

Dysplastic Changes in Patients with Recurrent Laryngeal Leukoplakia: Importance of Long-Term Follow-Up

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ABSTRACT: **Background:** Leukoplakia of the vocal cords may represent a pre-cancerous lesion of the larynx. The management of cases of recurrent leukoplakia with pathologically proven dysplasia is still controversial.

Objectives: To present a series of patients with recurrent vocal cord leukoplakia and to examine their malignant transformation rate in relation to the clinical characteristics, risk factors, and histological findings.

Methods: A retrospective cohort study was conducted between 1999 and 2017. The study comprised 52 patients with recurrent leukoplakia of the vocal cords who required ≥ 2 direct laryngeal procedures within a minimum of 3 months between each procedure. Malignant transformation rate over follow-up period, risk factors for malignant transformation, and interval to develop laryngeal squamous cell carcinoma were investigated.

Results: All patients presented with hoarseness. An average of three procedures per patient was performed (range 2–13). Ten male patients (19.2%) developed squamous cell carcinoma. Of these, four with severe dysplasia developed SCC within 19 months of the first direct laryngoscopy. In the six other patients, SCC developed within an average of 3.7 years. The follow-up period ranged from 9–253 months (mean 109 months). Heavy smoking and severe dysplasia in the first biopsy were found to be significant risk factors for developing squamous cell carcinoma, as was male gender.

Conclusions: We showed an increased malignant transformation rate in recurrent leukoplakia cases among heavy smokers and male patients. In addition, severe dysplasia at initial diagnosis was a risk factor for SCC development. Close follow-up of patients with recurrent leukoplakia is warranted.

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KEY WORDS: direct laryngoscopy (DL), larynx, leukoplakia, squamous cell carcinoma (SCC)

normal to dysplastic and malignant epithelium [1]. Overall, the malignant transformation rate of leukoplakia lesions of the vocal cords has been reported to occur in 2%–74% of cases, and thus poses a major concern [2–4]. The incidence of vocal cord leukoplakia in the United States was estimated to be 10.2 and 2.1 lesions per 100,000 individuals in males and females, respectively [5].

Some patients present with recurrent persistent leukoplakia of the vocal cords despite adequate follow-up and treatment. The natural history of recurrent leukoplakia is not well established [4,6,7]. Given that physical examination alone cannot rule out the presence of a malignant lesion, every leukoplakia should be biopsied. Moreover, even in the absence of dysplasia within the leukoplakia lesion, the malignant transformation rate in such patients is approximately 4% [1]. However, in patients with recurrent leukoplakia, the duration and frequency of surveillance and management are still controversial, and they vary among different centers [8].

Current treatment strategies include radiotherapy or a simple biopsy (full thickness including basement membrane) and repeated resections as needed, up to complete macroscopic excision of the leukoplakia [1,6,8]. In patients with recurrent laryngeal leukoplakia, repeated surgical procedures can result in significant vocal cord scarring and dysphonia. Thus, non-surgical options, such as prolonged follow-up or radiotherapy, may be preferred. However, radiotherapy carries its own potential morbidities and adverse effects.

Despite the existence of consensus on the diagnosis of laryngeal dysplasia, data is still emerging and more research is needed because the prediction of lesion progression and the behavior of residual epithelium is not possible without repeated biopsies [6,7].

The aim of the present study was to review a series of cases of patients with recurrent leukoplakia of the vocal cords who were treated surgically and followed at our institution, and to examine their malignant transformation rate in relation to the clinical characteristics, risk factors, and histological findings.

PATIENTS AND METHODS

This study was approved by the local institutional review board (IRB# 198/13).

Leukoplakia describes the presence of keratin and a change of the normal non-keratinizing squamous epithelium of the vocal cords [1]. Leukoplakia may denote the transformation of the normal epithelium toward a pre-malignant lesion. Histological findings presenting as leukoplakia range from

STUDY POPULATION

We retrospectively reviewed charts of patients with recurrent leukoplakia of the vocal cords who were treated at our department between January 1999 and July 2017. Charts of eligible patients were identified using the International Codes of Diseases-9 admission codes. Data recorded included age, gender, symptoms, smoking habits, findings on office laryngoscopy and during direct laryngoscopy (DL), and histopathology results.

INCLUSION CRITERIA

We included patients who presented with recurrent vocal cord leukoplakia that required ≥ 2 direct laryngeal procedures with a minimum of 3 month interval between each successive procedure. Excluded were patients who had a previous head and neck malignancy, previous laryngeal surgery, history of head and neck irradiation, or abnormal bilateral vocal fold mobility.

SURGICAL PROCEDURE

In our institution, the common practice is to recommend surgery for patients with recurrent leukoplakia. All of the patients in this study underwent an in-office laryngoscopy using the stroboscopic digital system (Kay Pentax, Laryngeal Strobe model 9400, Tokyo, Japan) before each surgical procedure. All endoscopic examinations were video recorded and reviewed during each follow-up visit. Patients were admitted for DL under general anesthesia. Suspicious lesions were fully microscopically resected using cold instruments and sent for pathology analysis. Patients were discharged 24 hours after the procedure and had their first follow-up an average of 4 weeks later.

Those who were diagnosed with dysplasia or who had recurrent macroscopic leukoplakia or lesions were further followed in 3-month intervals. Patients were divided into two groups according to their smoking habits: light smokers (defined as 0–20 pack-years smoking) and heavy smokers (defined as ≥ 20 pack-years smoking). The histopathological results were graded as non-dysplastic lesion, mild dysplasia, moderate dysplasia, and severe dysplasia, according to the World Health Organization classification [9].

STATISTICAL ANALYSIS

Categorical variables were described as numbers and percentage. Continuous variables were evaluated for normal distribution using histogram and Q–Q plot. Normally distributed continuous variables were described as mean and standard deviation. Skewed data was presented as median and interquartile range. Length of follow-up was evaluated using reverse censoring method. Categorical variables were compared between severity of dysplasia at the first DL using Fisher's exact test, ANOVA, and independent *t*-test samples. Log-rank test and univariate Cox regression were used to evaluate the association between baseline characteristics and cancer appearance.

RESULTS

Of the 161 patients who were initially identified, 52 met the inclusion criteria and were included in the study population. Of them, 37 (71%) were male. The mean age was 54 ± 1.3 years. All patients presented with hoarseness. A median of three procedures per patient was performed (IQR 2–4.75, range 2–13), for a total of 184 procedures. Clinical characteristics of the enrolled patients are summarized in [Table 1]. The most common histopathological finding at the initial biopsy was mild dysplasia in 22 patients (42%). Other histopathological results are shown in [Figure 1]. The follow-up period lasted between 9 and 253 months (mean 109). There were no patients lost during the follow-up period. Squamous cell carcinoma (SCC) developed in 10 patients (19%), all were male.

Figure 2 shows the malignant transformation rate of enrolled patients, according to the pathological findings in the first DL. Of these patients, one was initially diagnosed with no dysplasia, three with mild dysplasia, two with moderate dysplasia, and four with severe dysplasia. SCC occurred in all four patients with severe dysplasia within an average of 19 months from the

Table 1. Patients characteristics

Characteristics	Number
Age, years, mean \pm SD	54 \pm 1.3
Gender (%)	
Male	37 (71)
Female	15 (29)
Smoking (%)	
No or light	24 (46)
Heavy*	28 (54)
Complaints (%)	
Hoarseness	52 (100)
Reflux	13 (25)
Procedures, mean (range)	3 (2–13)
Follow-up months, mean (range)	109 (9–253)

*Heavy smoking ≥ 20 pack-year

Figure 1. Pathologic classification in the first biopsy

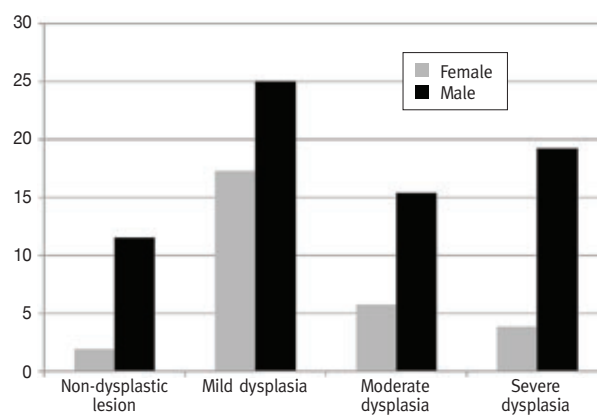


Figure 2. Malignant transformation rate, according to pathological findings in the first direct laryngoscopy

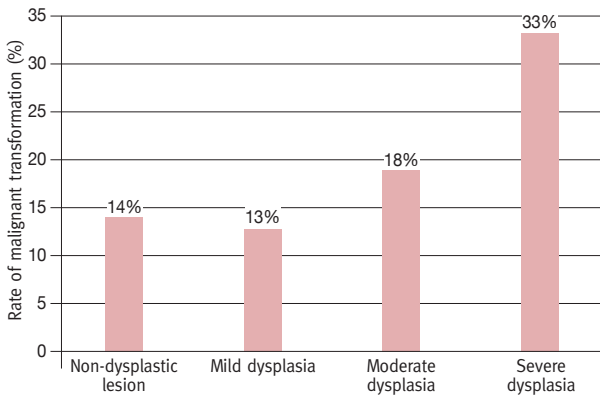
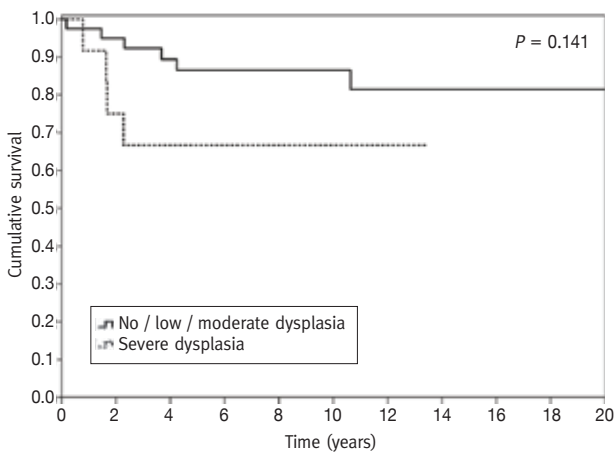


Figure 3. Kaplan–Meier curve, showing the incidence rate of squamous cell carcinoma in relation to the dysplasia grade in the first direct laryngoscopy. The dotted line represents patients diagnosed first with high grade dysplasia. The continuous line represent all other patients



first DL. In the other patients with less severe dysplasia, SCC occurred within a mean of 3.7 years from the first DL [Figure 3]. Only 2/10 patients who developed SCC were light smokers. Statistical analysis has shown that significant risk factors for developing SCC included heavy smoking ($P = 0.04$), severe dysplasia that was found on the first DL ($P = 0.041$), and male gender ($P = 0.05$). No statistically significant correlation was found between reflux symptoms and the development of SCC ($P = 0.09$).

DISCUSSION

The present study showed an increased malignant transformation rate and a shorter interval to development of SCC in patients

presenting with recurrent leukoplakia with increased severity of dysplasia at the initial diagnosis. We showed that even in patients without dysplasia or with mild or moderate dysplasia on the first biopsy, SCC had indeed developed over time.

A recent meta-analysis described a malignant transformation rate of 14% (95% confidence interval 8–22), with one study even reporting up to 74% [3,4]. The same systematic review showed that the malignant transformation rate is higher with increased severity of dysplasia grade. However, the review also pooled carcinoma in situ cases together with severe dysplasia, unlike our study population [4]. In the present study, 10 patients (19%) developed SCC, which is within the worldwide published range, and correlates with the latter study. This finding may show that the biological behavior of recurrent laryngeal leukoplakia is not linear in terms of malignant transformation to SCC, but is in line with a recent report [10].

In their series and literature review, Isenberg and colleagues [1] showed that in more than half of the biopsies from laryngeal leukoplakia, there was not dysplasia. However, there was still a risk for developing SCC. The reported overall mean time to malignant transformation was 5.8 years [4]. Our patients who eventually developed SCC presented sooner after the first DL, which supports our strict, close follow-up strategy of these patients.

Laryngeal SCC becomes more common with age. About 60% of the patients are between 55 and 74 years of age [11]. In the current study, the mean age of the patients was 54 years at the first procedure, which is in concordance with the age of patients reported by Plch and co-authors [12]. In the present study, it seems that smoking had a significant impact on malignant transformation risk.

The male-to-female ratio with recurrent dysplastic lesions in the present study is similar to that of other reports on precancerous lesions of the larynx [2,13]. Weller and collaborators [4] showed that there is insufficient data to declare that smoking and male gender are considered to be risk factors for malignant transformation in patients with recurrent leukoplakia. Interestingly, all 10 of the patients in our study who developed SCC were male, indicating that gender might be a risk factor for development of cancer in patients who have recurrent dysplastic lesions.

Some reports excluded all cases in which invasive SCC was diagnosed shortly after the initial biopsy to preclude selection bias of such lesions. Therefore, we used a 3 month interval between two successive DLs as an inclusion criterion. All of our patients underwent DL under general anesthesia and suspicious lesions were biopsied. In our practice, we do not use office biopsy under local anesthesia for follow-up. It was shown that transnasal flexible fiberoptic in-office laryngeal biopsy is safe and easy to perform [14]; however, DL still represents the definitive pathologic diagnostic procedure in assessing suspicious lesions of the larynx [15]

Invasive carcinoma developed in 13% of patients with mild or moderate dysplasia versus 25% of patients with severe dysplasia. Moreover, severe dysplasia patients developed invasive SCC in a shorter time period than mild or moderate dysplasia patients. These findings emphasize the need for close and active follow-up in patients with dysplasia, especially in those with severe dysplasia.

LIMITATIONS

The present study is limited by its retrospective nature. In addition, procedures were performed by different surgeons, which could have impacted results.

CONCLUSIONS

We showed an increased malignant transformation rate in recurrent leukoplakia cases, which is comparable to that reported in other recent series. Our treatment strategy included recurrent biopsies with removal of all visible pathological tissue and strict recorder follow-up visits at 3 month intervals.

We also noted an increased malignant transformation rate among heavy smokers and male gender. In addition, severe dysplasia at initial diagnosis was a risk factor for SCC development; therefore, close follow-up of patients with recurrent leukoplakia is warranted. Malignant transformation may occur even in mild and moderate dysplastic lesions; therefore, we recommend a close active follow-up as a safe strategy.

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Capsule

Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer

Clinical studies support the efficacy of programmed cell death 1 (PD-1) targeted therapy in a subset of patients with metastatic gastric cancer (mGC). With the goal of identifying determinants of response, Kin et al. performed molecular characterization of tissues and circulating tumor DNA (ctDNA) from 61 patients with mGC who were treated with pembrolizumab as salvage treatment in a prospective phase 2 clinical trial. In patients with microsatellite instability-high and Epstein-Barr virus-positive tumors, which are mutually exclusive, dramatic responses to pembrolizumab were observed (overall response rate [ORR] 85.7% in microsatellite instability-high mGC and ORR 100% in Epstein-Barr virus-positive mGC). For the 55 patients for whom programmed death-ligand 1

(PD-L1) combined positive score positivity was available (combined positive score cut-off value $\geq 1\%$), ORR was significantly higher in PD-L1(+) gastric cancer when compared to PD-L1(-) tumors (50.0% vs. 0.0%, $P < 0.001$). Changes in ctDNA levels at 6 weeks post-treatment predicted response and progression-free survival, and decreased ctDNA was associated with improved outcomes. These findings provide insight into the molecular features associated with response to pembrolizumab in patients with mGC and provide biomarkers potentially relevant for the selection of patients who may derive greater benefit from PD-1 inhibition.

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