Chapter

Premalignant Conditions of Larynx

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Abstract

Premalignant conditions of larynx encompass a variety of lesions that have the potential to evolve into malignant changes. The dysplastic premalignant epithelial changes of larynx have significantly increased Risk of developing in cancer than the hyperplastic stage of epithelial changes and this transformation significantly depends on the grade of dysplasia. Therefore, early diagnosis & prompt treatment should thus prevent the development of invasive carcinoma requiring more debilitating surgical resection. The histopathological examination is diagnostic & the evolution of advanced laryngoscopic surgical procedures including CO2 laser and newer treatment methods such as photodynamic therapy has shown promising results in their management.

Keywords: Premalignant lesions, larynx, keratosis, erythroplakia, leukoplakia

1. Introduction

The location of larynx is quiet unique that is it lies at the crossroads of air and food passages often referred to as part of the upper aerodigestive tract. It is also known as the organ of phonation, owing to its anatomical evolution & ability to produce voice. Indeed, from a physiologic point of view, it is essentially a valve or sphincter with a triple function: that of an open valve in respiration; that of a partially closed valve whose orifice can be modulated in phonation; that of a closed valve, protecting the trachea and bronchial tree during deglutition [1].

The larynx commences at the laryngeal inlet, (consisting of epiglottis anteriorly, aryepiglottic folds on either sides and interarytenoid fold posteriorly) and extends to the inferior border of cricoid cartilage, lying opposite the 3rd to 6th cervical vertebrae in adults and is somewhat higher in children. Structurally, it can be divided into three subsites, namely, the supraglottis, glottis and the subglottis by true and false vocal folds.

There are certain areas of larynx which are difficult to visualize through routine outpatient procedures like indirect laryngoscopy and these areas are of great clinical importance since many a times tumors tend to involve these subsites and are missed due to their anatomical location. Hence these areas require a special mention when discussing the anatomy.

Anterior commissure (anterior convergence of vocal folds and its insertion into the laminae of thyroid cartilage) is difficult to visualize through indirect laryngoscopy, it is located at the anterior junction of the two vocal folds, many a times a residual tumor is left behind during the surgical management; and if not managed properly, causes notable post-op morbidity. Between the two arytenoid

cartilages is present the posterior commissure. The vocal folds extend anteriorly to form a concentration of collagen fibres, known as anterior commissure tendon or Broyle's ligament which is attached to the deep layer of lamina propria and the inner perichondrium of the thyroid cartilage. Broyle's ligament, being devoid of glands, is resistant to the spread of tumors and hence acts as an effective safety barrier for further spread of malignancy. On the other hand, the mucosa of the glottis, lying superior and inferior to this ligament, is thrown back on the bare areas of thyroid cartilage, which can gave way to malignancies to invade the thyroid cartilage.

Histologically, two types of mucosal linings can be seen in larynx. Most of it is lined by pseudostratified ciliated columnar (respiratory) epithelium, except the vocal folds, the posterior glottis, a part of aryepiglottic folds and half of posterior surface of epiglottis, which are lined by non-keratinizing stratified squamous epithelium. The transition between the two epithelia, marked by the inferior arcuate line (present on the upper surface of vocal folds), is a common site for squamous cell carcinoma in larynx. The mucous glands, though freely dispersed throughout the mucosa of the larynx, are exceptionally numerous on the posterior surface of epiglottis and in the saccule. The mucus from the glands in the saccule are responsible for the lubrication of the vocal folds [2].

The malignancy was recognized long back in ancient times but the concept of premalignancy was not introduced till the end of 19th century. The term premalignant/precancer was introduced by Dubreuilh in 1896 for skin lesion and during the same era Durant described the first documented cases of laryngeal leukoplakia as "white cicatrices" adjacent to a malignant laryngeal lesion [3]. Later after almost 4 decades Jackson in 1923 conceptulized premalignancy of larynx as similar to a "large no. of citizens leaving their regular daily routine & mobilizing preparatory to invasion" [4].

Laryngeal cancer is the most common cause of head neck cancer in United States of America & is responsible for thousands of death each year [5]. The best chance of curing any cancer is via its early detection and eradication as morbidity and mortality are proportionately related to stage. Thus, appropriate management of precancerous laryngeal lesions in those patients fortunate enough to present at this stage is obviously vital.

The premalignant lesions of larynx are the identifiable local features that with time has a tendency to transform into invasive carcinoma. This change in the local sign occurs basically due to changes in the laryngeal cell that may lead to dysplastic or hyperplastic epithelial changes. WHO (World Health Organization) has defined premalignant lesions of larynx as morphological alterations of the mucosa caused by chronic local irritative factors as referable to local expression of generalized illness, presenting a higher probability of degeneration into the carcinoma with respect to surrounding mucosa. Moreover, WHO has classified these lesions on the basis of hyperplasia & various degree of dysplastic changes into simple squamous cell hyperplasia, mild dysplasia, moderate dysplasia, severe dysplasia & carcinoma in situ [6].

The epidemiology of premalignant lesions, reveals a scarce data. However, it is known that these lesions are more prevalent in males and are frequently seen in patients above 50 years of age.

A wide array of conditions have been implicated in the development & rapid transformation of premalignant lesions into an invasive cancer, including long-term tobacco exposure and alcohol abuse, various occupational professions related to the textile industry, chemical industries dealing with wood processing. A small proportion of carcinomas appears to be related to transcriptionally active human papillomavirus infection. So these factors basically changes the morphology of the glottis epithelial cells into hyperplastic & dysplastic changes. To understand this we must know the normal epithelial spread of larynx (**Table 1**) (**Figures 1** and **2**).

Nonkeratinized stratified squamous epithelium	Pseudostratified ciliated columnar epithelium with globet cells	Seromucinous glands
Anterior epiglottic surface	Ventricular folds	Posterior epiglottic surface
Upper half of the posterior epiglottic surface	Ventricle	False vocal cords
Superior margin of A-E folds	Saccule	Ventricle
Vocal cords	Subglottic region	Saccule & subglottis

Table 1.
Normal histology of larynx.

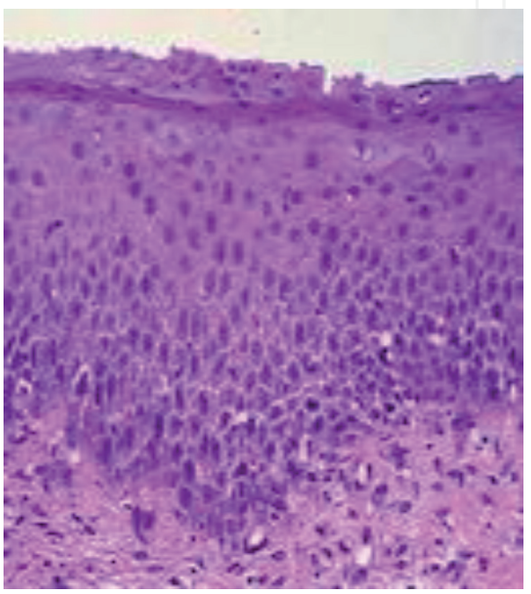

Figure 1.
Histological view of larynx (Nonkeratinized stratified squamous epithelium).

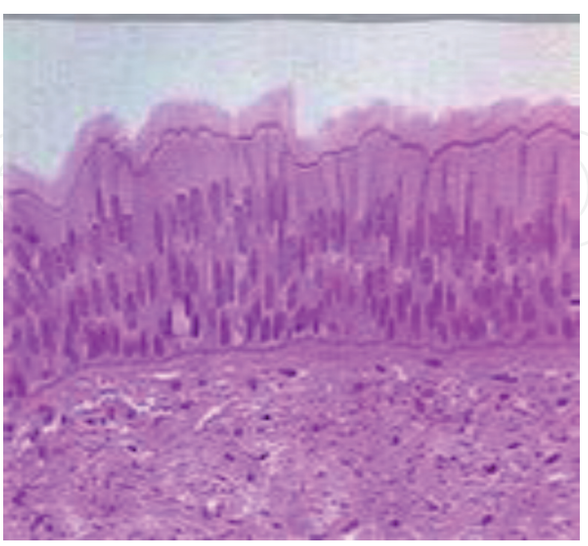

Figure 2.
Histological view of larynx (Pseudostratified ciliated columnar epithelium).

Although we are concerned about premalignant lesion only but this is important to understand the possible histological variety of malignant neoplasms that may arise in the larynx (**Table 2**) reflecting the different tissues from which they

Histological types	Squamous cell carcinoma	Muco epidermoid	Adenoid cystic	Sarcomas	Lymphoma	Neuroendocrine
Variants	1. Verrucous type 2. Spindle type 3. Basaloid type			1. Rhabdo myosarcoma 2. Chondro sarcoma		1. Carcinoid 2. Small cell

Table 2.
Histological Subtypes of Laryngeal Malignancies and their variants.

originate. The vast majority, however, are squamous carcinomas (up to 95%) and predominantly arise on the true vocal folds. All other histological subtypes will necessarily develop via a premalignant phase, but due to the paucity of such cases in the literature they have not been studied and characterized to the same extent as premalignant squamous carcinomatous lesions [7].

So it is the normal histological pattern which undergoes these various changes at the cellular & genetic level under the influence of various factors as already mentioned above, thus changes into a dysplastic or hyperplastic variation may occur, making it vulnerable to transform into a cancerous lesion.

The macroscopic changes of the lesions have no appearance & hence in clinical practice are commonly referred as: leukoplakia, erythroplakia, erythroleukoplakia, keratosis and chronic laryngitis although there is no consensus on this issue. The current laryngeal investigation systems for obtaining the high quality & resolution images so as to reveal the detailed morphology of glottis structures is one of the main task in laryngeal imaging & helps in diagnosis. These includes:

- Endoscopy–white light laryngoscopy
- Stroboscopy
- Contact endoscopy
- Autofluorescence
- Narrow band imaging (NBI)
- Ultrasound
- Computed axial tomography (CAT)/Magnetic resonance imaging (MRI)

So the appearance of lesion with these mentioned investigation system is no doubt of great help in diagnosis & prognosis of lesion but histopathological appearance is always diagnostic.

2. Etiology

The risk factors for pre malignant tumors of larynx are primarily similar to those of laryngeal carcinoma. These risk factors may cause conversion of a dysplastic lesion into metaplasia and eventually may lead to malignancy but the laryngeal

neoplasia is a preventable disease in the vast majority of cases, which points out the role of various environmental and social factors. The most commonly and strongly implicated factor remains smoking. Burning cigarettes release tar that contains polycyclic aromatic hydrocarbons which have been proven to be carcinogenic and act by damaging the nucleic acids in the cells. Similarly, alcohol consumption may be an independent risk factor & in such people, supraglottic carcinoma is frequently seen. Though alcohol is directly implicated in carcinogenesis, it may be associated with other co morbidities and deficiencies as in malnutrition or vitamin deficiencies. When alcohol consumption is combined with smoking, the risk of neoplasia multiplies.

Other known etiological factor for oropharyngeal carcinoma includes the Human Papilloma Virus or the HPV; the serotypes strongly associated with oropharyngeal carcinoma are 16 and 18 (as seen in carcinoma cervix) [8].

In most HPV positive laryngeal carcinomas, serotype 16 is frequently isolated, while in recurrent respiratory papillomatosis, serotypes 6 and 11 are commonly isolated.

Recurrent respiratory papillomatosis does not usually turn into squamous carcinoma, owing to different pathogenesis, however this transformation may be seen in patients who have a history of exposure to radiation.

The epidemiological studies have shown that the prevalence of HPV in patients of laryngeal carcinoma varies greatly i.e., between 0% to 58% (grossly around 25%), depending upon the investigations and the population [9]. Lately, studies have shown that HPV and carcinoma larynx are not strongly co related. On the other hand, it has been seen that HPV can be present in people with otherwise histologically normal epithelium of larynx and with no signs or symptoms [10].

The association of GERD (Gastro Esophageal Reflux Disorder) with laryngeal malignancy has been explored by many researchers. Olson in 1983 was the pioneer to study the role of chronic laryngopharyngeal reflux (LPR) in laryngeal carcinoma [11]. He found a significant relationship between these two pathologies, where the incidence of laryngeal carcinoma was higher in patients suffering from LPR [7]. On the contrary Chen et al. found no association between GERD and laryngeal neoplasia [12].

Many other environmental factors have been known to increase the risk of laryngeal malignancy such as industrial pollutants like asbestos, malnutrition, lower socioeconomic status etc. [13]. Exposure to radiation for managing other neck tumors like thyroid cancer can also predispose to laryngeal malignancies [14].

Even the role of genetic factors have been implicated to increase the susceptibility of an individual to develop laryngeal neoplasia such as enzymatic polymorphisms in elimination and detoxification of alcohol and smoke produced carcinogens [15].

3. Molecular genetics

The concept of field cancerization was introduced by Slaughter et al in a study of oral cancer [16]. He found that there occurred histopathological abnormalities in the epithelium surrounding the invasive cancer and the abnormalities ranged from keratosis, dysplasia and hyperkeratosis, epithelial hyperplasia etc. With this concept many researchers tried to study the genetics around the tumor site and premalignant conditions to predict their clinical outcome. In many tumor types, including HNSCC (Head and Neck squamous cell carcinoma), p53 inactivation apparently occurs in the transition from the preinvasive to the invasive state [17]. A second

17p13 locus may be altered earlier in progression. Existence of an alternate gene in this region has been implied in the genetic progression of brain and breast cancer [18, 19]. In a study by Califano et al the analysis of premalignant lesions was carried out a genetic level, they concluded that early genetic study of a premalignant lesion could aid and influence our treatment strategies from a conservative to a more aggressive one according to the genetic events detected [20].

4. Classification

Various classification of premalignant laryngeal lesions have been given by various authors, still it continues to be a controversial topic of laryngeal pathology for decades now, considering the classification, histological diagnosis and the treatment aspect as well. For clinical management of these lesions system based on the evaluation of the grade of hyperplasia and/or dysplasia of epithelium have been established (**Table 2**).

According to Hellquist et al [21] a distinction can be made between various lesions:

- Grade I lesions, presenting hyperplasia and/or keratosis with or without mild dysplasia where stratification is preserved and superficial cellular layers show cytoplasmic differentiation.

  The cellular and architectural atypia occur in the lower third part with nuclear crowding, cellular and nuclear pleomorphism with increased nuclear/cytoplasmic ratio.

- Grade II lesions characterized by moderate dysplasia. Histologic changes are similar to grade I but abnormalities extend up to two-third of the thickness of the epithelium, hence the differentiation & stratification is seen in superficial layers with numerous mitotic features.

- Grade III lesions, in which dysplasia is severe or of such type as to configure carcinoma in situ. Here, non-stratified & undifferentiated cells occupy from more than two-third up to the full thickness of the epithelium in majority of the cases there is no keratinization. Nuclear pleomorphism is seen with-bizarre large nuclei & the lesion is always contained by the basal lamina.

This grading is based on the classification proposed by the Kleinsasser in 19631 and later, by Delemarre, 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.

The modified Ljubljana [22, 23] classification, the modification done by a working group of European society of pathology in November 1997 in London, United Kingdom (UK) devised the classification to cater to specific clinical and histological laryngeal problems, as it does not follow the three grade criteria, so was divided it into four grades as follows:

1. Simple hyperplasia (SH) is benign group.

2. Abnormal hyperplasia (AbH) is benign group.

3. Atypical hyperplasia (AtH) is potentially malignant.

4. Carcinoma in situ is malignant.

The term dysplasia was accepted in laryngeal pathology first after the Toronto Centennial Conference on Laryngeal Cancer in 1974, almost after 11 years of proposed Kleinsasser classification. Several terms such as squamous intraepithelial neoplasia (SIN) and laryngeal intraepithelial neoplasia (LIN) were introduced. The term squamous intraepithelial neoplasia (SIN) was used for laryngeal precursor lesions by Friedmann and Osborn in 1976, and 10 years later Crissman and Fu opted for intraepithelial neoplasia of the larynx [24]. In addition, Friedmann and Ferlito used laryngeal intraepithelial neoplasia (LIN) [25]. An attempt to reconcile different schemes showed:

1. LIN I is regarded the equivalent of mild dysplasia

2. LIN II of moderate dysplasia and

3. LIN III of severe dysplasia and carcinoma in situ.

After that many editions of the World Health Organization (WHO) classification have been proposed & all such terms like as squamous intraepithelial neoplasia (SIN) and laryngeal intraepithelial neoplasia (LIN) were used but are now being abandoned and replaced by squamous intraepithelial lesions (SIL) [26, 27]. The essential update in the four editions of WHO was the attempt to induce a simplification from a four- to a two-tier system. The current WHO classification (2017) thus recommends the use of a two-tier system with reasonably clear histopathological criteria for the two groups:

1. Low-grade and

2. High-grade dysplasia.

Although the disadvantages like inter observer variability apart, subjectivities and uncertainties still remains but to a lesser degree.

Hence, it is very difficult to predict accurately which lesions will progress into invasive malignancy based only on clinical appearance. The diagnosis, treatment and prognosis of these lesions depend almost entirely on their histological abnormalities. In **Table 3** we have compared the different classifications given by different authors.

4.1 Clinical features

The most common presentation of patients harboring premalignant lesions is dysphonia which can be progressive or fluctuating. Rarely patients may even present with breathing difficulty or foreign body sensation throat.

The diagnosis is made by doing a flexible endoscopy. These lesions either appear as white keratotic patches, single, multiple or confluent (**Figures 3-5**). They are also seen as erythroplakia (red), mixed leucoerythroplakic (speckled) patches.

In general clinical appearance has shown to have poor correlation with the state of underlying epithelium [28, 29]. Still a few authors have found higher chances of malignancy and dysplasia with certain types of lesions. 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 [30].

Kleinsasser classification	WHO classification	Ljubljana classification	Modified Ljubljana classification	Freidmann and Ferlito (Laryngeal intraepithelial neoplasia)
Grade-I	Simple squamous cell hyperplasia	Simple hyperplasia	Simple hyperplasia	
Grade-II	Mild dysplasia	Abnormal hyperplasia (AbH)	Abnormal hyperplasia (AbH)	Laryngeal intraepithelial neoplasia- Grade-I
Grade III	Moderate dysplasia	Atypical hyperplasia (AtH)	Atypical hyperplasia (AtH)	Laryngeal intraepithelial neoplasia- Grade-II
	Severe dysplasia	Atypical hyperplasia (AtH)	Carcinoma in situ	Laryngeal intraepithelial neoplasia- Grade-III
	Carcinoma in situ	Carcinoma in situ		

Table 3.
Various classifications of laryngeal precancerous conditions.

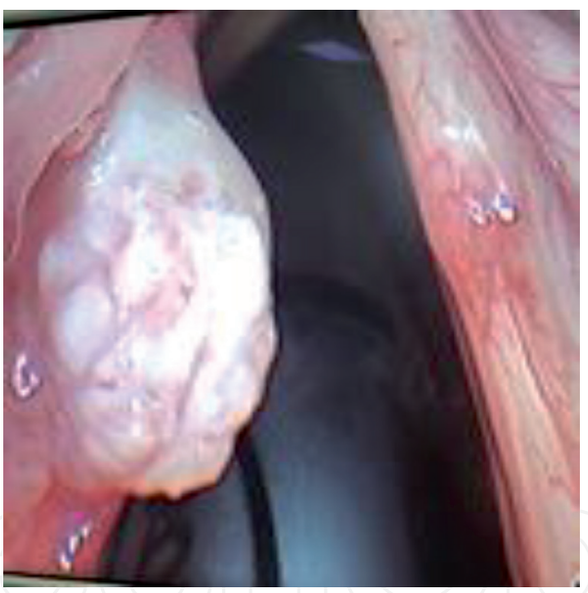

Figure 3.
Single keratotic lesion seen involving the left true vocal fold.

4.2 Management

The management of premalignant lesions is challenging for a clinician as it poses a diagnostic challenge and also because it requires close monitoring and follow up due to underlying risk of malignancy.

The laryngeal cancer represents about 1–2% of all malignant tumors. In 90% of cases carcinomas develop from precancerous epithelial lesions [31]. Prompt treatment after an early diagnosis is capable to prevent the development of an invasive neoplasm and the consequent recourse to more invasive laryngeal surgery [32, 33]. Lack of valid protocol or guidelines to manage such precancerous conditions makes it tough for an ENT surgeon to make a decision plan for their management.

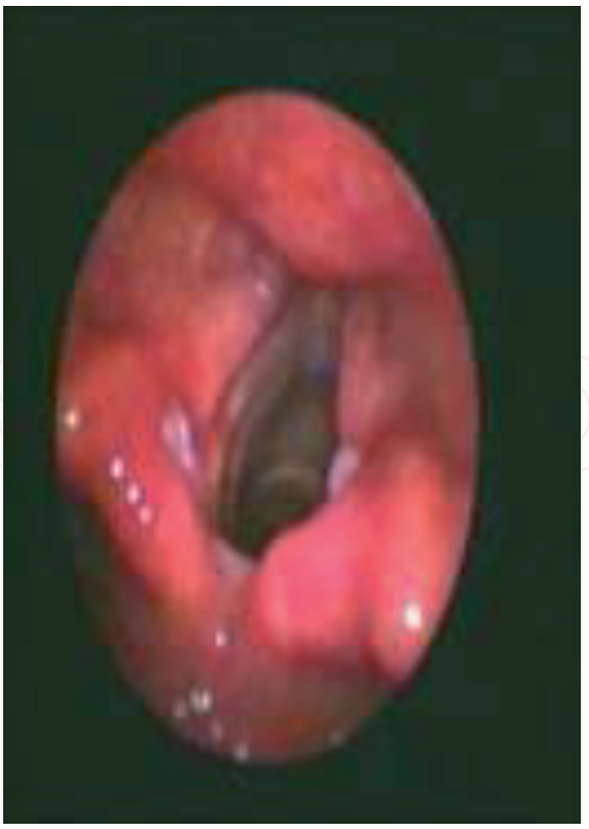

Figure 4.
Multiple Keratotic Lesion involving the bilateral arytenoids.

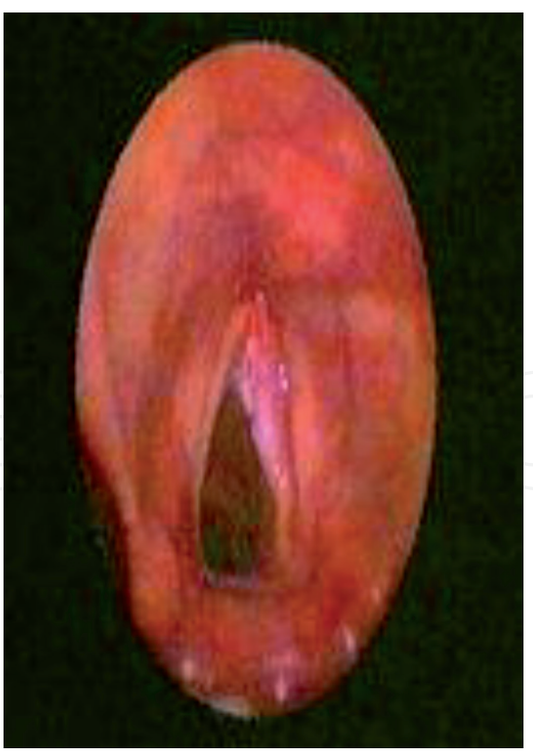

Figure 5.
Endoscopic image depicting a single confluent lesion involving the right Vocal Fold.

The dilemma in managing premalignant conditions lies in whether to manage it conservatively with close follow up or to do a biopsy. The invasiveness of the lesion and the prediction whether a lesion has a malignant potential cannot be assessed by clinical examination. Even various investigation modalities like

endoscopy, stroboscopy fail to analyse the invasiveness of lesion. Newer techniques such as contact endoscopy using highly magnified images (up to 150 X) using a rigid endoscope which is placed in direct contact with vocal fold epithelium and staining is done using 1% methylene blue dye. Though it has been found to have a high sensitivity and specificity still its limitation to unable to detect the dysplasia in deeper layers and the learning curve associated with it and requiring an expertise of a pathologist has made its application limited in the field of otorhinolaryngology [28, 32, 34].

In an attempt to formulate a plan a meeting of UK otolaryngologists and pathologists involved in the care of Head and Neck cancer was held and guidance in relation to premalignant conditions was issued [35]. In case of single (**Figure 3**) and multiple foci (**Figure 4**) they should be completely excised to all visible margins, if possible and in the presence of widespread, confluent leukoplakia (**Figure 5**), histopathological mapping of the lesion with multiple biopsies should be initially performed, followed by staged resection, if feasible. Once sending the biopsy specimen proper labelling and anatomical orientation should be presented on a template to the pathologist with photo documentation prior to histological analysis.

The patient's general condition and fitness for surgery, physiological age, comorbidity and the presence of other risk factors also play a vital role in planning a surgical procedure. The most essential step to be taken before planning the surgical procedure is a detailed and vivid discussion with the patient to inform him/her about the potential risks of hoarseness and change in voice quality postoperatively and about the possibility of recurrence.

4.3 Surgical treatment

The surgical procedure options are in the form of cold steel or carbon dioxide (CO_2) laser resection. Both are taken up via an endoscopic approach. If laser excision is planned, CO_2 laser is a preferred laser type. The use of the laser for ablation is to be discouraged, because no specimen is provided for diagnosis and it may be Associated with a possible higher risk of damage and impact on voice production. Hence, stripping of the cord is also not recommended due to the poor quality voice issues.

There are a few vital points which should be borne in mind while dissecting these lesions and they are as following: A proper plane of dissection should be achieved and the vocal ligament should be preserved so as to attain a good postoperative voice quality. An overzealous dissection can lead to postoperative scarring and poor voice outcomes. In such cases excision biopsy is performed with special care so as to preserve the deeper layers of vocal cords and the surrounding normal mucosa.

In case of anterior commissure lesions there is a risk of recurrence and their progression to cancer is reported in literature so adequate clearance and regular follow up is required in case the disease is progressing to anterior commissure.

4.4 Radiotherapy

Role of radiotherapy in premalignant conditions is only reserved for those patients, in whom the surgical intervention is contraindicated due to morbidity. Many studies have shown that radiation therapy to be ineffective in preventing the progression of dysplastic lesions to carcinoma; in fact, it may even precipitate malignant degeneration [30]. Therefore, the application of radiation therapy should be reserved for invasive carcinoma only.

4.5 Follow up

The follow up of such patients is the most vital part of their management since there is always a risk of recurrence and malignant transformation. In the literature no fixed protocol has been designed for the follow up plan of premalignant lesions but it has been noted that malignant transformation rate is higher with moderate to severe dysplasia as compared to mild dysplasia [15]. To simplify things we follow a self-designed protocol according to which we divide the patients into two groups that is the high risk and low risk group. Now patients in high risk group are those who have moderate, severe dysplasia and carcinoma in situ (according to WHO classification) and patients even with mild dysplasia but who are cigarette smokers, heavy alcohol consumers are included in this group. In high risk we follow the same protocol as T1 carcinoma that is for initial 2 years every month follow up, 2 monthly in the second year, 3 monthly in the third year and 6 monthly in fourth and fifth year.

In cases of low risk group the follow up plan was to do a regular monthly check up for at least 6 months. Following that clear instructions to the patient to revert back, if there is change in voice and on appearance of any suspicious symptoms.

4.6 Other treatment options

Photodynamic Therapy (PDT) is a minimally invasive treatment that involves the activation by light of a drug (photosensitizer) that generates cytotoxic reactive oxygen species. This therapy has been specially studied in cases of premalignant laryngeal lesions. A clinical trial was conducted in 2014 using a compound named 3-(1'-hexyloxyethyl) pyropheophorbide (HPPH) mediated photodynamic therapy [36]. The results of this phase I b trials were very promising with a fewer complications rate. Though this clinical trial is still underway and hence awaiting its approval. Its use in oral cancer lesions, especially for the recurrent ones has been established by many authors [37].

5. Conclusion

Early diagnosis, timely management and a regular follow of patients harboring premalignant lesions can prevent its progression to full blown laryngeal carcinoma. The newer treatment modalities in the form of photodynamic therapy though are in their initial phase of testing but they do show a potential in future management of such lesions.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

HPV	Human papilloma virus
LPR	Laryngopharyngeal Reflux
SH	Simple Hyperplasia
AbH	Abnormal Hyperplasia
AtH	Atypical Hyperplasia

SIN	Squamous intraepithelial neoplasia
LIN	Laryngeal intraepithelial neoplasia
WHO	World Health Organization
PDT	Photodynamic therapy
HNSCC	Head and Neck Squamous cell carcinoma
HPPH	3- (1'-hexyloxyethyl) pyropheophorbide

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