


Treatment experience with and clinicopathological analysis of vocal fold leukoplakia per appearance classification guidance: a cohort of 1442 patients

Chang Jiang Li, Min Chen, Jian Chen, Hai Tao Wu , Pei Jie He and Lei Cheng

Department of Otorhinolaryngology, Head and Neck Surgery, Shanghai Key Clinical Disciplines of Otorhinolaryngology, Eye, Ear, Nose and Throat Hospital of Fudan University, Shanghai, China

Main Article

Hai Tao Wu takes responsibility for the integrity of the content of the paper

Cite this article: Li CJ, Chen M, Chen J, Wu HT, He PJ, Cheng L. Treatment experience with and clinicopathological analysis of vocal fold leukoplakia per appearance classification guidance: a cohort of 1442 patients. *J Laryngol Otol* 2024;**138**:461–465. <https://doi.org/10.1017/S0022215123001573>

Received: 21 June 2022
Revised: 12 March 2023
Accepted: 29 August 2023
First published online: 15 September 2023

Keywords:

Laser; cancer; diagnosis; evidence-based medicine; voice

Corresponding authors:

Hai Tao Wu; Email: entwuhaitao@163.com
Pei Jie He; Email: hepj2002@sina.com
Lei Cheng; Email: tomorrowhot@163.com

Abstract

Objective. To analyse the comparative clinical outcomes and clinicopathological significance of vocal fold leukoplakia lesions treated by appearance classification and traditional methods.

Method. A total of 1442 vocal fold leukoplakia patients were enrolled. Group A patients were treated according to appearance classification and Group B patients were treated according to traditional methods.

Results. In Group A, 24.4, 14.9 and 60.6 per cent of patients had grade I, II and III dysplasia, respectively. Grade I dysplasia (63.4 per cent) was more than twice as frequent in Group B patients than in Group A patients, while grade II dysplasia (20.4 per cent) and grade III dysplasia (16.2 per cent) were significantly less frequent in Group B patients than in Group A patients ($p = 0.000$). There was a significant correlation between vocal fold leukoplakia appearance and the degree of dysplasia ($p = 0.000$). The recurrence and malignant transformation rates (17.6 and 31 per cent, respectively) in Group B were significantly greater than those in Group A (10.8 and 25.9 per cent, respectively) ($p = 0.000$).

Conclusion. Vocal fold leukoplakia appearance classification is useful for guiding treatment decision-making and could help to improve therapeutic accuracy.

Introduction

The pathological characteristics of vocal fold leukoplakia reflect the severity of the lesion. Epithelial atypical hyperplasia of the vocal fold leukoplakia can occur as a continuum of changes progressing from no dysplasia to mild, moderate or severe dysplasia and even malignancy.¹ During this process, vocal fold leukoplakia can be addressed initially with aetiological therapy, also called non-operative treatment, and later by surgical treatment. However, exploring a simple and scientific approach to identify vocal fold leukoplakia lesions likely to undergo malignant transformation is a key imperative to guide treatment decision-making.

As early as the 1970s, researchers stated that management decisions for vocal fold leukoplakia should be based on clinical manifestations rather than relying too much on ambiguous histological reports.² However, treatment decision-making is challenging in the absence of pathological classification, therefore researchers have been looking for some simple and practical methods to align the diagnosis of vocal fold leukoplakia more closely with pathological status.

Studies have shown that the clinical features of vocal fold leukoplakia significantly correlate with dysplasia, and treatment strategies are formulated accordingly.³ On this basis, we have established an appearance classification method for vocal fold leukoplakia and demonstrated a good correlation with the degree of dysplasia assessed by pathological examination.⁴ In addition, other studies have found that videostroboscopy and narrow band imaging have high sensitivity and specificity for differentiating vocal fold leukoplakia from laryngeal cancer.^{5,6}

There is a lack of robust evidence to support the methods used to guide the treatment of vocal fold leukoplakia. To date, although there has been some consensus on the diagnosis and treatment of vocal fold leukoplakia, a completely unified community has not been formed internationally.

Carbon dioxide (CO₂) laser surgery is an effective treatment for vocal fold leukoplakia. Although early surgical intervention can prevent malignant transformation of vocal fold leukoplakia, there is a lack of standardised treatment guidelines and surgical indications. The pathological results can vary greatly as a result of the lack of consensus on the surgical indications for vocal fold leukoplakia. For example, some low-risk lesions might be excessively operated on, while high-risk lesions might not be actively treated. Hence, building on our previous work, the present study primarily focused on the clinical outcomes of vocal fold leukoplakia lesions that were treated according to the appearance classification

to provide further evidence and reference for the clinical diagnosis and treatment of vocal fold leukoplakia.

Materials and methods

The Ethics Committee of the Eye, Ear, Nose and Throat Hospital of Fudan University approved this study. A total of 1442 patients with vocal fold leukoplakia lesions who were initially treated at the hospital between January 2003 and December 2018 were screened. Patients with pseudomembranous, mycetoid or tuberculoid lesions in the vocal fold leukoplakia were excluded. All cases were classified into two groups based on the treatment strategy (Groups A and B).

Until 2014, vocal fold leukoplakia was mainly treated based on traditional experience in our department. Subsequently, these lesions were managed according to appearance. Group A consisted of 503 patients treated according to the appearance of the vocal fold leukoplakia lesion. Of 503 patients, 178 patients who required surgical treatment but refused surgery were excluded. In total, 325 patients (315 men and 10 women, mean age 59 ± 9 years) who were surgically treated were recruited. Eighty-four patients had bilateral vocal fold leukoplakia lesions and 241 patients had unilateral lesions. A total of 409 vocal fold leukoplakia specimens were enrolled.

According to the appearance of the vocal fold leukoplakia under rigid laryngoscopy, lesions were classified into three groups: smooth flat, smooth hypertrophic and rough. In smooth flat leukoplakia, the lesions had smooth surfaces and clear bounds, which were even with the mucosal surface of the vocal folds. In smooth hypertrophy, although the lesions were also homogeneous, they stood separate from the surrounding mucosal surface of the vocal folds. Rough lesions had an irregular and nonhomogeneous appearance or presented as spot-shaped, grain-shaped or verrucosa-shaped lesions.

Smooth flat lesions were treated conservatively, while rough lesions were resected surgically. Patients voluntarily selected the treatment strategy for smooth hypertrophic lesions (conservative or surgical). Patients who opted for the conservative treatment strategy underwent laryngoscopy once per month to assess any changes in the lesion.

The following assessment criteria were applied in Group A: (1) cure: complete disappearance of vocal fold leukoplakia lesion; (2) improvement: reduction in vocal fold leukoplakia by ≥ 50 per cent; (3) invalid treatment: no more than 25 per cent decrease in the size of the lesion; and (4) progression: increase in the extent of lesions by 25 per cent, appearance of new lesions, transformation of lesion surface to rough from smooth or even malignant transformation. Patients with failed conservative therapy after six months or progression of the lesion were treated with surgery.⁴

A total of 1117 patients who presented at our hospital between 2003 and 2014 were recruited in Group B, and all of them had undergone surgery. There were 1078 men and 39 women, with an average age of 61 ± 11 years. These patients were not treated according to our proposed guidance but received traditional treatment. Some cases had no evident change in vocal fold leukoplakia six months after the non-surgical approach, and some underwent surgical resection owing to suspected malignant transformation.

Overall, 465 patients had bilateral lesions and 705 patients had unilateral lesions. A total of 1635 vocal fold leukoplakia specimens were enrolled. The treating specialists were blinded to the research objectives and had 10 years of working

experience. During the period of conservative treatment, the patients were advised to rest their voices and abstain from smoking and alcohol consumption.

Surgery was performed using a CO₂ laser. The lesions were excised under general anaesthesia administered by endotracheal intubation. All specimens were preserved for clinicopathologic analysis. The degree of atypical dysplasia was classified according to the World Health Organization: I, no or mild dysplasia; II, moderate dysplasia; and III, severe or carcinoma in situ. Data were collected in the outpatient clinic every two, four and six months for the first, second and third post-operative years, respectively. After three years, patients were followed up once per year. A second CO₂ laser surgery or partial laryngectomy was performed in cases of relapse or malignant transformation. The median follow-up period was 42 months (range, 24–86 months).

Statistical analysis

All statistical analyses were performed using SPSS software, version 23.0. Between-group differences concerning vocal fold appearance, degree of dysplasia, clinical outcomes and sex composition were assessed using the chi-square test. Between-group differences in age were assessed using student's *t*-test. The correlation test was performed by kappa analysis. Two-tailed *p* values < 0.05 were considered indicative of statistical significance.

Results

All lesions were evaluated by post-operative pathological examination and were classified as squamous epithelial hyperplasia associated with keratinisation, no or various degrees of dysplasia, or carcinoma in situ. A strong correlation was observed between the specialists for evaluating the vocal fold leukoplakia appearances and dysplasia degrees ($p = 0.000$, kappa value = 0.872; $p = 0.000$, kappa value = 0.824). There was no significant difference between Groups A and B concerning age or sex composition ($p = 0.595$, $p = 0.717$).

In Group A, 31, 161 and 217 cases were classified as smooth flat, smooth hypertrophic and rough vocal fold leukoplakia, respectively, based on appearance. Thirty-one cases of smooth flat vocal fold leukoplakia, 57 cases of smooth hypertrophic vocal fold leukoplakia and 12 cases of rough vocal fold leukoplakia were found to have grade I dysplasia. Forty-six of 161 smooth hypertrophic vocal fold leukoplakia lesions and 15 of 217 rough lesions had grade II atypical hyperplasia. In addition, there were 58 and 190 patients with grade III dysplasia in the smooth hypertrophic and rough vocal fold leukoplakia groups, respectively.

There was a significant relationship between the appearance of the vocal folds and the degree of dysplasia ($p = 0.000$, kappa value = 0.422). The appearance classification of vocal fold leukoplakia is shown in Figure 1.

In Group B, there were 1037, 133 and 465 cases with grade I, II and III dysplasia, respectively. The constituent ratio of atypical hyperplasia was significantly different from that in Group A (100, 61 and 248 cases with grade I, II and III dysplasia, respectively, $p = 0.000$). The percentage of grade I dysplasia (1037 out of 1635 patients, 63.4 per cent) was more than twice that in Group A (100 out of 409 patients, 24.4 per cent, $p = 0.000$). For grade II and III dysplasia, the results were the opposite of those for grade I atypical dysplasia between the groups. The proportions of cases with grade II

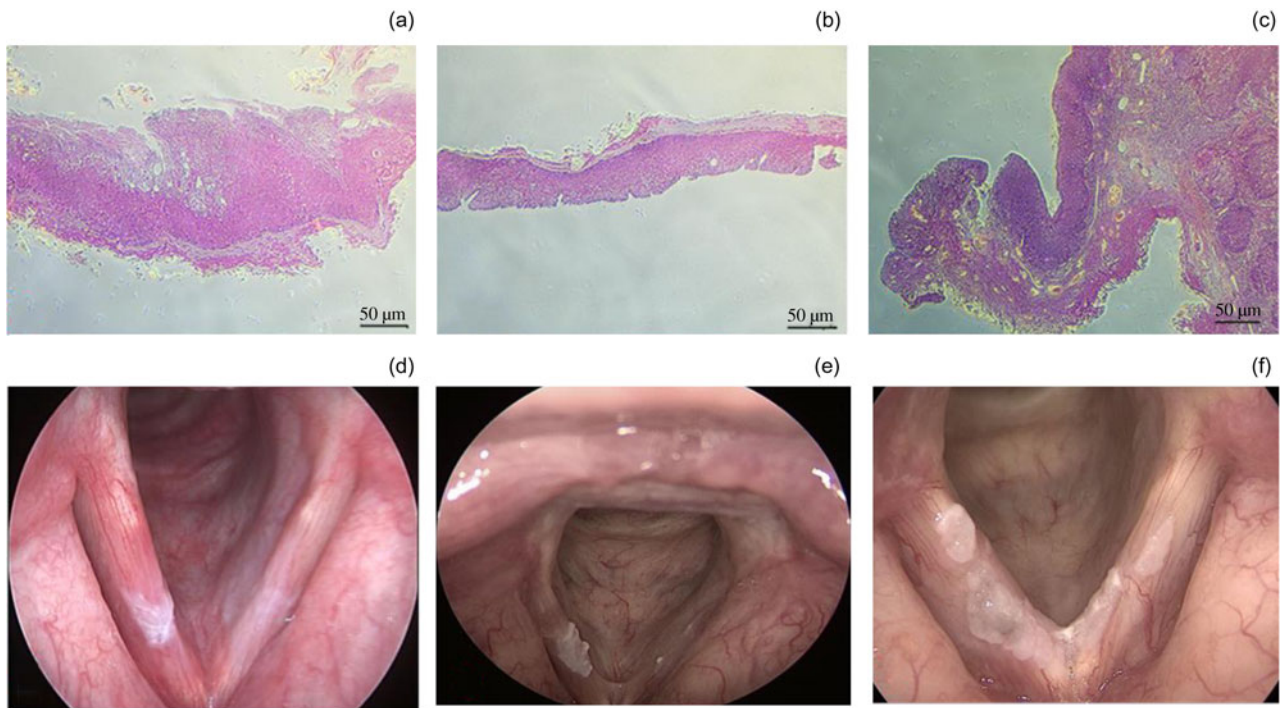


Figure 1. Typical images of vocal fold leukoplakia dysplasia ($\times 20$ magnification). (a) and (d) Mild atypical hyperplasia and smooth flat vocal fold leukoplakia. (b) and (e) Moderate atypical hyperplasia and smooth hypertrophic lesion. (c) and (f) Severe atypical hyperplasia with even canceration and rough lesions.

and III dysplasia in Group A were 14.9 per cent (61 out of 409 patients) and 60.6 per cent (248 out of 409 patients), respectively; the corresponding proportions in Group B were 8.1 per cent (133 out of 1635 patients) and 28.4 per cent (465 out of 1635 patients), respectively. The rates of grade II and III dysplasia in Group A were significantly higher than those in Group B ($p = 0.000$). The relevant data are listed in Table 1.

During the follow-up period, 66 patients in Group A and 231 patients in Group B were lost to follow up. Overall, in Group B, 156 out of 886 patients (17.6 per cent) showed recurrence of lesions and 275 out of 886 patients (31 per cent) showed malignant transformation, which was significantly higher than the values found in Group A (recurrence rate 10.8 per cent (28 out of 259), cancerous rate 25.9 per cent (67 out of 259), $p = 0.000$ for both). Nevertheless, the initial curative efficacy in Group A (63.3 per cent, 164 out of 259 patients) was significantly better than that in Group B (51.4 per cent, 455 out of 886 patients, $p = 0.000$). A second or third CO₂ laser surgery and partial laryngectomy were performed for recurrent and cancerous lesions. No deaths occurred at the study endpoint.

Discussion

Vocal fold leukoplakia lesions are associated with a risk of malignancy. However, most published studies reporting the malignancy rate of vocal fold leukoplakia lesions are based on small sample sizes and their results are quite different. According to a meta-analysis by Weller *et al.*, the overall malignant transformation rate was 14 per cent and the average cancer duration was 5.8 years (range, 1.8–14.4 years), whereas the malignancy rate reported by Bouquot *et al.* ranged from 1 to 40 per cent.⁷

More importantly, several studies have investigated the relationship between the degree of dysplasia and the cancer rate. The reported malignancy rate for mild and moderate dysplasia was 10.6 per cent, while that for severe dysplasia was 30.4 per cent.⁸ According to a systematic review published in 2016, the rate of malignant transformation ranges from 0 to 41.7 per

cent in mild dysplasia, from 0 to 48.0 per cent in moderate dysplasia, from 14.3 to 44.4 per cent in severe dysplasia and from 11.1 to 75 per cent in carcinoma in situ. In general, the more severe the dysplasia, the greater the risk of cancer.

However, it is worth noting that moderate dysplasia is more prone to malignant transformation than previously believed.⁹ Indeed, it is difficult to determine the true malignant transformation rate of vocal fold leukoplakia because of the difficulty in determining the stage of the lesions and whether the lesions were already cancerous at the beginning without surgery. Currently, surgery is indispensable in determining the nature of lesions. These studies demonstrated that not all vocal fold leukoplakia lesions necessarily undergo transformation into laryngeal cancer and that surgical treatment for this disease can be reduced. Our results also illustrate this point. In our study, the rates of malignant transformation in Groups A and B were 25.9 and 31 per cent, respectively. This probability is within the range reported in the literature.

The cancer rate of patients in Group B was significantly higher than that in Group A, which seems to imply that some patients in Group B might not have received timely treatment. From this perspective, treatment decision-making based on the vocal fold leukoplakia appearance classification could help to improve the prognosis.

Currently, CO₂ laser treatment is the main surgical treatment for vocal fold leukoplakia. However, there have been few studies of the post-operative recurrence rates of vocal fold leukoplakia, and the results have been inconsistent. In published studies, the post-operative recurrence rates of vocal fold leukoplakia have ranged from 9.5 to 46.4 per cent.^{10–13} In the present study, 17.6 per cent of patients in Group B developed recurrence compared to only 10.8 per cent of patients in Group A. This recurrence rate is comparable to that reported in the literature. However, the difference is that a subset of patients was treated according to the appearance classification, suggesting that using the appearance classification of vocal fold leukoplakia to guide treatment could also

Table 1. The outcomes of 1442 vocal fold leukoplakia patients treated with carbon dioxide laser surgery

	Group A	Group B	<i>p</i>
Total number of patients (<i>n</i>)	325	1117	
Age (years)	59 ± 9	61 ± 11	0.595
Sex (<i>n</i>)			
– Male	315	1078	0.717
– Female	10	39	
Total specimens (<i>n</i>)	409	1635	
– Unilateral	241	705	
– Bilateral	84	465	
Dysplasia degree (<i>n</i> (%))			
– I (no and mild)	100 (24.4)	1037 (63.4)	0.000
– II (moderate)	61 (14.9)	133 (20.4)	0.000
– III (severe and carcinoma in situ)	248 (60.6)	465 (16.2)	0.000
Appearance classification (<i>n</i> (%))			
– Smooth flat	31 (7.6)		
– Smooth hypertrophic	161 (39.4)		
– Rough	217 (53.1)		
Prognosis (<i>n</i> (%))			
– Recurrence	28 (10.8)	156 (17.6)	0.000
– Canceration	67 (25.9)	275 (31)	0.000
– Cured	164 (63.3)	455 (51.4)	0.000
– Loss to follow up	66 (20.3)	231 (20.7)	
Follow-up period (months (median))	24–86 (42)		

reduce recurrence compared to the traditional method. Unfortunately, many patients were lost to follow up and a more detailed study is needed.

The reported proportion of mild to moderate atypical hyperplasia in vocal fold leukoplakia ranges from 18.3 to 73 per cent, while the reported proportion of severe atypical hyperplasia and carcinoma in situ ranges from 5.9 to 35 per cent.¹⁴ In our study, the rate of grade I dysplasia, including no and mild dysplasia, was as high as 63.4 per cent (1037 out of 1635 patients) in the group treated with the conventional therapeutic approach; the corresponding rate was significantly lower in patients treated according to the appearance classification of vocal fold leukoplakia (24.4 per cent, 100 out of 409 patients, $p = 0.000$). Although this method cannot completely avoid surgical removal of vocal fold leukoplakia lesions in grade I dysplasia, it can greatly reduce the surgical treatment for these patients.

The resection rates of lesions with grade II (14.9 per cent, 61 out of 409 patients) and III (60.6 per cent, 248 out of 409 patients) atypical hyperplasias in Group A patients were much higher than those in Group B patients (grade II 8.1 per cent, 133 out of 1635 patients; grade III 28.4 per cent, 465 out of 1635 patients) and the published literature. This finding indicates that severe atypical hyperplasia lesions that should be surgically treated can be more easily identified using appearance classification compared to the traditional approach.

In addition, we assessed the relationship between appearance and pathological classifications. Although the kappa value was

only 0.422, which is a moderate level ($0.4 < \text{kappa} \leq 0.6$), the correlation was statistically significant ($p = 0.000$). This outcome might have been affected by the sample size. The results suggest that appearance classification is reliable for guiding the treatment of vocal fold leukoplakia. This approach could reduce unnecessary operations and improve therapeutic efficacy.

With the application of narrow band imaging in recent years, researchers have found that this technique offers good resolution for lesions of various tissues.¹⁵ The most important prognostic determinant of vocal fold leukoplakia is the identification of high-risk lesions before treatment.^{16,17} Studies have shown the good efficacy of narrow band imaging in early differentiation between laryngeal carcinoma and precancerous lesions.

The intraepithelial papillary capillary loop of laryngeal precancerous lesions and carcinomas under narrow band imaging was first described in detail by Ni *et al.* The reported sensitivity and specificity of narrow band imaging for the differentiation of laryngeal malignant and benign lesions (88.9 and 93.2 per cent, respectively) were higher than those under white light, especially for invasive cancer.¹⁸ Popek *et al.* also reported an advantage of narrow band imaging over white light in diagnosing laryngeal cancer and precancerous lesions.¹⁹ However, Pietruszewska *et al.* concluded that type III vocal fold leukoplakia lesions, according to the appearance classification on white light imaging, are at risk for malignant transformation, while with narrow band imaging, type V and VI lesions are at-risk lesions.²⁰ This finding indicates that appearance classification also plays a role beyond narrow band imaging in some aspects.

In addition, the interpretation and manipulation of narrow band imaging require more technical expertise, training and special equipment, despite its superiority, which are difficult to achieve for primary healthcare centres, especially in developing countries. In contrast, the appearance classification of vocal fold leukoplakia lesions is more economical, useful, simple, fast and intuitive, and can be applied in medical centres at all levels.

- It is difficult to distinguish high-risk vocal fold leukoplakia without biopsy
- Based on traditional methods, some vocal fold leukoplakia lesions are surgically treated, but such aggressive therapy may be unnecessary and leads to improper clinical management
- High consistency between the appearance and dysplasia degree of vocal fold leukoplakia illustrates the viability of the appearance classification method of diagnosis
- Compared with the traditional method of diagnosis, the appearance classification method can significantly reduce recurrence and cancerous transformation rates
- The appearance classification method can increase the diagnostic sensitivity and specificity of vocal fold leukoplakia

The present study demonstrated that some patients with vocal fold leukoplakia, especially those with smooth flat and smooth hypertrophic lesions, might be overtreated surgically. This situation could be avoided to some extent if our guidance is applied according to morphological classification. Our approach could help to ease the burden on patients and society. Most patients can be followed up for a relatively long time, and it is advised that there should be no hurry in performing surgery. If a lesion changes in size or develops a rough appearance, it is never too late for surgery. Our results also suggest that the morphological classification of vocal fold leukoplakia lesions is closely related to the pathological diagnosis based on surgical specimens. Our classification method could help to reduce excessive surgery, especially for cases of smooth vocal fold leukoplakia, and increase the surgical treatment rate for lesions with severe dysplasia.

Conclusion

Our findings suggest that our approach using the appearance classification could help to improve treatment decision-making for vocal fold leukoplakia and improve treatment accuracy and prognosis. Because of the study's retrospective nature, unknown sources of bias might have influenced our results. A prospective study is required to provide more definitive evidence for the clinical value of vocal fold leukoplakia appearance classification.

Acknowledgements. This research was supported by the Science and Technology Commission of the Shanghai Municipality of China (grant number: 20Y11901900, 21Y11912000), the Health and Family Planning Commission of the Shanghai Municipality of China (grant number: 2019SY059), the Shanghai Health Bureau (grant number: 20214Y0082) and the Double First-class Scientific Research Projects of Fudan University (grant number: IDF158017/028).

Competing interests. None declared

References

- Jackson C. Cancer of the larynx: is it preceded by a recognizable precancerous condition? *Trans Am Laryngol Assoc* 1922;**44**:182–201
- Gabriel CE, Jones DG. Hyperkeratosis of the larynx. *J Laryngol Otol* 1973;**87**:129–34
- Lee DH, Yoon TM, Lee JK, Lim SC. Predictive factors of recurrence and malignant transformation in vocal cord leukoplakia. *Eur Arch Otorhinolaryngol* 2015;**272**:1719–24
- Li CJ, Zhang N, Wu HT. A new classification of VFL by morphological appearance guiding the treatment. *Acta Otolaryngol* 2018;**138**:584–9
- El-Demerdash A, Fawaz SA, Sabri SM. Sensitivity and specificity of stroboscopy in preoperative differentiation of dysplasia from early invasive glottis carcinoma. *Eur Arch Otorhinolaryngol* 2015;**272**:1189–93
- East JE, Tan EK, Bergman JJ, Saunders BP, Tekkis PP. Meta analysis: narrow band imaging for lesion characterization in the colon, oesophagus, duodenal ampulla and lung. *Aliment Pharmacol Ther* 2008;**28**:854–67
- Bouquot JE, Gnepp DR. Laryngeal precancer. a review of the literature, commentary, and comparison with oral leukoplakia. *Head Neck* 1991;**13**:488–97
- Weller MD, Nankivell PC, McConkey C. The risk and interval to malignancy of patients with laryngeal dysplasia: a systematic review of case series and meta-analysis. *Clin Otolaryngol* 2010;**35**:364–72
- Annelienke M, Wouter S. Grade of dysplasia and malignant transformation in adults with premalignant laryngeal lesions. *Head Neck* 2016;**38**:2284–90
- Chen M, Chen J, Cheng L, Wu H. Recurrence of VFL after carbon dioxide laser therapy. *Eur Arch Otorhinolaryngol* 2017;**274**:3429–35
- Minni A, Barbaro M, Rispoli G, Diaferia F, Bernardeschi D, Filippo R. Treatment with laser CO₂ cordectomy and clinical implications in management of mild and moderate laryngeal precancerosis. *Eur Arch Otorhinolaryngol* 2008;**265**:189–93
- Dispenza F, De Stefano A, Marchese D, Martines F, Dispenza C. Management of laryngeal precancerous lesions. *Auris Nasus Larynx* 2012;**39**:280–3
- Zhukhovitskaya A, Battaglia D, Khosla SM, Murry T, Sulica L. Gender and age in benign vocal fold lesions. *Laryngoscope* 2015;**125**:191–6
- Isenberg JS, Corzier DL, Dailey SH. Institutional and comprehensive review of laryngeal leukoplakia. *Ann Otol Rhinol Laryngol* 2008;**117**:74–9
- Schweinfurth JM, Powitzky E, Ossoff RH. Regression of laryngeal dysplasia after serial microflap excision. *Ann Otol Rhinol Laryngol* 2001;**110**:811–4
- Klimza H, Jackowska J, Tokarski M, Piersiala K, Wierzbicka M. Narrow-band imaging (NBI) for improving the assessment of vocal fold leukoplakia and overcoming the umbrella effect. *PLoS One* 2017;**29**:1–7
- Huang F, Yu J, Zhang F, He C, Li S, Shao J. The usefulness of narrow-band imaging for the diagnosis and treatment of VFL. *Acta Otolaryngol* 2017;**137**:1002–6
- Ni XG, He S, Xu ZG, Gao L, Lu N, Yuan Z *et al*. Endoscopic diagnosis of laryngeal cancer and precancerous lesions by narrow band imaging. *J Laryngol Otol* 2011;**125**:288–96
- Popek B, Bojanowska-Poźniak K, Tomasik B, Fendler W, Jeruzal-Świątecka J, Pietruszewska W. Clinical experience of narrow band imaging (NBI) usage in diagnosis of laryngeal lesions. *Otolaryngol Pol* 2019;**73**:18–23
- Pietruszewska W, Morawska J, Rosiak O, Leduchowska A, Klimza H, Wierzbicka M. VFL: which of the classifications of white light and narrow band imaging most accurately predicts laryngeal cancer transformation? Proposition for a diagnostic algorithm. *Cancers (Basel)* 2021;**13**:3273–86