Predictive factors of progression to carcinoma in vocal fold leucoplakia

Original Article

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Abstract

Objectives: To assess possible risk factors for progression in vocal fold leucoplakia.
Study Design: Observational retrospective study.
Material and Methods: Clinical data analysis of every patient submitted to microlaryngoscopy (MLS) with biopsy, excisional whenever possible, of vocal fold leucoplakia from January 2010 to December 2020 in the Otorhinolaryngology department of a tertiary hospital centre.
Results: One or more MLS were performed on 163 patients. Histological results were squamous cell carcinoma in 50 (30,7%), pre-malignant lesion in 68 (41,7%) and benign lesion in 45 (27,6%). Patients with a more severe dysplasia grade on the first biopsy had higher rates of malignant transformation (p=0,017). On the other hand, age, gender, tobacco or alcohol consumption, smoking cessation or the presence of gastroesophageal reflux disease weren't associated with the progression to carcinoma.
Conclusion: The main risk factor for progression to carcinoma is the histological grade on the first biopsy.
Keywords: Leucoplakia; laryngeal cancer; vocal fold premalignant lesion

Introduction

Larynx cancer is one of the most common head and neck cancers and squamous cell carcinoma (SCC) is the most common histological subtype. Even though the incidence of laryngeal cancer has decreased in the past years due to a concomitant decrease in tobacco abuse, its 5 year's survival hasn't changed[1]. One possible explanation could be that, there is still a significant number of patients being diagnosed in advanced stages of the disease (stage III or IV) since prognosis in laryngeal cancer is correlated with the stage at diagnosis[2].

Vocal fold leucoplakia is a macroscopic white plaque lesion of the laryngeal mucosa caused by the accumulation of keratin on

the epithelium[3]. On a histological level, this lesion can represent hyperplasia, dysplasia or malignancy and around 50% of the lesions can be pre-malignant or malignant[4]. In addition to this, it has been recognised that leucoplakia can progress to SCC even when the histological analysis shows a benign lesion without dysplasia[5]. As such, the presence of leucoplakia requires a histological examination and these lesions should be followed carefully to allow for an earlier detection of laryngeal cancer in cases of progression.

The main objective of this study is to analyse possible risk factors associated with progression to carcinoma in benign or pre-malignant vocal fold leucoplakia.

Methods

Observational retrospective study including every microlaryngoscopy (MLS) performed due to vocal fold leucoplakia from January 2010 to December 2020 in the otorhinolaryngology department of a tertiary hospital centre. Patients with malignant histological lesions or patients with a previous documentation of vocal fold dysplasia or malignancy were excluded. Furthermore, patients that had performed MLS due to leucoplakia before this period were also excluded. Every surgery was performed by different experienced surgeons and pathological analysis was performed by different anatomopathologists from the same hospital. Lesions were classified as benign, pre-malignant or malignant and pre-malignant lesions included mild, moderate and severe dysplasia and carcinoma in situ. Dysplasia was classified taking into consideration the World Health Organization (WHO) 2005 system[6]. The main outcome was progression to carcinoma. Treatment and follow-up in every patient were identical and it was in accordance to the strategy used in the department. Every patient was counselled to stop smoking and to reduce alcohol consumption. Every MLS was performed with cold blade instruments and lesions were removed as completely as possible with clear margins whenever possible. Patients with dysplastic lesions were followed regularly, every 3-6 months, with shorter intervals of 1-3 months in cases of severe dysplasia or carcinoma in situ. Whenever a new lesion was observed, a new MLS was performed. Recommended minimum follow-up was 5 years for every patient independent of dysplasia grade. Moreover, in cases of carcinoma in situ without clear margins, patients were submitted to a cordectomy to ensure total removal of the lesion and to rule out the presence of SCC. When there was a SCC on the cordectomy's pathological analysis, the lesion was categorized as malignant.

All data was collected in March 2021 by the analysis of patients' digital clinical information. Patients were considered exposed to gastroesophageal reflux disease (GERD) when there was data of a previous diagnosis by a gastroenterologist or a primary care physician. A descriptive analysis was performed with relative and absolute frequencies for categorical variables, mean and standard deviation (SD) for normally distributed continuous variables and median and interquartile range for non-normally distributed continuous variables. Normality of variables was assessed with the Kolmogorov-Smirnov test. The assessment of possible risk factors for progression to SCC was performed with the chi-square test or Fischer's exact test for categorical variables and with the Student's T test for normally distributed continuous variables.

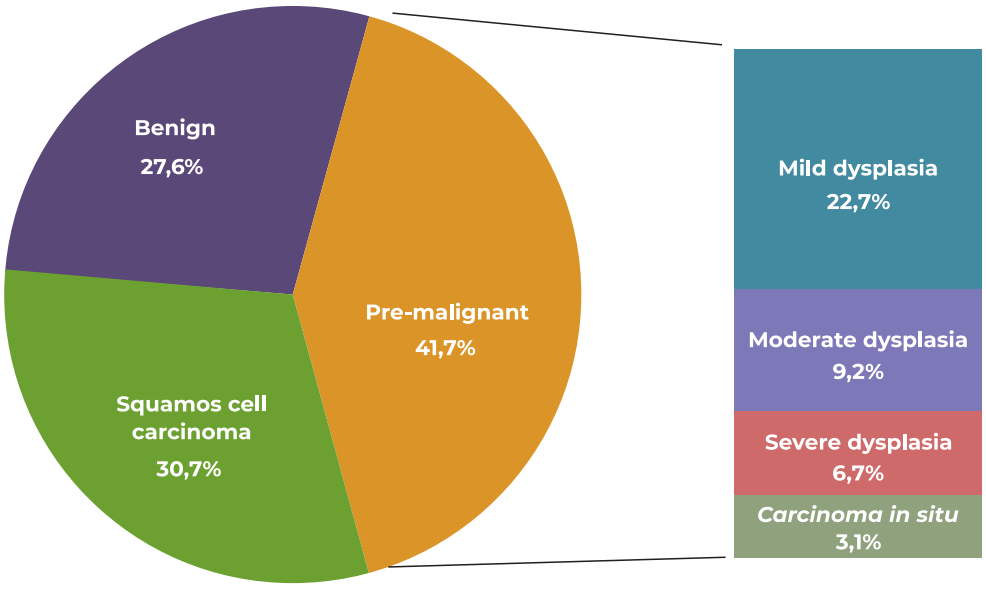
All statistical analysis was performed with the 27th version of the IBM® SPSS® Statistics software and associations were considered significant when $p<0,05$.

Ethical approval was obtained from the Hospital Ethics Committee (Comissão de Ética do Hospital de São João, E.P.E) with the number 25/2022.

Results

A total of 163 patients submitted to one or more MLS due to vocal fold leucoplakia were included. Histologically, 50 patients (30,7%) presented a SCC; 68 (41,7%) had a premalignant lesion and 45 (27,6%) had a benign lesion

Figure 1
Leucoplakia's Histology



as represented in Figure 1. For the analysis of possible risk factors for progression to carcinoma, patients with malignant disease were excluded and only the 113 patients with benign or pre-malignant histology were analysed.

Mean age was 58,67 ± 12,532 years and 93 (82,3%) patients were male. Leucoplakia was localised on the left vocal fold in 37 (32,7%) patients, on the right vocal fold in 42 (37,2%) and was bilateral in 34 (30,1%). Furthermore, 84 (74,3%) patients smoked, where 33 (29,2%) claimed to have stopped smoking after the diagnosis, 17 (15%) reported alcohol consumption, 16 (14,4%) had a clinically diagnosed GERD and 6 (5,3%) reported vocal abuse. Median follow-up was 24 (8 - 43,5) months. During this period 39 patients had a new lesion and were submitted to an additional MLS, where 25 (22,1%) performed a total of 2 surgeries, 8 (7,1%) performed 3 and 6 (5,3%) were submitted to 4 MLS.

During follow-up 15 (13,3%) patients progressed to SCC. Comparison of different characteristics between patients that progressed to SCC and patients that didn't progress are listed on Table 1. The only factor associated with progression to carcinoma was the histology on the first biopsy (p=0,017), where higher grades of dysplasia were associated with higher progression rates. On the other hand, age, gender, tobacco or alcohol consumption, smoking cessation or the presence of GERD weren't associated with the progression to carcinoma. Furthermore, when only premalignant lesions are taken into consideration (n=68), the initial grade of dysplasia was still the only factor associated with the progression to SCC (p=0,004).

Discussion

Vocal fold leucoplakia can have a benign, premalignant or malignant histology with reports of up to 50% of the lesions being non-benign in the literature[4]. This study included 163 patients submitted to MLS due to vocal fold leucoplakia in a tertiary hospital centre where 31% of the lesions were malignant and 43% were pre-malignant. These results are higher than what has been reported previously[4]. Thus, patients with leucoplakia should be followed carefully and a biopsy should be performed since the percentage of malignant and pre-malignant lesions could be higher than what was previously thought.

It has been established that vocal fold leucoplakia is associated with progression to SCC even in cases of benign lesions without

Table 1
Comparison of different characteristics between malignization and non-malignization groups; GERD – Gastroesophageal Reflux Disease

	Non-malignization (n=98)	Malignization (n=15)	p
Age mean ± SD	58,35 ± 12,893	60,80 ± 9,958	0,483
Gender n (%)			0,069
Male (n=93)	78 (83,9%)	15 (16,1%)	
Female (n=20)	20 (100%)	0 (0%)	
Tobacco consumption n (%)			1,000
Yes (n=84)	73 (86,9%)	11 (13,1%)	
No (n=29)	25 (86,2%)	4 (13,2%)	
Smoking Cessation n (%)			0,745
Yes (n=33)	28 (84,8%)	5 (15,2%)	
No (n=51)	45 (88,2%)	6 (11,8%)	
Alcohol Consumption n (%)			1,000
Yes (n=17)	15 (88,2%)	2 (11,8%)	
No (n=96)	83 (86,5%)	13 (13,5%)	
GERD n (%)			0,691
Yes (n=16)	15 (93,8%)	1 (6,3%)	
No (n=97)	83 (85,6%)	14 (14,4%)	
Initial Histology n (%)			**0,017**
No dysplasia (n=45)	42 (93,3%)	3 (6,7%)	
Mild Dysplasia (n=37)	33 (89,2%)	4 (10,8%)	
Moderate Dysplasia (n=15)	13 (86,7%)	2 (13,3%)	
Severe Dysplasia (n=11)	8 (72,7%)	3 (27,3%)	
Carcinoma in situ (n=5)	2 (40%)	3 (60%)	

dysplasia[5]. The main objective of this study was to assess possible risk factors associated with progression to SCC in patients with benign or pre-malignant vocal fold leucoplakia. The median age of this population was 58,67 ± 12,53 years old, 82,3 % of the patients were male and 74,3% were smokers, similarly to what was previously reported by Lee *et al*[7]. On the other hand, the prevalence of excessive alcohol consumption (15%) was inferior to what was expected and reported previously[7], which could be explained by an information bias due to lack of information on digital clinical data.

In patients with leucoplakia, the initial grade of dysplasia was the only factor associated with progression to SCC and there was no association with age, gender, tobacco or alcohol consumption, smoking cessation or the presence of GERD. Male gender is considered a risk factor for laryngeal cancer since this gender presents a higher prevalence of tobacco and alcohol consumption and some studies report a possible role for sexual hormone receptors on laryngeal carcinogenesis[8]. As reported previously, we found no association of gender or age with progression to carcinoma[7]. On the other hand, in a study with 1184 German patients with vocal fold leucoplakia there were significant higher malignization rates in male patients with a Hazard Ratio (HR) of 4,09 (p<0,001) and patients with more than 65 years old, with a

HR of 4,90 (p<0,001)[9]. The lack of association in this study could have occurred due to a smaller sample size.

Even though tobacco and alcohol consumption are traditionally acknowledged as the most important risk factors for laryngeal cancer[10], a meta-analysis has concluded the data presented in previous studies regarding the role of alcohol and tobacco on progression of dysplastic vocal fold lesions to cancer was insufficient[11]. In the present study, tobacco and alcohol consumption or smoking cessation weren't associated with malignization in patients with leucoplakia. Furthermore, Theodosiu et al reported that smoking cessation after diagnosis didn't affect the progression rates of pre-malignant vocal fold lesions but the time to malignant transformation was higher in patients that stopped smoking (31,5 months) when compared to patients that didn't (19,5 months)[12].

GERD wasn't associated with malignization in this population of patients with vocal leucoplakia as previously reported[7]. On the other hand, Yang *et al* found that vocal fold leucoplakia recurred more often in patients with GERD, with an Odds Ratio (OR) of 8,43 in a multivariate analysis adjusted to smoking and alcohol consumption[13]. Thus, even though leucoplakia seems to recur more often in patients with GERD, it doesn't seem to be associated with a higher risk of progression to malignant squamous cell carcinoma.

In this study, the only factor significantly associated with progression to SCC was the initial histological grade. Even when only pre-malignant lesions were taken into account, the initial histological grade was still the only factor significantly associated. Although it is universally believed that more severe grades of dysplasia are associated with higher malignization rates, the European Laryngological Society has stated on their 2021 position paper on laryngeal dysplasia that the data presented in the literature is controversial[14]. In fact, a previous systematic review showed that the rates of progression reported in the literature for different grades of dysplasia were highly variable, and it wasn't possible to reach a conclusion regarding the role of the initial grade of dysplasia on malignancy rates[15]. Furthermore, while some studies show that more severe grades of dysplasia are associated with higher rates of progression to carcinoma[4,7,11], others report no association[8,16]. The present study supports an association of the initial grade of dysplasia with malignant transformation.

This study has several limitations. Firstly, it is a retrospective observational study which can lead to information bias. Furthermore, surgeries were performed by different surgeons and biopsies were analysed by different pathologists. On the other hand, this allows for a more realistic approximation to clinical practice in most hospitals. Lastly, the subjective WHO 2005 system was used to classify different dysplasia grades, which has been updated in 2017. This WHO 2017 system acknowledges two different categories: low grade dysplasia (which includes the previous hyperplasia, mild dysplasia and moderate dysplasia involving up to half of the epithelium) and high grade dysplasia (including moderate dysplasia involving more than half of the epithelium, severe dysplasia and *carcinoma in situ*)[17]. Lastly, since many patients missed follow-up appointments, median follow-up was only 24 (8 - 43,5) months.

Conclusion

Vocal fold leucoplakia should always be submitted to a biopsy since they can be pre-malignant or malignant in an important number of the cases. In non-malignant vocal fold leucoplakia, the most important risk factor for progression to carcinoma seems to be the initial histological grade.

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Data Confidentiality

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

Privacy Policy, Informed Consent and Ethics Committee Authorization

The authors declare that they have the consent of the Ethics Committee of the Centro Hospitalar Universitário de São João to carry out this work, under number 25/2022.

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Availability of scientific data

There are no datasets available, publicly related to this work.

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