant. The answer cards from these tests were then analysed statistically.

Statistical analysis

We used SPSS 22.0 software (IBM, Armonk, New York, USA) for the statistical analysis. The participants' answers retrieved before and after training were used to calculate accuracy, sensitivity, specificity, positive predictive value and negative predictive value for the diagnoses of malignant vocal fold leukoplakia in white light imaging and narrow-band imaging modes. We used the chi-square test to determine the difference between the two groups, and statistical significance was set at $p < 0.05$. We further used the kappa test to evaluate the consistency of participants in predicting the nature of vocal fold leukoplakia and provide a diagnostic classification, before and after narrow-band imaging training. A kappa value of less than 0.20 was regarded as poor agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as good agreement and more than 0.81 as very good agreement.

Results

Vocal fold leukoplakia clinical features

The images for 30 cases of vocal fold leukoplakia and laryngoscopy, from 26 patients, were included in this study. The patients comprised 25 men and 1 woman, with a median age of 58 years (34–67 years). In 22 cases, vocal fold leukoplakia occurred unilaterally, while the occurrence was bilateral in 4 cases. Of the 30 vocal fold leukoplakia lesions, 19 (63.3 per cent) were benign, with 2 cases of chronic inflammation, 9 cases of simple squamous cell hyperplasia, 4 cases of mild atypical hyperplasia and 4 cases of moderate atypical hyperplasia. Eleven lesions (36.7 per cent) were malignant, with seven cases of severe atypical hyperplasia or carcinoma in situ, and four cases of squamous cell carcinoma.

White light versus narrow-band imaging

Here, we discuss the comparison of white light imaging with narrow-band imaging (before and after training) in the diagnosis of vocal fold leukoplakia. Before training, the accuracy of white light imaging for the diagnosis of vocal fold leukoplakia was 0.633, while that for the diagnosis of narrow-band imaging was 0.698 ($\chi^2 = 5.697$, $p = 0.017$). After training, the accuracy of narrow-band imaging diagnosis significantly improved to 0.770 ($\chi^2 = 7.895$, $p = 0.005$).

Before training, the sensitivity, specificity, positive predictive value and negative predictive value for the diagnosis of malignant vocal fold leukoplakia were 0.736, 0.574, 0.500 and 0.790, respectively, for white light imaging, and were 0.891, 0.587, 0.555 and 0.903, respectively, for narrow-band imaging. The sensitivity ($\chi^2 = 17.327$, $p = 0.000$) and negative

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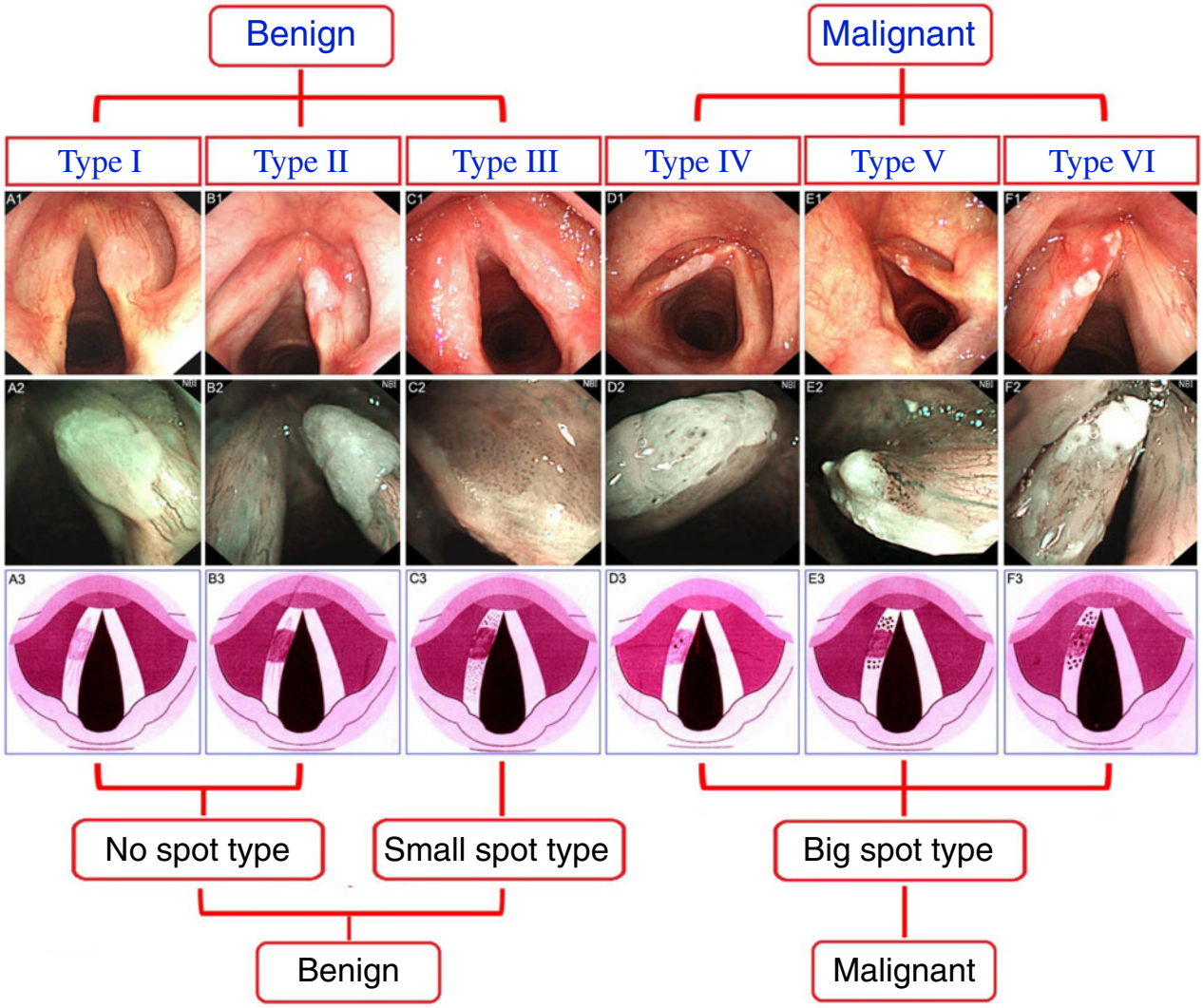

Fig. 1. The narrow-band imaging diagnostic classification modified for vocal fold leukoplakia.

predictive value ($\chi^2 = 512.585$, $p = 0.000$) of narrow-band imaging before training were significantly better than those of white light imaging. However, the specificity ($\chi^2 = 0.135$, $p = 0.713$) and positive predictive value ($\chi^2 = 2.069$, $p = 0.150$) did not differ between the two groups.

After training, the sensitivity, specificity, positive predictive value and negative predictive value of narrow-band imaging diagnosis was 0.918, 0.684, 0.627 and 0.935, respectively, which were significantly better than the values for white light imaging. The specificity of narrow-band imaging diagnosis improved significantly after training ($\chi^2 = 7.777$, $p = 0.005$).

The consistency of the diagnosis of vocal fold leukoplakia by laryngologists was: fair (in terms of agreement) ($\kappa = 0.282$) in the white light imaging mode, moderate ($\kappa = 0.424$) in the narrow-band imaging mode before training, and moderate ($\kappa = 0.549$) in the narrow-band imaging mode after training (Table 1).

Consistency evaluation of new vocal fold leukoplakia classification

Our consistency evaluation of the new vocal fold leukoplakia classification using narrow-band imaging, based on the responses of the 20 laryngologists, revealed that their judgement of types I–VI vocal fold leukoplakia was either poor or fair (Figure 2). However, after combining types I and II benign leukoplakia, consistency improved to moderate ($\kappa = 0.507$). Similarly, consistency was moderate after combining types IV, V and VI malignant leukoplakia ($\kappa = 0.567$).

Discussion

Vocal fold leukoplakia is a common cause of hoarseness and a common pre-cancerous lesion in laryngeal cancer. Although the morphological and pathological features of vocal fold leukoplakia under routine laryngoscopy are closely associated,[11] subjective factors that influence this association, such as laryngologists' clinical experience, are relatively strong, thereby reducing objectivity in the diagnostic process.

In a recent diagnostic classification method, Li *et al.*[12] proposed evaluation of only the roughness of leukoplakia, but not the mucosal red zone around it. In addition, previous studies have shown that under routine laryngoscopy, hyperaemia[13] and vascular stippling[4] are closely associated with dysplasia and the malignancy of vocal fold leukoplakia.

The application of narrow-band imaging laryngoscopy in head and neck tumours has gained popularity among clinicians, as it aids in the early detection of cancer.[14] The main advantage of narrow-band imaging endoscopy is its ability to utilise the short-wavelength irradiation light absorbed by

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Table 1. Comparison of roles of white light imaging and narrow-band imaging in vocal fold leukoplakia diagnosis

Parameter	White light imaging	Narrow-band imaging before training	Narrow-band imaging after training
Accuracy	0.633 (324/600)	0.698 (419/600)	0.770 (462/600)
Sensitivity	0.736 (162/220)	0.891 (196/220)	0.918 (202/220)
Specificity	0.574 (218/380)	0.587 (223/380)	0.684 (260/380)
PPV	0.500 (162/324)	0.555 (196/353)	0.627 (202/322)
NPV	0.790 (218/276)	0.903 (223/247)	0.935 (260/278)
Kappa	0.282	0.424	0.549

Data represent percentages (numbers of judgements of malignant/benign leukoplakia lesions out of total numbers of true positive/negative histopathological diagnoses) unless indicated otherwise. Twenty laryngologists judged 30 cases of leukoplakia (hence a total of 600 judgement results). PPV = positive predictive value; NPV = negative predictive value

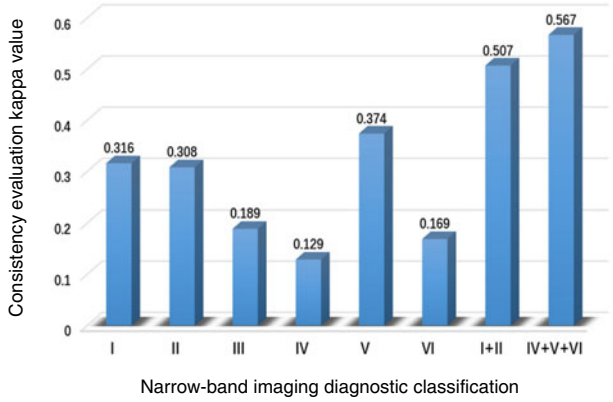

Fig. 2. Consistency evaluation of the new narrow-band imaging classification of vocal fold leukoplakia by 20 laryngologists.

haemoglobin, to highlight the abnormally dilated microvessels (i.e. intra-epithelial papillary capillary loop) on the mucosal surface. These abnormally dilated microvessels correspond to mucosal congestion and vascular stippling in white light imaging; hence, the information provided by narrow-band imaging can counter the deficiency of white light imaging laryngoscopy when classifying vocal fold leukoplakia. In addition, with this technology, a biopsy can be avoided when predicting the pathological nature of some lesions,[15] thereby avoiding unnecessary trauma and playing an important role in the functional protection of vocal folds.

Five intra-epithelial papillary capillary loop typing criteria for laryngeal lesions were first summarised by Ni *et al.* according to the characteristic dynamic changes of intra-epithelial papillary capillary loop morphology on the mucosal surface of laryngeal lesions during the development process from a normal state to dysplasia and cancer.[8] This classification had an accuracy of 90.4 per cent for the diagnosis of laryngeal lesions, which was significantly higher than that of conventional white light imaging endoscopy (76.9 per cent). In addition, its sensitivity and specificity for the diagnosis of laryngeal cancer were 88.9 per cent and 93.2 per cent, respectively. Sensitivity and specificity for the diagnosis of early laryngeal cancer type Va (severe dysplasia plus carcinoma in situ) were 100 per cent and 79.5 per cent, respectively. This indicated that the Ni classification could be used to improve the diagnostic efficiency of narrow-band imaging endoscopy for laryngeal cancer (including early laryngeal cancer). A meta-analysis further showed that the overall sensitivity and specificity for the diagnosis of laryngeal cancer type V were 0.82 and 0.93, respectively.[16]

Most scholars use the Ni classification with narrow-band imaging endoscopy for the differential diagnosis of vocal fold leukoplakia and early vocal fold cancer, as it improves the accuracy of pre-operative judgements of benign and malignant vocal fold lesions. However, different studies have reported mixed results for narrow-band imaging endoscopy diagnoses of vocal fold leukoplakia and early vocal fold cancer, with accuracy rates ranging from 70.6 per cent to 94.5 per cent, and sensitivity values ranging from 58.6 per cent to 97.0 per cent.[17–21]

To improve the accuracy and consistency of the differential diagnosis of benign and malignant vocal fold lesions obtained using the Ni classification with narrow-band imaging endoscopy, we proposed a new diagnostic classification of vocal fold leukoplakia that comprises subdivisions based on narrow-band imaging endoscopy.[9] This new diagnostic classification of vocal fold leukoplakia aimed to overcome the blocking effect of leukoplakia on mucosal microvessels, thereby improving the consistency between the narrow-band imaging endoscopy diagnosis and the pathological diagnosis. In order to explore whether the new diagnostic classification of vocal fold leukoplakia by narrow-band imaging could improve the diagnostic ability, we invited 20 laryngologists to participate in a clinical assessment that entailed differentiating between benign and malignant vocal fold leukoplakia cases.

A new training course on the endoscopic diagnosis of vocal fold leukoplakia by narrow-band imaging was introduced, and its role in improving the ability of narrow-band imaging to provide an endoscopic diagnosis was observed. Further, we analysed the consistency of laryngologists' assessments of vocal fold leukoplakia, determined using the new narrow-band imaging diagnostic classification, and examined the ability of this classification to improve lesion typing, in order to establish whether its clinical application by laryngoscope operators should be recommended. Our results revealed that narrow-band imaging endoscopy was better than white light imaging endoscopy in terms of the accuracy of categorising benign and malignant vocal fold leukoplakia (0.698 *vs* 0.633).

The accuracy of narrow-band imaging endoscopy in differentiating between benign and malignant vocal fold leukoplakia significantly improved to reach 0.770 after the narrow-band imaging training. Though moderate, the training also improved the consistency of laryngologists' judgements on the nature of vocal fold leukoplakia, indicating that their understanding of mucosal microvascular morphology in the narrow-band imaging mode had an impact on their judgement.[22] In addition, the narrow-band imaging training significantly improved the specificity of the diagnosis of malignant vocal fold leukoplakia, indicating that narrow-band imaging

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training could reduce the misdiagnosis rate of vocal fold leukoplakia.

In this study, we observed that consistency of the new diagnostic classification of vocal fold leukoplakia by narrow-band imaging as summarised was not good, especially for types III, IV and VI. This highlights the need for further improvement, taking into account the cumulative learning process associated with clinical experience. For instance, most participants mistook the small brown intra-epithelial papillary capillary loop spots (type III) on the surface of vocal folds as malignant vocal fold leukoplakia. Therefore, type III should be clearly differentiated from types IV and V to limit clinical misdiagnosis.

During the identification of small and large spots, attention should be paid to size, uniformity of distribution and boundary clarity.[23] In addition, types I and II are benign, while types IV, V, and VI are malignant, and all the types within benign or malignant categories were associated with similar findings under narrow-band imaging endoscopy. In order to facilitate beginners' understanding of the classification scheme of vocal fold leukoplakia, we combined types I and II into a 'no spot' type, and types IV, V, and VI into a 'large spot' type. Laryngologists' consistency in diagnosis was significantly higher after this combination than that before the combination. We therefore suggest that diagnostic typing of vocal fold leukoplakia can be simplified into three types, namely: a 'no spot' type, a 'small spot' type and a 'large spot' type (Figure 1). Exploration of the benefits of diagnostic typing by narrow-band imaging should be conducted, as the clinical applications are currently unclear.

- Narrow-band imaging endoscopy is superior to the white light imaging endoscopy for differentiating benign and malignant vocal fold leukoplakia
- The narrow-band imaging training course had a positive effect on the accurate diagnosis of vocal fold leukoplakia
- The new endoscopic diagnostic classification by narrow-band imaging needs to be further simplified to facilitate clinical application

This study had the following limitations. First, few cases of vocal fold leukoplakia were examined, which could bias the diagnosis results. Second, all the vocal fold leukoplakia cases used for testing were assessed using image data and not real-time dynamic video data, hence the diagnostic information provided was limited. Finally, this study only investigated the differences in judgements before and after training, without examining intra-observer consistency. Therefore, the impact of such training should be further evaluated, to confirm our results and determine its sustainability.

Conclusion

Our study findings suggest that narrow-band imaging endoscopy is superior to white light imaging endoscopy for differentiating between benign and malignant vocal fold leukoplakia. In addition, clinical training for the new classification of vocal fold leukoplakia has a positive effect on the accurate diagnosis of vocal fold leukoplakia. To some extent, laryngologists' clinical experience might affect the accuracy of judging intra-epithelial papillary capillary loop spots under the narrow-band imaging mode.[24] In order to increase the adoption of diagnostic classification of vocal fold leukoplakia based on narrow-band imaging, the classification ought to be simplified further to allow beginners to master the classification scheme quickly.

A comprehensive analysis of the information obtained under white light imaging and narrow-band imaging endoscopy should be conducted, to allow compensation for the blocking effect of leukoplakia on the intra-epithelial papillary capillary loop, which would improve the diagnostic accuracy of vocal fold leukoplakia. This, however, requires a multicentre, prospective, real-time and dynamic clinical study to further summarise the methods of diagnosing vocal fold leukoplakia and improve laryngologists' skills for accurate vocal fold leukoplakia diagnosis.

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Competing interests. None declared

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