

Diagnostic Yield of Office-Based Laryngeal Biopsy in Patients With Leukoplakia; A Case Study With Review of the Literature

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SUMMARY: Objective. To review the authors experience in un-sedated office-based biopsies of patients with vocal fold leukoplakia and to review the literature.

Material and Method. A retrospective review of 29 patients was conducted.

Results. A total of 41 office-based procedures were performed (eight patients had bilateral vocal fold lesions and four patients had the procedure performed twice). In 26 out of the 41 biopsies, the pathology revealed benign lesion. In eight cases, the pathology showed dysplasia (four high-grade and four low-grade). Seven biopsies revealed squamous cell carcinoma. Five patients underwent suspension micro-laryngoscopy for definitive diagnosis. Four of whom had a change in their diagnosis.

Conclusion. Un-sedated office-based biopsy of vocal fold leukoplakia is an alternative to suspension microlaryngoscopy in case of carcinoma or nonmalignant lesions.

KEY WORDS: Leukoplakia—Biopsy—Vocal fold.

INTRODUCTION

Leukoplakia of the vocal fold is defined as a whitish mucosal lesion with an estimated incidence of 2.1-10.2% per 100,000 persons.^{1,2} The etiology is multifaceted with smoking, laryngopharyngeal reflux and phono-traumatic behavior being the most commonly reported risk factors. Genetic predisposition plays an important pathogenic role. Genetic markers such as CDKN24 and interleukin-10 polymorphism are reliable predictors of disease progression.^{3,4} Given that the vocal fold mucosal lining is nonkeratinizing, the presence of leukoplakia invariably denotes an underlying pathologic process. Mucosal changes can range from hyperplasia to dysplasia, to carcinoma *in situ* to cancer. Despite the description of several predictors for malignancy, the diagnosis is based primarily on histologic examination. Tissue samples are routinely obtained using conventional suspension micro-laryngoscopy, with dysplasia and/or cancer being reported in almost one out of two patients.^{5,6}

With the advent in technology and instrumentation, un-sedated office-based laryngeal biopsy has recently become a viable alternative to suspension microlaryngoscopy with the main added-value being cost containment and avoidance of general anesthesia.⁷⁻⁹ Despite these benefits, the diagnostic yield of office-based biopsy has always been a concern, with the major constraint being the size and depth of the tissue sample. Several studies on the yield and accuracy of office-based laryngeal biopsy have been reported over the last two decades with no clear consensus.¹⁰⁻²⁰ The aim of this manuscript is to cast further information on the diagnostic yield of office-based laryngeal biopsy in patients with leukoplakia.

The authors present their experience in 41 procedures and review the literature on this topic. The findings of this case series will be an addition to the existing literature.

MATERIAL AND METHOD

After obtaining Institutional Review Board approval, a retrospective review of the medical records and laryngeal endoscopic recordings of patients with suspicious vocal fold lesions (leukoplakia, erythroplakia, and/or nonspecific mucosal lesions) and who underwent un-sedated office-based laryngeal biopsy between January 2017 and December 2019 was conducted. All patients were evaluated using either flexible laryngoscopy or direct telescopic laryngeal examination with or without video-stroboscopy. All patients were offered office-based laryngeal biopsy as an alternative to suspension microlaryngoscopy at their initial assessment (surgical technique section below). Patients who accepted to undergo office-based laryngeal biopsy were included in this review. Patients who underwent suspension microlaryngoscopy for biopsy, and those who had incomplete medical records or whose laryngeal endoscopic recordings were missing were excluded. A total of 29 patients were enrolled in this study and a total of 41 procedures were reviewed. Demographic data was collected and included gender, age, smoking, laterality of lesion (unilateral vs. bilateral), and number of procedures. Tissue sampling (sufficient vs. insufficient) and the yield of office-based laryngeal biopsy are reported.

Descriptive statistics were used to compute the means and the standard deviation of the continuous variables and the frequencies of the categorical variables. All analyses were conducted using Statistical Package for the Social Sciences version 24 software package.

Technique for office-based laryngeal biopsy

All procedures were performed in a clinic setting without sedation. Intramuscular glucopyrrolate (200 μ g/1 ml) was administered prior to the procedure in all patients in order to reduce pooling of secretions in the larynx. With the

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patient fully awake and in the upright sitting position, local nasal anesthesia, and decongestion were applied to both nasal cavities using sponges soaked with 1% lidocaine HCL with 1:100,000 Epinephrine and 0.1% Xylometazoline Hydrochloride. The oropharynx and hypopharynx were anesthetized using xylocaine spray (2%). Xylocaine gel was also applied to the dorsum of the tongue in patients who underwent the transoral fiberoptic approach. Topical anesthesia to the larynx was achieved by dripping 2% lidocaine HCL via the working channel of the fiberoptic endoscope (Ref 11001UD1 by Karl Storz), and while the patient was asked to sustain phonation. After having insured complete anesthesia of the laryngeal mucosa, a 3 mm cup forceps was advanced through the working channel of the fiberoptic scope to the targeted lesion. [Figure 1](#) on the average two biopsies were taken from each lesion. Following the procedure, patients were instructed to remain nothing per os and resume oral intake only 1 hour after the procedure in order to avoid risk of aspiration.

RESULTS

Demographic data

Twenty-nine patients, 24 males and five females were included in this study. The mean age was 58.58 years \pm 12.23 years. Twenty-three patients were smokers. Twenty-one patients had unilateral vocal fold lesions and eight patients had bilateral vocal fold lesions. [Table 1](#).

Yield of un-sedated-office based biopsy

A total of 41 office-based procedures were performed (eight patients had bilateral vocal fold lesions and four patients had the procedure performed twice). Among these four patients, one had the biopsy done before and after radiation therapy for SCC, and the other three had associated

TABLE 1.
Demographic Data

Total number of subjects (N)	29
Total number of biopsies	41
Age (years) \pm SD	58.58 \pm 12.23
Gender (n)	
• Male&&• Female	24&&5
Smoking (n)	
• Smokers&&• Nonsmokers	23&&6

morbidities that precluded repeated biopsies for follow up under general anesthesia. The procedures were well-tolerated by all patients. Tissue sampling was adequate in all procedures except in one where the depth invasion could not be assessed. In 26 out of the 41 biopsies, the pathology revealed benign lesion. In eight cases, the pathology showed dysplasia (four high-grade and four low grade). Squamous dysplasia is defined by the WHO as “altered epithelium with an increased likelihood for progression to squamous cell carcinoma (SCC).” It is classified based on a two-tier grading: high grade and low grade dysplasia.²¹ Seven biopsies revealed SCC. Five patients underwent suspension micro-laryngoscopy for further confirmation of their diagnosis, either because of insufficient tissue for examination (n = 1), or for highly suspicious lesions (n = 4). Four out of the five patients had a change in their diagnosis. One patient previously diagnosed with mild dysplasia had his diagnosis changed to SCC. One patient previously diagnosed with right vocal fold SCC, had evidence of both right and left vocal fold SCC under microscopic examination. One patient previously diagnosed with SCC with no invasion had evidence of invasion (following biopsy under general anesthesia), and one patient previously diagnosed with mild-moderate dysplasia had his diagnosis changed to severe dysplasia.

DISCUSSION

Estimating the prevalence of carcinoma in patients with vocal fold leukoplakia has always been a daunting task. Despite the use of patient’s characteristics and clinical morphologic features as predictors of malignancy and/or malignant transformation, the diagnosis of malignancy in leukoplakia remains primarily histologic. Tissue samples are obtained either via suspension micro-laryngoscopy and biopsy or via an office-based procedure. The major challenges to this latter are the adequacy of tissue sampling and their diagnostic yield. The results of this investigation revealed that tissue samples were adequate in all 41 procedures except in one case where the depth of invasion could not be assessed. With respect to the diagnostic yield, in four patients the pathology report was not commensurate with the clinical presentation that was highly suspicious of malignancy. In 10% of the cases, the diagnosis changed following suspension micro-laryngoscopy and biopsy. The indications for SML were presence of highly suspicious lesions (n = 4),

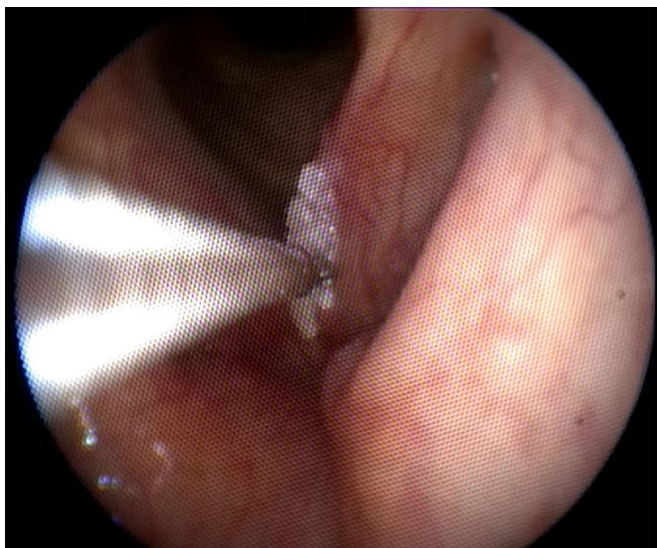


FIGURE 1. A flexible endoscopic image showing biopsy of a left vocal fold leukolakia using a cup forceps.

TABLE 2.
Review of the Literature on Office Based Laryngeal Biopsy in Patients With Leukoplakia and/or Suspicious Lesions

	Total Number of Patients (N)	Type and Number of Laryngeal Lesions (n) (Leukoplakia, Erythroplakia vs. Nonspecific Mucosal Lesion)	Adequate Tissue Removal	Laryngeal Dysplasia/ Cancer (as Reported by the Authors)	Yield of Laryngeal Biopsies (Adequate Sampling/Number of Patients With SCC /Sensitivity and Specificity)
Omori et al 2000	114	Laryngeal/pharyngeal n = 54	95.2%	Laryngeal/pharyngeal cancer (n = 12)	Laryngeal/pharyngeal cancer n = 11
Sharma et al 2005	116	Suspicious lesions n = 12	94.5%	Dysplasia 8.33% SCC 66.7%	Suggestive of SCC 1 out of 12
Naidu et al 2011	11	9	64%	SD 33.3% (3 out of 9) SCC 44.4% (4 out of 9)	Rate of diagnostic office- based biopsies 64% (n = 11)
Cohen et al 2013	102	Leukoplakia, erythroplakia, lesion on immobile VF, cauliflower appearance	94.1%	SD 17.7% SCC 35.4%	Sensitivity 69.2% Specificity 96.1%
Zalvan et al 2013	26	Nonspecific VF lesions 69%	NS	54%	Office based biopsy and operative biopsy were the same in 81%
Richards et al 2014	76	-	NS	SD 23 SCC 4	Sensitivity 60% Specificity 87%
Lippert et al 2014	116	73	NS	62 out of 116	Office based biopsy diagnostic in 83.6% Non-diagnostic in 17 out 116
Cha et al 2016	581	581	99.1%	Premalignant 101 SCC 193	Sensitivity 78.2% Specificity 100%
Wellenstein et al 2017	201	138	97.5%	SD 21.4% SCC 57.2%	Insufficient sample 1 out of 201
Hassan et al 2018	43	Suspicious glottic lesions (n = 16) Supraglottic/pyriform (n = 11)	100%	41 cases	Sensitivity 100% Specificity 75.6%
Mohammed et al 2018	115	53	95.7%	38 cases	89% did not require further interventions
Saga et al 2018	30	Suspicious lesions n = 30	96.7%	26 cases	30% required another biopsy under general anesthesia
Hamdan et al 2020	29	Suspicious lesions n = 41	97.57%	16 cases	39% 4 patients underwent 2 office biopsies 6 patients underwent operative biopsy

Abbreviations: SD, severe dysplasia; SCC, squamous cell carcinoma; NS, not specified; VF, vocal fold.

and insufficient tissue sample for assessment of basement membrane invasion ($n = 1$). In summary, there were 15 true positive and four false negative. The prevalence of benign lesion and malignant lesions were 63% and 17% of cases, respectively, whereas the prevalence of dysplasia of various degrees was 20%.

These findings are in agreement with numerous reports in the literature showing a large variability in the diagnostic yield of tissue sampling and in the prevalence of dysplasia and/or carcinoma. In 2000, *Omori et al* described the usage of video-endoscopic-assisted laryngeal surgery in 114 patients with various laryngeal pathology, among whom 36 had been diagnosed with vocal fold hyperplasia, and 12 with laryngeal or pharyngeal cancer. The authors reported successful removal of sufficient tissue for pathologic examination in all cases, and advocated the application of this procedure for tissue sampling in patients with benign and malignant lesions of the vocal folds.¹⁰ In 2005, *Sharma et al* studied the yield and complications of trans-nasal flexible laryngo-oesophagoscopy in 116 patients, 10 of whom with laryngeal pathology. The histologic results were definitive in 11 out of 12 laryngeal biopsies, 9 out of whom had invasive SCC and/or dysplasia. In only one patient, the pathology was inconclusive suggestive of SCC.¹¹ In 2013, *Cohen et al* reported the reliability of trans-nasal flexible fiberoptic laryngeal biopsy in an office-setting in 102 patients. Adequate tissue for histologic examination was obtained in 94.1% of cases. Invasive carcinoma and carcinoma in situ were reported in 35.4% and 17.7% of cases, respectively. The false negative rate in patients with benign pathology was 33%.¹² In keeping with the aforementioned, *Zalvan et al* in 2013 reported a similarity between office-based biopsy and operating room biopsy in 81% of cases. The study included 26 patients with laryngopharyngeal lesions, 69% of whom with vocal fold pathology. Thirteen percent of the lesions diagnosed as benign in the office setting were found to be malignant in the operating room biopsies. Similarly, 20% of the samples diagnosed as non-benign in the office-setting turned out to be benign in the operating room setting.¹³ In 2014, *Lippert et al* reported in-office biopsy in 116 patients with suspicious lesions, 62.9% of whom were laryngeal. Eight-eight patients had their diagnosis in the office with no further need for operative biopsy. In five cases, a second biopsy in the office was needed in order to confirm the diagnosis. In the overall sample, 17 patients had their office diagnosis changed following operative biopsies.¹⁴ In a review of 76 patients who underwent both office-based biopsy and direct microlaryngoscopy and biopsy, *Richard AL et al* in 2014 reported sensitivity and specificity of office-based analysis as 60% and 87% respectively. The positive and negative predictive values were 78% and 74%, respectively. In conclusion, the authors advocated direct laryngeal biopsies in patients with suspicious dysplastic and or malignant lesions. Office biopsy diagnosis was reassuring only in patients with benign lesion on pathologic examination.¹⁵ In 2016, in another study by *Cha et al* on 581 patients who underwent office-based biopsy, the sensitivity and specificity

for malignancy were 78.2% and 100%, respectively. The false negative rate for glottic lesions was 27%. It is worth noting that non-fungating lesions had higher false negative rate than fungating lesion. Moreover, the positive and negative predictive value for malignancy were 100% and 87.3%, respectively.¹⁶ In 2017, *Wellenstein et al* in their report on the safety of flexible endoscopic biopsy, the procedure was successful in 196 out of 201 cases. Laryngeal biopsies accounted for 68.7% of the total biopsies and SCC was diagnosed on 57.2% of patients.¹⁷ In 2018, in a study by *Hassan et al* on the accuracy of transoral flexible laryngoscope biopsy in patients with laryngeal or pharyngeal suspicious lesions (leukoplakia or ulceration), the authors reported specificity of 74.6% and sensitivity of 100%. The study was conducted on 43 patients, 31 of whom were diagnosed with squamous cell carcinoma, and 12 had either dysplasia or benign lesions. Those 12 patients underwent direct laryngoscopy showed invasive carcinoma in 10 patients.¹⁸ That same year, *Mohammed et al* reported the yield of office-based transnasal biopsy of 115 patients, 53 of whom with laryngeal pathology (45 glottic and eight supraglottic). In 89% of the cases, there was no need for further surgical intervention. Thirty-eight patients out of 53 had either dysplasia or malignancy.¹⁹ In another study by *Saga et al* on the application of flexible endoscopy-based biopsy in 30 patients with laryngopharyngeal lesions, the authors reported a sensitivity of 73% and a specificity of 100%. In seven patients, the office-based biopsy showed no evidence of malignancy whereas direct laryngoscopy and biopsy under general anesthesia confirmed the presence of carcinoma.²⁰ Refer to **Table 2** for a summary of the literature.

Though this review provides an additional series to the current literature, it has its limitations. These include the retrospective nature of this study, the relatively small number of patients enrolled, and the limited number of patients who underwent both office-based laryngeal biopsy and suspension microlaryngoscopy. This has precluded the ability of the authors to compute sensitivity and specificity.

CONCLUSION

Un-sedated office-based biopsy of vocal fold leukoplakia is an alternative to suspension microlaryngoscopy. Tissue sampling is adequate in most cases with a high diagnostic yield. Patients with highly suspicious lesions or recurrence, need to undergo suspension microlaryngoscopy. In this case study, 10% of the participants had their diagnosis changed following suspension microlaryngoscopy.

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