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ORIGINAL RESEARCH

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The sensitivity of laryngeal findings in predicting high-grade dysplasia in patients with vocal fold leukoplakia undergoing office-based biopsies: A retrospective analysis of 100 cases

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Abstract

Objective: To investigate the sensitivity of laryngeal findings in predicting high-grade dysplasia/carcinoma in situ (CIS) and squamous cell carcinoma (SCC) in patients with vocal fold leukoplakia.

Methods: A retrospective review of the medical records and video recordings of the laryngeal examination of patients with vocal fold leukoplakia who underwent unsedated office-based laryngeal biopsy in a tertiary referral center between January 2022 and August 2023 was conducted. Laryngeal findings included the size, surface, projection, and edges of the lesion. Vocal fold leukoplakia was classified according to the WHO as benign, low-grade dysplasia, high-grade dysplasia/CIS, and squamous cell carcinoma.

Results: Seventy patients with 100 vocal fold leukoplakia were included. Size was found to have the highest sensitivity with an AUC of 0.730 (95% CI [0.618–0.842], $p = 0.002$) followed by surface and projection with AUCs of 0.672 (95% CI [0.548–0.795], $p = 0.019$) and 0.675 (95% CI [0.546–0.804], $p = 0.017$), respectively. Furthermore, the odds of diagnosing high-risk lesions (high-grade dysplasia/CIS and SCC) were the greatest when the lesion was large and rough (OR = 10.28; 95% CI [3.08–34.36]).

Conclusion: The morphological features of vocal fold leukoplakia may assist the physician in predicting the risk of malignancy. Large and rough lesions were more likely to harbor high-grade dysplasia/CIS and SCC compared to small and smooth lesions.

KEYWORDS

dysplasia, laryngoscopy, leukoplakia, office-based, vocal folds

1 | INTRODUCTION

Vocal fold leukoplakia is defined as a whitish mucosal lesion of the vocal fold.[1] The main risk factors for its development are smoking,

Jad Hosri and Jessica Aoun are the co-first authors of this manuscript as they have equally contributed to this manuscript.

reflux disease, and genetic predisposition with various genetic markers such as CDKN24 being identified.[2,3] The presence of leukoplakia invariably denotes pathological changes in the mucosal lining. Dysplasia may be present in one out of two patients with a high predisposition to cancer being noted in a large percentage of cases. What is most alarming is that non-dysplastic lesions may also progress to malignancy along the course of the disease. Several predictors of malignancy have been described in the literature in an attempt to stratify patients with vocal fold leukoplakia into low risk versus high risk for cancer. These include the size of the lesion among other morphological features seen on laryngeal examination. Mucosal lesions that extend beyond half the vocal fold usually carry a worse prognosis than those that are limited to less than half the vocal fold.[4] Similarly, flat and smooth lesions are less likely to harbor malignant cells in comparison with elevated lesions with a rough surface.[5] Other predictive signs of malignancy include the extent of mucosal waves on laryngeal videostroboscopy and the pattern of vascularity seen using narrow-band imaging.[6] A decrease in mucosal waves during phonation, for instance, denotes invasion of the deep structures of the vocal fold and is considered an ominous sign by many.[7]

Numerous studies in the literature highlighted the sensitivity of the morphological features of vocal fold leukoplakia in predicting high-grade dysplasia/carcinoma in situ (CIS) and squamous cell carcinoma (SCC). The sensitivity was computed based on the pathological findings of the biopsy taken in the operating room under direct laryngoscopy. Based on many reviews, the sensitivity of the morphological features ranged between 61.4% and 86.3%.[8–11] With the reform in laryngology practice toward office-based surgery, patients with vocal fold leukoplakia are now invariably offered laryngeal biopsy in an office setting under local anesthesia. Despite the advances in technology in terms of instrumentation, there are still limitations to office-based laryngeal biopsies, among which are the reduced sensitivity and diagnostic yield secondary to sample size and depth.[12]

This study aimed to investigate the sensitivity of laryngeal findings in predicting high-grade dysplasia/CIS and SCC in patients with vocal fold leukoplakia who had their biopsies performed in-office under local anesthesia.

2 | MATERIALS AND METHODS

2.1 | Patient characteristics

After obtaining Institutional Review Board approval (IRB BIO ID: 2022-0280), a retrospective review of the medical records and video recordings of the laryngeal examination of patients with vocal fold leukoplakia who underwent un-sedated office-based laryngeal biopsy between January 2022 and September 2023 was conducted. All patients were examined using the flexible nasopharyngoscope with distal chip camera (HD Video Rhino-Laryngoscope from KARL STORZ) with or without videostroboscopy. Patients with incomplete medical records and/or with no laryngeal endoscopic recordings were excluded. A total of 70 patients were included in this study, and a comprehensive review of 100 vocal fold leukoplakia was conducted.

2.2 | Data characteristics

Demographic data including gender, age, smoking, laryngopharyngeal reflux (LPR), and laterality of lesion (unilateral vs. bilateral) were collected. Given the retrospective nature of this study and the limited information available to us in the medical records on the extra-laryngeal signs of LPR, which precluded the use of the Reflux Sign Assessment (RSA) tool,[13] the Reflux Finding Score was used instead.[14] The RFS is a validated questionnaire that consists of 10 items depicting signs of laryngopharyngeal reflux on laryngeal examination. A score above 7 is suggestive of LPR.[14] Preoperative laryngeal findings describing the morphology of the vocal fold lesion included the size of the lesion (>50% or <50% of the entire length of the vocal cord), its surface (rough or smooth), projection (elevated or flat), and edges (regular or irregular) (Figure 1A,B). Two otolaryngologists, blinded to the patient's demographic data and pathology results, independently reviewed the laryngeal endoscopic recordings and categorized the lesions' morphology based on the established characteristics mentioned earlier. To assess the reliability of the reported findings, inter-rater reliability was analyzed by calculating the intra-class correlation

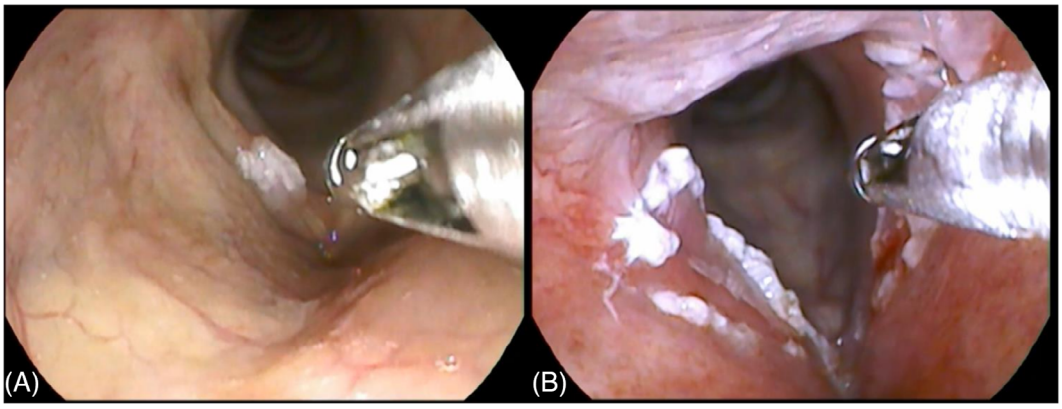

FIGURE 1 (A) Endoscopic image showing a raised right vocal fold leukoplakia with a large size and rough surface. (B) Endoscopic image showing bilateral, raised leukoplakia with a rough surface occupying the entire length of the vocal folds.

coefficient (ICC) based on a single measurement, absolute agreement, and two-way mixed-effects model.

2.3 | Histological characteristics

The histological assessment of laryngeal leukoplakia was performed using the new fifth edition of the WHO classification.[15] Lesions were classified as benign, low-grade dysplasia, high-grade dysplasia/CIS, and squamous cell carcinoma (SCC). Low-grade dysplasia is characterized by augmentation of the basal hyperplasia and cytologic atypia limited to the lower portions of the epithelium (Figure 2A). High-grade dysplasia is characterized by the extension of dysplasia beyond the inner third of the epithelium to almost complete thickness of the epithelium (Figure 2B). Invasive squamous cell carcinoma (SCC) can be recognized by the presence of disorganized growth, loss of polarity and maturation, increased nuclear-to-cytoplasmic ratio, hyperchromasia, dyskeratosis/paradoxical maturation, increased and atypical mitoses, desmoplastic stroma, and inflammatory infiltrates (Figure 2C). Benign and low-grade dysplasia were labeled as low-risk lesions, whereas high-grade dysplasia/CIS and squamous cell carcinoma were considered as high-risk lesions.

2.4 | Statistical analysis

Descriptive statistics were used to compute the means and the standard deviation of the continuous variables and the frequencies of the categorical variables. The chi-square test was used to determine the association between the morphological and histological characteristics. Spearman's coefficient was calculated to determine the correlation between laryngeal findings and histological grading. The strength of the correlation was classified as mild if $r < 0.3$, moderate if $r = 0.3–0.6$, and strong if $r > 0.6$. The diagnostic accuracy/sensitivity of the laryngoscopic findings was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC) analysis and by calculating the odds ratio. All the analyses were conducted using Statistical Package for the Social Sciences (SPSS, version 29.0; Chicago, IL, USA), and a p-value less than 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Demographic data

Seventy patients with 100 vocal fold leukoplakia were included in this study. The majority of the study population were males (80%) and smokers (60%). The mean age of the participants was 59.66 ± 14.3 years. Forty patients had unilateral vocal fold leukoplakia, and 30 patients had bilateral vocal fold leukoplakia. The mean RFS of the total study group was 9.52 ± 1.77 (Table 1).

3.2 | Morphological features and histological findings

The size of the lesion was more than 50% of the entire length of the vocal fold in 51 cases. Fifty-five lesions had a rough surface, 45 were raised, and 60 had irregular edges.

When classified histologically, 59% of the vocal fold leukoplakia were benign. The remaining were stratified as low-grade dysplasia, high-grade dysplasia/CIS, and SCC in 16%, 10%, and 10% of the cases,

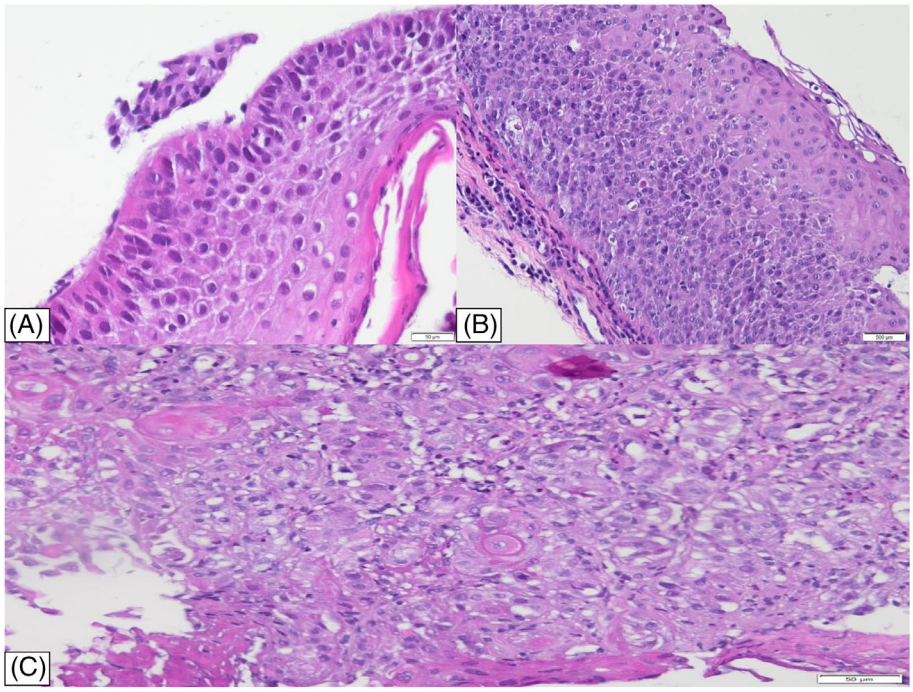

FIGURE 2 (A) Low-grade dysplasia characterized by basal hyperplasia and cytologic atypia limited to the lower portions of the epithelium. (B) High-grade dysplasia involving almost the entire thickness of the epithelium. (C) Invasive squamous cell carcinoma characterized by disorganized growth, loss of polarity, and increased nuclear-to-cytoplasmic ratio.

TABLE 1 Demographic characteristics of the study population.

Demographic data ($N = 70$)	Value
Gender (*n* [%])	
Male	56 (80)
Female	14 (20)
Age in years (mean ± SD)	59.66 ± 14.31
Laterality (*n* [%])	
Unilateral	40 (57.1)
Bilateral	30 (42.9)
Smoking (*n* [%])	36 (56.3)
RFS (mean ± SD)	9.52 ± 1.77

Abbreviations: RFS, reflux finding score; SD, standard deviation.

TABLE 2 Morphological and histological features of vocal fold leukoplakia.

Features ($N = 100$)	Value
Size	*n* (%)
<50%	49 (49)
>50%	51 (51)
Surface	*n* (%)
Smooth	45 (45)
Rough	55 (55)
Projection	*n* (%)
Flat	55 (55)
Raised	45 (45)
Edges	*n* (%)
Regular	40 (40)
Irregular	60 (60)
Histology	*n* (%)
Benign	59 (62.1)
Low-grade dysplasia	16 (16.9)
High-grade dysplasia/CIS	10 (10.5)
Squamous cell carcinoma	10 (10.5)

Abbreviation: CIS, carcinoma in situ.

respectively. Only 5% of the biopsies taken were non-diagnostic and could not be assessed for histological grading (Table 2). Of the 10 patients with vocal fold SCC, 3 patients underwent surgery (type 3 cordectomy under general anesthesia), 5 underwent radiotherapy, and 2 underwent combined treatment (office-based blue laser therapy and radiotherapy). The final pathology of the three patients who underwent surgery under general anesthesia was SCC, that is, commensurate with the pathology of the first biopsy taken in-office under local anesthesia. Of the 5 patients with non-diagnostic pathology, two underwent direct laryngoscopy and biopsy under general anesthesia, one patient was observed closely with no further intervention, and 2 patients were lost for follow-up. The pathology of the vocal fold lesions of the two patients who underwent biopsy under general anesthesia revealed low-grade dysplasia in one and moderate dysplasia in the second.

3.3 | Sensitivity of laryngeal findings

To determine the sensitivity of each laryngeal finding in predicting high-grade dysplasia/CIS and SCC, the ROC curves were constructed and AUC was calculated. Size was found to have the highest sensitivity with an AUC of 0.730 (95% CI [0.618–0.842], $p = 0.002$) followed by surface and projection with AUCs of 0.672 (95% CI [0.548–0.795], $p = 0.019$) and 0.675 (95% CI [0.546–0.804], $p = 0.017$), respectively. Combined ROC analysis of the size and surface of the lesion revealed an AUC of 0.760 (95% CI [0.642–0.878], $p < 0.001$) (Figure 3). The coordinates of the curve describing the sensitivity and 1-specificity values according to data are represented in the Supplementary Material S1.

Furthermore, the odds of diagnosing high-risk lesions (high-grade dysplasia/CIS and SCC) were the greatest when the lesion was large and rough (OR = 10.28; 95% CI [3.08–34.36]) (Table 3).

3.4 | Correlation between laryngeal findings and histological grading

Lesions greater than 50% of the length of the vocal fold were more likely to harbor high-grade dysplasia/CIS and SCC (80% and 100%, respectively) in comparison with lesions less than 50% of the total length of the vocal fold (20% and 0%, respectively) ($p < 0.001$). The correlation between the size of the lesion and the histological grading was moderate ($r = 0.376$, $p < 0.001$).

Lesions with a rough surface were more likely to harbor high-grade dysplasia/CIS and SCC (80% and 90%, respectively; $p = 0.005$) and so were elevated lesions (70% and 80%, respectively; $p = 0.013$). Both surface texture and projection were weakly correlated with histological grading ($r = 0.283$, $p = 0.005$, and $r = 0.286$, $p = 0.005$, respectively).

When combined, large and rough lesions were more likely to develop SCC and high-grade dysplasia/CIS (90% and 70%, respectively) than small and smooth lesions (10% and 30%, respectively) ($p < 0.001$). The combination of size and surface texture had a stronger correlation with the pathology of the vocal fold leukoplakia ($r = 0.435$, $p < 0.001$, 95% CI [0.250–0.589]) than the combination of size and projection ($r = 0.342$, $p < 0.001$, 95% CI [0.145–0.513]) or the combination of all three features together ($r = 0.346$, $p < 0.001$, 95% CI [0.149–0.516]) (Table 4).

3.5 | Correlation between RFS and degree of dysplasia

Among the participants, 86.2% had a RFS above 7 suggestive of laryngopharyngeal reflux. The prevalence of a positive RFS (above 7) was 88.2% in patients with low-risk lesions in comparison with 78.6% in those with high-risk lesions ($p = 0.392$). When looking at the signs of

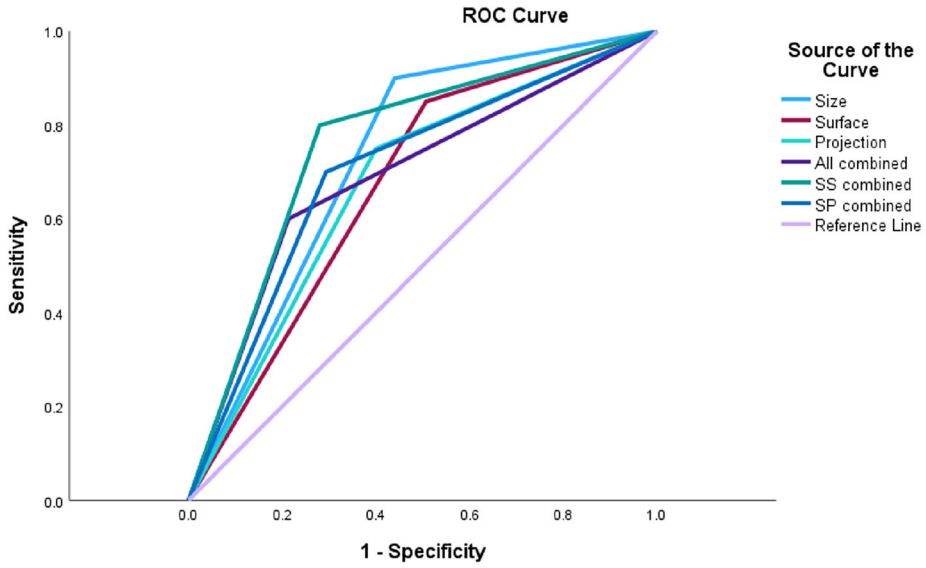

FIGURE 3 ROC curves of size, surface, projection, size/surface, size/projection, and size/surface/projection.

TABLE 3 Odds ratios of morphological features for the diagnosis of high-risk lesions.

		95% confidence interval	
Features	**OR**	**Lower**	**Upper**
Size	11.45	2.48	52.92
Surface	5.52	1.49	20.41
Projection	4.5	1.48	13.69
Edges	3.14	0.96	10.29
Size/surface	10.28	3.08	34.36
Size/projection	5.62	1.91	16.52
Size/surface/projection	5.53	1.93	15.83

Abbreviation: OR, odds ratio.

laryngopharyngeal reflux across different degrees of dysplasia, there was no correlation between the mean RFS and the histological grading ($r = 0.033$, $p = 0.792$).

4 | DISCUSSION

Estimating the sensitivity of endoscopic findings in predicting high-grade dysplasia/CIS and SCC in patients with vocal fold leukoplakia is a topic of growing interest given the high rate of malignant transformation of these lesions. Although the diagnosis is primarily based on histological examination, relying on the morphological features seen on endoscopy as predictors of malignancy and/or malignant transformation is of paramount importance in individualizing treatment strategies. The main morphological features investigated in the literature are the size of the lesion, the texture of its surface, its projection, and the regularity of its edges. Other relevant features that may be of value include the color of the lesion, the presence of hyperemia or vascular stippling, and the vibratory behavior of the vocal fold during phonation.

The results of this investigation revealed that the morphological features of vocal fold leukoplakia have a high sensitivity in predicting high-grade dysplasia/CIS and SCC. The size, surface, and projection of the lesion were found to have a sensitivity of 73%, 67.2%, and 67.5%, respectively. When the size and surface were combined, the sensitivity increased to 76%. Moreover, there was a moderate correlation between size and surface combined and the grade of dysplasia on histological examination.

Our findings are in agreement with many studies in the literature on the sensitivity of laryngeal findings in predicting high-grade dysplasia/CIS and SCC in patients with vocal fold leukoplakia who had undergone biopsies under direct laryngoscopy. In 2015, Young et al. investigated the association between the endoscopic characteristics and histological grading in 68 patients with vocal fold leukoplakia and noted that features such as non-homogenous color, irregular texture, large size, and presence of hyperemia correlated significantly with the presence of severe dysplasia, carcinoma in situ, and/or invasive carcinoma.[4] In 2016, Fang et al. established a clinical scoring system using demographic data and lesion characteristics in 112 patients with vocal leukoplakia who underwent operative excisional biopsy. The authors noted that the patient's age, non-homogenous lesion texture, and presence of hyperemia are independent risk factors predicting malignancy.[8] In 2017, Zhang et al. explored the correlation between the morphological features and histological findings of 1635 lesions of the vocal folds. Exophytic and non-homogenous lesions with a rough surface carried a higher risk of cancerization and severe dysplasia (11.2% and 8.2%, respectively) compared to flat and smooth lesions with uniform homogeneous surfaces (0.9% and 1%, respectively).[5] In agreement with the aforementioned, in 2018, Chen et al. stressed the importance of the patient's age, lesion size, and morphology in predicting malignancy and managing these lesions. The study included 375 patients diagnosed with vocal fold leukoplakia who underwent

TABLE 4 Association between morphological features and histological grading.

Features (*n* [%])	Benign (*n* = 59)	Low-grade dysplasia (*n* = 16)	High-grade dysplasia/CIS (*n* = 10)	SCC (*n* = 10)	*p*-value
Size					
<50%	36 (61)	6 (37.5)	2 (20)	0 (0)	<0.001*
>50%	23 (39)	10 (62.5)	8 (80)	10 (100)	
Surface					
Smooth	29 (49.2)	8 (50)	2 (20)	1 (10)	0.005*
Rough	30 (50.8)	8 (50)	8 (80)	9 (90)	
Projection					
Flat	35 (59.3)	10 (62.5)	3 (30)	2 (20)	0.013*
Raised	24 (40.7)	6 (37.5)	7 (70)	8 (80)	
Edges					
Regular	25 (42.4)	8 (50)	3 (30)	1 (10)	0.230
Irregular	34 (57.6)	8 (50)	7 (70)	9 (90)	

Abbreviations: CIS, carcinoma in situ; SCC, squamous cell carcinoma.
*Statistically significant.

complete resection using a carbon dioxide (CO_2) laser under general anesthesia. Squamous cell carcinoma was found in 30.6% of rough lesions compared to only 5.2% and 0% in elevated/smooth and flat/smooth lesions, respectively.[9] In 2020, Rzepakowska et al. assessed the role of preoperative endoscopy in predicting malignancy in a cohort of 57 patients with vocal fold leukoplakia. All malignant lesions were large and thick, 92.3% had a heterogeneous color and irregular texture, and 61.5% had the presence of hyperemia. However, only color and hyperemia were identified as significant predictors of malignancy after multivariable logistic regression.[10] In a study on 138 patients with 175 vocal cord leukoplakia lesions, Li et al. analyzed the relationship between the laryngeal findings and pathological features and found that thick and hyperemic lesions had 3.94 and 23 times the odds of predicting high-risk transformation, respectively. The authors stressed the need to consider these parameters as independent predictors for the risk of cancerization in vocal fold leukoplakia.[11]

The similarity between the results of our review and those documented in the literature can be attributed to the high diagnostic yield of office-based biopsies in comparison with biopsies performed in the operating room under general anesthesia. In 2014, Castillo Farias et al. compared the effectiveness of in-office biopsies to direct laryngoscopy in diagnosing pharyngolaryngeal lesions in 88 patients and reported a diagnostic accuracy of 81.8%.[16] Similarly, in 2016, Cha et al. evaluated the accuracy of office-based biopsies in 581 patients and reported sensitivity, specificity, positive predictive value, and negative predictive value of 78.2%, 100%, 100%, and 87.3%, respectively. The authors concluded that office-based biopsy can be used for early detection of laryngeal malignancy in the presence of suspicious vocal fold lesions.[17] In 2021, a systematic review by Owusu-Ayim et al. assessed the precision of in-office biopsies in diagnosing laryngopharyngeal tumors. Sixteen studies were included in the review with a total of 1572 biopsies that were performed using flexible endoscopy. In the outpatient setting, 81.6% of cases were accurately diagnosed with a median sensitivity and specificity of 73% and 96.7%, respectively, for in-office biopsies.[18]

The results of this investigation reinstate the sensitivity of the laryngeal findings in predicting high-grade dysplasia/CIS and SCC in vocal fold leukoplakia biopsied in the office. Nevertheless, this study has its limitations. One is its retrospective nature. Second, the authors did not evaluate other morphological features such as the presence or absence of hyperemia, the thickness of the tumor, or its color, which could play a substantial role in predicting malignancy in patients with vocal fold leukoplakia.

5 | CONCLUSION

The morphological features of vocal fold leukoplakia seen on laryngeal endoscopy have a high sensitivity in predicting high-grade dysplasia/CIS and SCC in patients undergoing office-based laryngeal biopsy. The physician should be extremely diligent in the evaluation of patients with vocal fold leukoplakia, particularly those with large and rough lesions. Treatment strategies need to be individualized.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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