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

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

G. RICCI, E. MOLINI, M. FARALLI, C. SIMONCELLI
Otorhinolaryngology and Cervico-Facial Surgery Clinic, University of Perugia, Perugia, Italy

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.

Key words
Larynx • Precancerous lesions • Laryngeal cancer • Treatment

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. 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, 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. 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., 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 and, later, by Delemarre, 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 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, whereas others consider these carcinomas separate pathological entities.

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.

**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 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>
<thead>
<tr>
<th>Table I. Distribution of patients based on presence of epithelial dysplasia according to Friedmann’s classification.</th>
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<tr>
<td>N. cases (%)</td>
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<tr>
<td>Keratosis without dysplasia</td>
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<td>with moderate dysplasia</td>
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<td>with severe dysplasia or carcinoma in situ</td>
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<th>Table II. Distribution of patients according to sex and age classes.</th>
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<td>3rd</td>
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<tr>
<td>Males</td>
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<td>Females</td>
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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 CO₂ 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 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 hemilaryngectomy, 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 hemicord.

<table>
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<tr>
<th>Smoking</th>
<th>Keratosis without dysplasia</th>
<th>LIN 1</th>
<th>LIN 2</th>
<th>LIN 3</th>
<th>Total</th>
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<tr>
<td>Non-smokers</td>
<td>18 (18.8%)</td>
<td>7 (15.1%)</td>
<td>8 (19.1%)</td>
<td>0</td>
<td>33 (16%)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>4 (4.2%)</td>
<td>7 (15.1%)</td>
<td>6 (14.3%)</td>
<td>0</td>
<td>17 (8.1%)</td>
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<td>≤20 cig/day</td>
<td>46 (46.9%)</td>
<td>19 (41.2%)</td>
<td>16 (38.1%)</td>
<td>14 (60.9%)</td>
<td>95 (45.9%)</td>
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<tr>
<td>&gt;20 cig/day</td>
<td>29 (30.2%)</td>
<td>13 (28.6%)</td>
<td>12 (28.5%)</td>
<td>9 (39.1%)</td>
<td>63 (30.4%)</td>
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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 CO2 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 10 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-
months of the diagnosis of a precancerous lesion is
appearance of invasive carcinoma within just a few
most serious one. In fact, it is well known that the ap-
evident and does not necessarily correspond to the
area surrounding the lesion that is clinically most
correctly performing biopsies, which must include
noma. This finding emphasises the importance of
sia in the same lesion, in areas adjacent to the carci-
possibility that there may be lower grades of dyspla-
lesion, proving to be inadequate and suggesting the
biopsy was not indicative of the true grade of the
worthwhile pointing out that in no less than 10 cases,
higher cure rate using CO2 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 diag-
nosis and the development of carcinoma is directly
related with the grade of dysplasia: the higher the
grade of cellular atypia, the more rapid the develop-
ment into invasive carcinoma (theory of the invers-
ely proportional relationship 5). Moreover, the pro-
gressive rise in the mean age of the patients present-
ing 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 in-
direct proof not only of the tendency for these lesions
to evolve but also of the fact that, from an epidemio-
logical standpoint, the risk factors for precancerous
lesions of the larynx are the same as those for laryn-
geal cancer. Smoking and the consumption of alcohol
are known risk factors for laryngeal cancer 24–27, 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 re-
sponsible for the change in the disease 18. It is also
worthwhile pointing out that in no less than 10 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 dyspla-
sia in the same lesion, in areas adjacent to the carci-
noma. 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 ap-
pearance 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 dyspla-
sia and the risk of developing laryngeal cancer, partic-
ularly when risk factors persist, makes scrupulous clin-
ical control of patients with laryngeal dysplasia manda-
tory, particularly when high-grade dysplasias are in-
volved. Nonetheless, it is likely that there are other fac-
tors besides those already known that can influence
progression of the disease. This would explain why le-
sions 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 le-
sions of lower grades can develop into malignancies
without going through any intermediate stages.
Studies on the oncogenes of tissues presenting dys-
plastic 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 dys-
plasia of the lesion. More specifically, the discrimi-
nator between low-risk and high-risk lesions is be-
tween LIN 1 and LIN 2. Patients with LIN 2 and LIN
3 lesions have a much greater likelihood of develop-
ing 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 fol-
low-up is stressed since recurrences may occur even
many years after the initial diagnosis.

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