Retrospective study on precancerous laryngeal lesions: long-term follow-up

Studio retrospettivo sulle precancerosi laringee: follow-up a lungo termine

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Parole chiave

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Summary

The classification and the most appropriate treatment of dysplastic lesions of the larynx continue to be controversial issues. Aim of present study was to evaluate the incidence of precancerous lesions of larynx, their potential to evolve in relation to grade of dysplasia, and the most appropriate treatment. The study is based on the review of a series of 207 patients (157 (75.9%) male, 50 (24%) female) with keratosis of the laryngeal epithelium, with or without dysplasia. Patients were divided into four groups, according to Friedmann's classification (1986), based on presence and grade of any dysplasia. The follow-up period ranged from approximately 7 to 16 years. With regard to progression of the disease, 159 of the 185 patients considered were cured following initial treatment (85.9%), whereas 26 (14.1%) had recurrences. Of the latter, 19 had a single recurrence and 7 had multiple recurrences. Progression to carcinoma occurred in a total of 12 cases, above all in patients with the highest grades of dysplasia. Results emerging from this study confirm not only that dysplastic lesions of the larynx have the potential to evolve into frankly malignant lesions, but also that this capacity to evolve is significantly correlated with grade of dysplasia of the covering epithelium. Therefore, the histological classification of precancerous lesions of the larynx, based on the presence or absence of atypical cells and on their severity, is clearly valid from a clinical standpoint, representing, above all, an important prognostic factor. As far as treatment is concerned, mucosal stripping at site of the lesion is considered to be the treatment of choice for precancerous lesions of the larynx. Nevertheless, in patients presenting keratosis with a higher grade of dysplasia, it is mandatory to consider more aggressive treatment.

Riassunto

La classificazione delle lesioni displastiche della laringe ed il loro più adeguato trattamento costituiscono tuttora argomenti assai controversi. Lo scopo di questo lavoro è stato quello di valutare l'incidenza delle lesioni precancerose della laringe, il loro potenziale carattere evolutivo in rapporto al grado di displasia ed il loro trattamento più adeguato. Lo studio si è basato sulla revisione di un gruppo di 207 pazienti affetti da cheratosi dell'epitelio laringeo, con o senza displasia. I pazienti sono stati suddivisi, secondo la classificazione di Friedmann (1986), in quattro gruppi in base alla presenza ed al grado della displasia eventualmente riscontrata. Il periodo di follow-up è risultato compreso tra 7 e 16 anni circa. Per quanto riguarda l'evoluzione della malattia, dei 185 pazienti considerati, 159 (85,9%) sono risultati guariti al primo trattamento, mentre 26 (14,1%) hanno presentato recidive. Di questi ultimi, 19 hanno presentato un'unica recidiva, mentre in 7 si sono manifestate recidive multiple. L'evoluzione in carcinoma si è avuta in 12 casi complessivamente, soprattutto nei pazienti con gradi più elevati di displasia. I risultati forniti da questo studio confermano che le lesioni displastiche della laringe possiedono un potenziale carattere evolutivo verso lesioni francamente maligne, e che tale capacità evolutiva risulta significativamente correlata al grado di displasia dell'epitelio di rivestimento. Pertanto, la classificazione istologica delle lesioni precancerose della laringe basata sulla presenza o meno di atipie cellulari e sulla loro gravità presenta una indubbia validità sul piano clinico e costituisce soprattutto un importante fattore prognostico. Dal punto di vista terapeutico, lo stripping della mucosa sede della lesione è considerato il trattamento di elezione delle precancerosi laringee. Tuttavia, nei soggetti affetti da cheratosi con displasia più elevata sembra senza dubbio opportuno considerare la necessità della attuazione di un trattamento più aggressivo.

Introduction

It is well known that >90% of malignant tumours of the larynx are carcinomas that often develop from precancerous epithelial lesions [1 2]. Early detection, followed by prompt excision, should thus prevent the development of invasive tumours requiring far more destructive and debilitating surgery. Nevertheless, both the classification of dysplastic lesions of the larynx and the most appropriate treatment have been the topic of endless debate ever since 1877, when Schwimmer [3] coined the term leukoplakia to refer to the whitish appearance of lesions of the oral cavity. In 1978, WHO (World Health Organization) [4] defined

precancerous laryngeal lesions as "morphological alterations of the mucosa caused by chronic local irritative factors or referable to a local expression of generalized illnesses, presenting a higher probability of degeneration into carcinoma with respect to the surrounding mucosa". These lesions can be classified based on clinical or histopathological criteria. Clinically, the lesions most significant from a precancerous standpoint are white and red pachydermia, referred to, respectively, as leukoplakia and erythroplakia [5]. However, it has now been unanimously acknowledged that the diagnosis of a precancerous lesion of the larynx and the evaluation of its potential to progress must be based on the histological characteristics of the lesion itself; the histological nature of leukoplakia is completely unpredictable prior to biopsy [6], due to the fact that identical macroscopic appearances can correspond to different histological patterns.

The lowest common denominator of hyperplastic-dysplastic laryngeal lesions is an increase in the epithelial layers of the larynx, which is referred to using the all-embracing term of keratosis [7]. This can be distinguished as keratosis without dysplasia, or simple hyperplasia, when hyperplasia involves the layer of the basal cells of the stratified epithelium or undifferentiated reserve cells of the columnar epithelium, or as keratosis with dysplasia, when maturation of the cell elements is altered. In mild dysplasia, cell stratification is easily identified, whereas in the severe form, the altered cell maturation leads to subversion of cell polarity, with severe alterations in stratification.

The histological classifications of precancerous laryngeal lesions, most closely followed in the literature for clinical purposes, are based on evaluation of the grade of hyperplasia and/or dysplasia of the epithelium. According to Hellquist et al. [8], a distinction can be made between Grade 1 lesions, presenting hyperplasia and/or keratosis with or without mild dysplasia, Grade 2, characterised by moderate dysplasia, and Grade 3, in which dysplasia is severe or of such type as to configure carcinoma in situ. This classification is based on that proposed by Kleinsasser in 1963 [1] and, later, by Delemarre [9], distinguishing a first class characterised by simple squamous cell hyperplasia, a second class represented by squamous cell hyperplasia with atypia and a third class represented by carcinoma in situ.

More recently, Friedmann [10] proposed that dysplastic lesions of the larynx be considered on the same scale as corresponding lesions of the uterine cervix, which are viewed as different development phases of a single picture of intraepithelial neoplasia. Thus, this classification distinguishes keratosis without dysplasia from keratosis with mild dysplasia (Laryngeal Intraepithelial Neoplasia, or LIN 1), moderate dysplasia (LIN 2), and severe dysplasia or carcinoma in situ (LIN 3). It should be pointed out that several Authors have grouped carcinoma in situ together with severe dysplasia [6 11-13], whereas others consider these carcinomas separate pathological entities [14-17].

The present retrospective study aimed at examining the potential for precancerous laryngeal lesions to progress towards malignancy, correlating this potential with the grade of atypia and the treatment adopted.

Table I. Distribution of patients based on presence of epithelial dysplasia according to Friedmann's classification.

	N. cases (%)
Keratosis	
without dysplasia	96 (46.4)
with mild dysplasia	46 (22.2)
with moderate dysplasia	42 (20.3)
with severe dysplasia or carcinoma in situ	23 (11.1)

Material and Methods

The study is based on the review of a series of 207 patients (157 (75.9%) male and 50 (24.1%) female (male/female ratio approximately 3:1)) presenting keratosis of the laryngeal epithelium, with or without dysplasia, based on the histological examination of 207 laryngeal biopsies performed at this Clinic between November 1987 and December 1991.

The patients were subdivided using Friedmann's classification, based on the presence and grade of any dysplasia observed (Table I). Of these patients, 96 (46.4%) presented keratosis without dysplasia, 46 (22.2%) keratosis with mild dysplasia (LIN 1) and 42 (20.3%) keratosis with moderate dysplasia (LIN 2). Lastly, 23 (11.1%) patients presented severe dysplasia or carcinoma in situ (LIN 3).

Patients presenting keratosis without dysplasia and those with mild or moderate dysplasia were followed up approximately every two months for the first year and thereafter every six months. The patients with severe lesions or carcinoma in situ were checked approximately every two months for the first year and every 3-4 months thereafter. The follow-up period

Table II. Distribution of patients according to sex and age classes.

	Decade					
	3rd	4th	5th	6th	7th	8th
Males	4	7	36	49	47	14
Females	6	12	7	18	6	1

Table III. Subdivision of patients based on grade of dysplasia and smoking.

Smoking	Keratosis without dysplasia	LIN 1	LIN 2	LIN 3	Total
Non-smokers	18 (18.8%)	7 (15.1%)	8 (19.1%)	0	33 (16%)
Ex-smokers	4 (4.2%)	7 (15.1%)	6 (14.3%)	0	17 (8.1%)
≤20 cig/day	46 (46.9%)	19 (41.2%)	16 (38.1%)	14 (60.9%)	95 (45.9%)
>20 cig/day	29 (30.2%)	13 (28.6%)	12 (28.5%)	9 (39.1%)	63 (30.4%)

ranged from 7 to 16 years.
Patients presenting keratosis without dysplasia and those with mild or moderate dysplasia were submitted to excisional biopsy with direct suspension microlaryngoscopy, without further treatment; patients presenting lesions with severe dysplasia or carcinoma in situ were treated with conventional surgery or surgery via CO_2 laser, depending on the site and extent of the lesion [10 cordectomies in laryngeal fissure, 12 laser excisions, 1 subtotal laryngectomy since during the operation, the lesion proved to be different from the previous biopsy evaluation (invasive carcinoma)].

Results

The highest incidence of hyperplasia of the laryngeal mucosa is observed in the fifth, sixth and seventh decades, particularly among men (Table II).
Overall mean age of the patients was 53.1±12.4 years (range 20-76). The 157 male patients ranged in age from 26 to 76 years (mean: 55.4±10.8), whereas the 50 female patients were between 20 and 70 years old (mean: 45.5±13.6). Subdividing the patients into different groups according to histological classification, mean age was 49.7±11.4 for subjects with keratosis without dysplasia, 50.7±12.6 for those with mild dysplasia (LIN 1), 59.6±9.8 for those with moderate dysplasia (LIN 2), and 60.7±8.1 for patients with severe lesions or carcinoma in situ (LIN 3).
There were numerous smokers among the patients, as listed in Table III which also indicates the number of cigarettes smoked and the grade of dysplasia. However, it is even more interesting to note that none of the non-smoking patients had any type of recurrence. Instead, data regarding the use of alcohol do not seem to be reliable, as most of the population examined denied such use (only a few cases out of the 207 patients examined).
The vocal cords represent the most frequent location of dysplastic lesions (176 cases, 85%).
As far as concerns evolution of the lesions, of the 96 patients presenting keratosis without dysplasia, 10 were excluded from the study either because they withdrew prior to follow-up or because a repeat biopsy within a short time period revealed the presence of invasive carcinoma, indicating the inadequacy of the initial biopsy. Of the remaining 86 patients, 10 presented further progression of the disease: 6 towards a dysplastic lesion of the same grade and 3 towards a Grade 2 lesion (in one case, this developed later into invasive carcinoma 7 years after the initial biopsy), over a period ranging from 7 months to 5 years. One case developed directly into invasive carcinoma 9 years after diagnosis of keratosis. The patients who developed cancer were treated respectively via laser cordectomy and cordectomy in laryngeal fissure.
Of the 46 patients with keratosis with mild dysplasia (LIN 1), 4 were not included in the analysis of data as they left the study prior to follow-up, 3 presented a recurrence of the same grade, and in one patient the lesion evolved towards a Grade 2 that, in turn, developed into invasive carcinoma 3 years after the initial diagnosis. One case developed directly into invasive carcinoma 5 years after keratosis was diagnosed.
Considering the 42 patients with lesions classified as LIN 2, 2 were excluded from the study since invasive heteroplasia was diagnosed shortly after the first biopsy, demonstrating that the initial biopsy was not representative of the lesion, and 4 left the study prior to follow-up. Of the remaining 36 patients, 9 presented further progression: 6 towards a lesion of the same grade after 3 to 5 years (in 2 cases with subsequent development into cancer 2 to 5 years after the initial diagnosis), and 3 towards invasive carcinoma between one and 6 years later. Of the 5 patients who developed cancer, 3 underwent vertical hemi-laryngectomy, frontolateral laryngectomy and laser cordectomy, whereas 2 were operated elsewhere.
Of the 23 subjects with severe dysplastic lesions or carcinoma in situ (LIN 3), one was excluded, since, during surgery, the lesion proved to be malignant, requiring subtotal laryngectomy, and one patient left the study at an early stage. In 3, the disease progressed further. One patient who underwent cordectomy in laryngeal fissure for carcinoma in situ of the vocal cord presented invasive carcinoma of the left hemi-

larynx with lesions in the ipsilateral laterocervical lymph nodes (T3, N1, M0) approximately 18 months, postoperatively. The patient refused surgery and thus underwent radiotherapy. Another patient presented recurrence of carcinoma in situ with the onset of invasive carcinoma 2 years after undergoing CO_2 laser cordectomy; the lesion required total laryngectomy. The third patient presented a recurrence of severe dysplasia on the vocal cord operated 3 years earlier and was treated again via laser excision of the tumour.
Briefly, of the 185 patients with dysplastic lesions of the larynx, considered overall, 159 (85.9%) cases were resolved with the first treatment, while 26 (14.1%) had recurrences. Of these 26 patients, 19 had a single recurrence and 7 presented multiple recurrences. Development into cancer occurred in a total of 12 cases, with direct progression in 8 cases (one of which involving a patient who had presented keratosis without dysplasia, one patient with keratosis with mild dysplasia, 3 patients with moderate dysplasia, and 2 with lesions characterised by severe dysplasia or carcinoma in situ). In 4 patients, cancer was manifested following recurrences of dysplasia (all of which were Grade 2).
The latency period between the initial diagnosis and the development of cancer was 7-9 years (mean: 8) for patients with keratosis without dysplasia, 3-5 years (mean: 4) for those with mild dysplasia, 1-6 years (mean: 3.2) for patients with moderate dysplasia, and 1.5-3 years (mean: 2.1) for those with severe dysplasia.

Discussion

Data emerging from the present study confirm that dysplastic lesions of the larynx can potentially develop into frankly malignant lesions, obviously epithelial in type. This capacity to develop is significantly correlated with the grade of dysplasia of the covering epithelium, since the percentage of malignant transformation increases in proportion to the increase in the severity of the dysplasia. In fact, of the 86 subjects classified as having keratosis without dysplasia, 2 later developed invasive carcinoma (1 of whom through an intermediate stage, i.e., a Grade 2 lesion), accounting for 2.3%. Of the 42 patients with lesions classified as LIN 1, two presented progression to carcinoma (here again, with an intermediate stage constituted by a Grade 2 lesion), with a malignant transformation rate of 4.8%. Of the 36 patients classified as LIN 2, 5 progressed to cancer, representing a malignant transformation rate of 13.9%. Lastly, of the 21 patients classified in the LIN 3 group, 3 (14.3%) presented recurrence of cancer.
A comparison of these data with those reported by others, who used the same classification criteria for precancerous laryngeal lesions as those adopted in our study (Table IV), reveals a close correspondence of the rates of transformation into invasive carcinoma, above all in those patients with mild and moderate dysplasias. Instead, the malignant transformation of Grade 3, while similar to the findings of Gallo et al. [7] differs from the values presented by other Authors [18 19]. These differences can undoubtedly be attributed to the different classification criteria adopted, the type of treatment performed as well as duration of follow-up, which must be appropriate in length, considering the fact that the tendency to transformation may occur even l0 years after the initial diagnosis [20 21].
Although subject to these types of variables, the histological classification of precancerous lesions of the larynx, based on the presence or absence of cellular atypia and on their severity, undoubtedly has clinical validity and, above all, it represents an important prognostic factor that, likewise, cannot be disregarded as far as treatment strategy is concerned. Furthermore, with regard to patients with LIN 3 lesions, several Authors have sustained that those with severe dysplasia must be distinguished from those with carcinoma in situ, based on the assumption that, in the latter, prognosis is less favourable [14 16 19].
From a therapeutic standpoint, mucosal stripping of the site of the lesion is commonly considered the treatment of choice for precancerous laryngeal le-

Table IV. Incidence of transformation of dysplastic laryngeal lesions into carcinoma, according to various Authors.

First Author, year (ref.)	Keratosis without dysplasia	LIN 1	LIN 2	LIN 3	Total
Velasco, 1987 (29)	1/46 (2.2%)		6/31 (19.3%)	2/10 (20%)	9/86 (10.3%)
Sllamniku, 1989 (21)	18/604 (4.1%)	15/204 (7.3%)	4/23 (17.3%)	25/90 (27.7%)	62/921 (6.7%)
Blackwell, 1995 (19)	0/6	3/26 (11.5%)	5/15 (33.3%)	5/18 (27.8)	15/65 (20%)
Gallo, 2001 (6)	6/143 (4.1%)	4/56 (7.1%)	6/28 (21.4%)	3/32 (9.3%)	12/259 (7.3%)
Motta, 2001 (16)		5/89 (5.6%)	1/14 (7.1%)	5/38 (13.1%)	11/141 (7.8%)
Perugia, 2003	2/86 (2.3%)	2/44 (4.8%)	5/36 (13.9%)	3/21 (14.3%)	12/185 (6.5%)

sions [20 22]. Nevertheless, as emerges from this study – and in agreement with other Authors [6 16] – patients with keratosis without dysplasia and those with mild dysplasia present a low risk of developing cancer, whereas those with LIN 2 or LIN 3 lesions are at a much higher risk. Consequently, in the latter patients, it seems appropriate to consider more aggressive treatment [6 23]. Interestingly, Motta et al. [16] indicated a higher cure rate using CO_2 laser in the treatment of laryngeal dysplasias of all grades.

Other indirect evidence of the progressive nature of laryngeal keratosis comes from observations on the period of latency i.e., onset of carcinoma and mean age of the patients in the different dysplasia classes. In fact, the period of latency between the first diagnosis and the development of carcinoma is directly correlated with the grade of dysplasia: the higher the grade of cellular atypia, the more rapid the development into invasive carcinoma (theory of the inversely proportional relationship [6]). Moreover, the progressive rise in the mean age of the patients presenting lesions of increasing severity (from 49.7 years for patients without dysplasia to 60.7 years for those with severe dysplasia or carcinoma in situ) offers indirect proof not only of the tendency for these lesions to evolve but also of the fact that, from an epidemiological standpoint, the risk factors for precancerous lesions of the larynx are the same as those for laryngeal cancer. Smoking and the consumption of alcohol are known risk factors for laryngeal cancer [24 26 27], and this is also in agreement with our case histories. The failure to alter one's lifestyle – which was constantly observed in those patients who presented progression of the initial lesion – may well be the real factor responsible for the change in the disease [18]. It is also worthwhile pointing out that in no less than l0 cases, the biopsy was not indicative of the true grade of the lesion, proving to be inadequate and suggesting the possibility that there may be lower grades of dysplasia in the same lesion, in areas adjacent to the carcinoma. This finding emphasises the importance of correctly performing biopsies, which must include the area surrounding the lesion that is clinically most evident and does not necessarily correspond to the most serious one. In fact, it is well known that the appearance of invasive carcinoma within just a few months of the diagnosis of a precancerous lesion is generally considered a diagnostic error, i.e., failure to recognise a cancerous process already present when the first biopsy was performed [7].

Lastly, it seems superfluous to stress that the existence of a correlation between the grade of epithelial dysplasia and the risk of developing laryngeal cancer, particularly when risk factors persist, makes scrupulous clinical control of patients with laryngeal dysplasia mandatory, particularly when high-grade dysplasias are involved. Nonetheless, it is likely that there are other factors besides those already known that can influence progression of the disease. This would explain why lesions of the same grade develop into carcinoma only in certain patients (even if all patients continue to make the same mistakes in terms of lifestyle and despite the fact that all receive the same treatment) and why lesions of lower grades can develop into malignancies without going through any intermediate stages.

Studies on the oncogenes of tissues presenting dysplastic lesions will no doubt throw further light on these aspects, indicating whether they will evolve or not [28 29].

Conclusions

The results of this study lend themselves to several fundamental considerations, the most important of which being that laryngeal keratosis undoubtedly has the potential to develop into invasive carcinoma. This potential is proportionate to the grade of dysplasia of the lesion. More specifically, the discriminator between low-risk and high-risk lesions is between LIN 1 and LIN 2. Patients with LIN 2 and LIN 3 lesions have a much greater likelihood of developing cancer than those presenting keratosis without dysplasia or mild dysplasia. This must be taken into account in treatment strategies, which must naturally be more aggressive in patients at a higher risk.

In terms of preventing recurrences, in general, and frankly cancerous recurrences, in particular, giving up smoking is fundamental: indeed, lesions recurred only in those patients who had not abstained from the habit.

Lastly, the importance of extended and careful follow-up is stressed since recurrences may occur even many years after the initial diagnosis.

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