

# Premalignant Lesions of the Larynx and their Management

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## Abstract

The classification and the most appropriate treatment of the precancerous lesions of the larynx continue to be controversial. It is an established fact that the dysplastic lesions of the larynx have the potential to evolve into malignant lesion. It is also well-known that the capacity of this transformation significantly correlates to the grade of dysplasia of the epithelium. The diagnosis, treatment, and prognosis of these lesions depend almost entirely on their histological abnormalities.

**Keywords:** Leukoplakia, Keratosis, Carcinoma *in situ*, Larynx.

## INTRODUCTION

About 90% of malignant tumors of the larynx are carcinomas that often develop from premalignant lesions.<sup>1</sup> Therefore, early detection and prompt treatment should thus prevent the development of invasive cancer requiring more debilitating surgical resection. WHO (World Health Organization) defined premalignant lesions of the larynx as “morphological alterations of the mucosa caused by chronic local irritative factors or referable to local expression of generalized illnesses, presenting a higher probability of degeneration into carcinoma with respect to surrounding mucosa”.<sup>2</sup>

However, it has been unanimously accepted that the diagnosis of a premalignant lesions of the larynx must be based on the histological characteristics of the lesion.<sup>2</sup> The histological classification of premalignant lesions, most closely followed for clinical purposes, is based on evaluation of the grade of hyperplasia and/or dysplasia of the epithelium. According to Hellquist et al.<sup>3</sup> a distinction can be made between Grade 1 lesions, presenting hyperplasia and/or keratosis with or without mild dysplasia, Grade 2 lesions characterized by moderate dysplasia, and Grade 3 lesions, in which dysplasia is severe or of such type as to configure carcinoma *in situ*. This grading is based on the classification proposed by the Kleinsasser in 1963<sup>1</sup> and later, by Delemarre,<sup>4</sup> distinguishing a first class characterized by

simple squamous cell hyperplasia, a second class represented by squamous cell hyperplasia, with atypia and third class represented by carcinoma *in situ*.

Freidmann,<sup>5</sup> proposed that dysplastic lesions of the larynx can be considered on the same scale as corresponding lesions of the uterine cervix. Thus, this classification distinguishes keratosis without dysplasia to keratosis with mild dysplasia (Laryngeal intraepithelial neoplasia or LIN 1), moderate dysplasia (LIN 2), and severe dysplasia or carcinoma *in situ* (LIN 3).

A classification proposed in Ljubljana, Slovenia, followed for more than 25 years, does not follow the three grade criteria but was devised to cater to specific clinical and histological laryngeal problems.<sup>6,7</sup> The working group of the European Society of Pathology re-evaluated and further formulated the histological criteria of Ljubljana classification in November 1997 in London, UK. The system is divided into 4 grades as follows:

1. Simple hyperplasia (SH) is benign group.
2. Abnormal (AbH) hyperplasia is benign group.
3. Atypical Hyperplasia (AtH) is potentially malignant.
4. Carcinoma *in situ* is malignant.

Malignant transformation of these lesions is a well-known fact. Simple and abnormal hyperplasia is considered benign forms with 0.7% and 1% risk of malignant transformation respectively. Atypical hyperplasia is precancerous lesion in the essential meaning of the word,



Fig. 1: Micro-laryngoscopic picture of left vocal cord keratosis



Fig. 2: Micro-laryngoscopic picture of scattered dysplastic lesions of bilateral vocal cords

with 9.5% of malignant alteration within 15 years.<sup>6</sup> Some studies have shown that the cases with atypical and severe dysplasia present the most threatening group associated with highest risk of cancer ranging from 19-28%.<sup>8,9</sup> Laryngeal precancerous lesions have no specific macroscopic appearance, and are variously referred as:

1. Chronic laryngitis.
2. Keratosis (Fig. 1)
3. Leukoplakia: A white patch.
4. Erythroplakia: A red patch.

5. Hyperplastic—dysplastic laryngeal lesions (Fig. 2): Is an increase in the epithelial layers of the larynx which is referred to using all embracing term of keratosis. This can be associated with mild, moderate or severe dysplasia.

The surface morphology and keratin layer formation of these lesions has no specific meaning, nor any significant relationship with their malignant potential.<sup>6,10</sup> Histopathological diagnosis informs a clinician how to treat patients with benign, potentially or actually malignant lesions.

## MANAGEMENT

The surgeon is often confronted with a myriad of management dilemmas once the diagnosis of precancerous laryngeal lesions is made. Following questions need to be addressed:

1. Is the lesion malignant?
2. Should the lesion be biopsied or followed closely?
3. How different pathological entities should be managed?
4. Are there medical measures to treat them or prevent recurrence?
5. How to follow these patients and detect recurrence or transformation early?

What adds to the confusion is a natural tendency of such lesions to partially or completely regress, stabilize without further progression, or progress to invasive malignancy.

The overall appearance of the lesion is considered to be the most important factor in determining management. The management decision depending mainly on whether there are single or multiple lesions, or widespread cohesive disease is as follows:

- a. Single (Fig. 3) and multiple foci (Fig. 4) should be completely excised to all visible margins, if possible.
- b. In the presence of widespread, confluent leukoplakia, histopathologic mapping of the lesion with multiple biopsies should be initially performed, followed by staged resection if feasible. There should be a low threshold for rebiopsy in the presence of widespread disease.
- c. Other factors that may be important in deciding management include the patient's general condition and fitness for surgery, physiological age, comorbidity and the presence of other risk factors.
- d. A discussion with the patient should be undertaken to inform him/her of the potential risks of hoarseness and



**Fig. 3:** Micro-laryngoscopy picture of single hyperplastic lesion right vocal cord



**Fig. 4:** Multifocal hyperplastic lesions right cord with associated erythroplasia

change in voice quality postoperatively, and of the possibility of recurrence.

It is very difficult to predict accurately which lesions will progress to invasive malignancy based only on clinical appearance. Studies have proven that the clinical appearance bears little correlation with the underlying pathology.<sup>11</sup> What makes decision making difficult is that simple hyperplasia, dysplasia, and or carcinoma can all coexist in same lesions. Even, stroboscopy has not proved to be reliable method of determining the presence of malignancy or depth of invasion.<sup>12</sup> Following features in decreasing order of importance, ulceration, erythroplasia, surface granularity, increased keratin thickness (verrucous appearance), increased size, recurrence after excisional biopsies and long duration have all been associated with carcinoma.<sup>11</sup> The initial management such lesion should begin with

determination whether it is a low-risk or high-risk lesion based on history and clinical examination. High-risk lesions are those who have:

- a. WHO classification severe dysplasia or carcinoma *in situ* (Ljubljana classification atypical hyperplasia or carcinoma *in situ*) or
- b. Patients with mild or moderate dysplasia with one or more of the following:
  - i. Continued smoking.
  - ii. Persistent hoarseness.
  - iii. A lesion visible on endoscopy.

Tobacco or ethanol abuse, occupational risk factors, diet and vitamin deficiency, irradiation exposure, viral exposure (i.e., HPV), and laryngotracheal reflux have all been epidemiologically associated with laryngeal carcinogenesis. Therefore, the patient needs appropriate counseling regarding these risk factors as part of the overall treatment plan.

### Conservative Measures

A one month trial of conservative measures is reasonable in the absence of any worsening of vocal symptoms, an enlarging lesion or clinical signs of invasive carcinoma. Conservative measures include instructing the patient on proper hydration, reduction of dehydrants (i.e. caffeine and alcohol), and elimination of any vocal abuse tendencies. All patients should be counseled regarding measures to reduce risk factors, especially stop smoking or ethanol intake. Symptomatic patients with laryngopharyngeal reflux should also be counseled about the potential risks, and should be offered antireflux treatment.

### CHEMOPREVENTION

Chemoprevention with retinoids, selenium, and other agents is still controversial. However, clinical response to retinol palmitate for laryngeal hyperplasia with an induction dose of at least 300000 IU followed by a maintenance dose of 1500000 IU<sup>13</sup> was assessed by Issing et al. There was a complete response in 75% of the patients and a partial response in the remainder. None of the lesions progressed to cancer. One principal drawback to using retinoids is that the lesions tend to recur when treatment is discontinued. Also, there may be significant side effects due to mucocutaneous toxicities. Increased incidence of lung cancer when betacarotene was used for primary cancer prevention in heavy smokers has been reported.<sup>14,15</sup>

Therefore, patients need to be cautioned regarding potential adverse effects.

### MODALITY OF SURGICAL TREATMENT

- a. Cold steel or CO<sub>2</sub> laser resection is recommended.
- b. If laser excision is contemplated, carbon dioxide laser is the preferred tool.
- c. The use of the laser for ablation is to be discouraged because no specimen is provided for diagnosis and may be associated with a possible higher risk of damage and impact on voice.
- d. The procedure of vocal cord stripping is not recommended.
- e. For primary lesions that have not been treated previously, radiotherapy should be offered with discretion only in rare circumstances and a very small numbers of patients, e.g. poor access for resection in a high grade lesion.
- f. All biopsies, including those from multiple foci, should be mounted, orientated and presented on an anatomic template to the pathologist, for photodocumentation prior to histological processing.

Since the introduction of endolaryngeal microsurgery, several basic microsurgical techniques have been described for the removal of vocal fold lesions. These techniques include conventional incision or dissection, bimanual retraction and cutting, microflap technique and the CO<sub>2</sub> laser. Until recently, only a few microsurgical methods have emerged as new choices for the treatment of vocal fold lesions. Lee et al<sup>16</sup> introduces an innovative method that can precisely remove benign sessile vocal fold lesions with epithelial keratosis or hyperplasia without jeopardizing the intermediate or deep layer of the lamina propria.

We prefer laryngeal microoperation under the micro-suspension laryngoscope and CO<sub>2</sub> laser type I cordectomy (Fig. 5). It is an effective and safe cure procedure; it provides a definite diagnostic method for the vocal cord dysplasia.

### Follow-up

All patients should be closely followed with:

- a. Use of a flexible nasendoscope or rigid Hopkins rod to view the larynx on office basis.
- b. Color photodocumentation must be done and retained in the notes.
- c. Stroboscopy is helpful if available, but is not really essential.

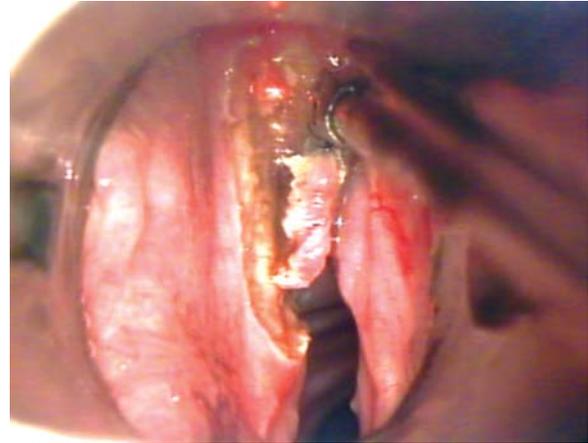


Fig. 5: CO<sub>2</sub> laser resection being performed of left cord dysplastic lesion



Fig. 6: MLS copy picture depicting CO<sub>2</sub> laser cordectomy being performed with meticulously preserving vocal fold ligament

High-risk patients should be followed up in the same manner as T1 laryngeal carcinoma: monthly for the first year, two monthly for the second year, three monthly in the third year and six monthly in years 4 and 5

Low risk lesions-patients who have mild or moderate dysplasia with no visible lesion or hoarseness, or who are not smoking should be followed up for a minimum of 6 months. Following that, if the patient agrees then they may be discharged with instructions to return if there is a change in voice or other suspicious symptoms appear. It should be noted that there were diverse opinions regarding the follow-up duration of low-risk patients. Some clinicians recommended at least a 2 year follow-up, as the mean duration of risk of progression has been documented to be of that duration. Others recommend early discharge from clinic, with open or early return should patients develop

anxiety, recurrence of their hoarseness, or 'throat symptoms'.

Radiation therapy has not been shown to prevent the progression of dysplastic lesions to carcinoma; in fact, it may even precipitate malignant degeneration. Therefore, radiation therapy should be reserved for invasive carcinoma. Due to multicentricity of the cancer in hyperplastic lesions, random biopsies are discouraged. Excision biopsy is performed with special emphasis on preserving the structural integrity of the deeper uninvolved layers of the vocal fold and surrounding normal mucosa (Fig. 4).<sup>11</sup>

In the absence of carcinoma, the most hyperplastic lesions occur on the superior or ventricular surface of the vocal fold.<sup>11</sup> Therefore, dissection to the phonating edge of the vocal fold is not necessary for complete excision. The lesion is carefully dissected of the deeper layers of the lamina propria using precise phonosurgical technique (Fig. 6). This minimizes the chances of adversely affecting vocal function due to extensive vocal fold fibrosis. At the completion of the procedure, the specimen is labeled and sent for serial section to avoid missing a focus of carcinoma.

Difficulty in dissecting the lesions off the deeper layers of the lamina propria or vocalis muscle suggests an invasive carcinoma or significant fibrosis from previous surgery.

### Persistent or Recurrent Precancerous Lesions

The management of the recurrent or persistent premalignant lesions depends mainly on their histology.

1. Recurrent, focal mild or moderate dysplasia should be excised if possible.
2. Recurrent, widespread mild or moderate dysplasia can be observed or excised: excision is especially undertaken if there is change in appearance (erythroplasia) or texture (heterogenous, proliferative features).
3. Recurrent, focal severe dysplasia: should be managed as a T1 laryngeal carcinoma with resection where possible. Radiotherapy may be considered by the multidisciplinary team in certain circumstances, including:
  - Patients who have had two or more recurrences
  - Patients who continue to smoke
  - Patients who have a high-risk of anesthetic complications
  - Patients who have access problems for surgery
  - Patient preference.
4. Persistent or recurrent widespread severe dysplasia: Radiotherapy should be considered as an option by the multidisciplinary team and discussed with patients who

have persistent or recurrent widespread severe dysplasia, especially in patients who continue to smoke.

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