Laryngeal Dysplasia: What does the Evidence Tell Us?

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ABSTRACT
Management of laryngeal dysplasia often poses a clinical conundrum, especially so with its unpredictable propensity for malignant transformation. The wide heterogeneity in published results and the dearth of level I evidence makes it challenging to arrive at a consensus or best practice guidelines. In 2010, ENT UK had developed such a guideline based on critical analysis of previously published data and professional opinion. This article examines the available evidence, and attempts to highlight the best possible modalities in investigation and management strategies as objectively as possible.

Keywords: Carcinoma-in Situ, Dysplasia, Laryngeal, Leukoplasia, Vocal fold.

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INTRODUCTION
Dysplasia is a histological diagnosis in the presence of abnormal maturation of cells and disorderly growth from the base upward. Confirmation of the diagnosis on histopathological examination would require the following cytologic characteristics: hyperchromatism, increased nuclear–cytoplasmic ratio, poikilocytosis and anisocytosis, coupled with architectural changes which include but not limited to basal cell hyperplasia, abnormal mitoses, and drop-shaped rete ridges. It is these features that form the foundation for accurate histological interpretation, regardless of the classification used.

Atypia refers to individual cell changes, whereas dysplasia refers to the changes in the epithelium as a whole. These changes can be appreciated under light microscopy, and the degree of nuclear atypia determines the grade severity. Regardless of the grade severity, the basement membrane of the cell remains intact; once the basement membrane is breached, it is then termed as invasive carcinoma and no longer precancerous lesion.

Repeated injury to squamous epithelium from carcinogenic substances, tobacco smoke for instance, would result in hyperplastic followed by dysplastic changes arising from the cell’s inbuilt mechanism of coping with insult and repair. The vocal folds are lined by non-keratinized stratified squamous epithelium, similar to the oral cavity mucosa in the propensity to develop premalignant lesions, and the subsequent potential for malignant transformation.

Laryngeal dysplasia has been reported to occur in 2–10 per 100,000 population, with a pooled overall malignant transformation rate (MTR) of 14% (CI 8–22%). Although a higher grade lesion would mean a higher risk of malignant transformation, in which mild/moderate lesions have a 10.6% risk and severe/carcinoma in situ (CIS) have a threefold higher (30.4%) risk of transforming, the time to progression is not dependent on the severity. The mean time to malignant transformation is 5.8 years, hence the emphasis on the need for judicious follow-up. It is not surprising to see a mild dysplasia progressing directly to invasive carcinoma or a severe dysplasia remaining indolent. Clinical progression of laryngeal dysplasias from mild/moderate/severe dysplasia to CIS, and subsequent invasive carcinoma is not often observed, possibly owing to the natural history of the disease is such, sampling errors and variability in pathology reporting, in turn giving rise to the wide variation in management strategies.

HISTOLOGICAL GRADING
A histological grading system requires consistency in interpretation, reproducibility, clinical applicability and the ability to predict risk of malignant transformation. Numerous grading systems have been reported in the past for laryngeal intraepithelial lesions. The WHO 2005 classification espoused the three-tier system of mild, moderate and severe dysplasia. However, several inter-observer studies, in which pathologists used all three classifications, showed no significant advantage with only moderate inter-observer agreements. The 4th Edition of the World Health Organization Classification of Head and Neck Tumours, published in 2017, has adopted a
two-tier system, based on the morphological criteria of the amended Ljubljana classification, where the lesions are called squamous intraepithelial lesions (SIL): low-grade SILs and high-grade SILs.\textsuperscript{10}

**CLINICAL ASSESSMENT**

Patients with laryngeal dysplasia may be asymptomatic or present with hoarseness, and a leukoplakia or erythroplakia patch may be evident on flexible nasendoscopy in the clinic setting. The vibratory properties of the superficial lamina propria (SLP) is affected by this hyperkeratotic patch and may be demonstrable on videoendoscopy, should this facility be available, although not mandatory. Photo-documentation of the lesion at presentation is highly recommended as a baseline reference, as well as for comparison purposes during follow-up.\textsuperscript{31}

Although individual studies have demonstrated the benefits of narrow band imaging (NBI) in head and neck cancers and pre-cancerous lesions, a recent systematic review failed to pool data on such efficacy in laryngeal precancerous lesions due to the wide heterogeneity in published results.\textsuperscript{12} Nevertheless, high diagnostic accuracy rates have been reported. In a prospective study of 158 patients, DeVito et al.\textsuperscript{13} reported a high sensitivity rate of 97% (CI, 84.2–99.9%), and specificity rate of 92.5% (CI, 79.6–98.4%) in identifying early laryngeal cancer and precancerous lesions. Kraft et al.\textsuperscript{14} showed high sensitivity rate of 97% for NBI (versus 79% for white light assessment), in 205 patients who underwent microlaryngoscopy, in picking up laryngeal cancer and precursor lesions; the specificity rates were similar for NBI and whitelight at 95 and 96%, respectively. Clinicians should consider NBI use where available, thus minimizing interobserver variability arising from subjective clinical assessment with pure white light imaging alone.

**TREATMENT STRATEGIES**

The decision on treatment modality is a shared process between the treating surgeon and the patient, and should ideally consider the patient’s comorbidities, preferences, fitness for intervention, histological grading, extent of lesion and availability of treatment facility. The patient must be advised of the anticipated changes in voice quality due to vocal fold scarring, more so for revision procedures. At present, the consensus statement developed by ENT UK in 2010 is probably the best available practice guidelines to fall back on as a reference point. A flowchart developed by Cosway and Paleri utilizing the contents of the consensus statement elegantly summarizes and describes the stepwise approach to management of patients with laryngeal dysplasia (Flow chart 1).\textsuperscript{15}

Management is essentially guided by the appearance of the lesion i.e., single/multiple foci versus widespread disease, and may be summarized as follows:\textsuperscript{11}

Single/multiple lesion must be completely excised in the initial seating up to all visible margins as possible, as the primary excision has a dual role of diagnostic and therapeutic purpose. On the other hand, histologic mapping with multiple biopsies is advocated for widespread confluent lesions, and staged resection to be performed in subsequent seating. Cold steel instrument or CO\textsubscript{2} laser is the recommended surgical tool. Vocal cord stripping is not recommended, contrary to that practiced in Ljubljana, where in all patients with atypical hyperplasia were subjected to this procedure.

The importance of specimen presentation to obtain accurate results cannot be emphasized enough. As part of the recommendation, all specimens must be mounted, orientated and presented on an anatomic template for photo-documentation and histologic interpretation. Larger biopsies are preferable when possible, to enable more accurate orientation and interpretation of the lesion. Presence of dysplasia at surgical margins is not an indication for further biopsy or excision. However, the patient must be followed through and a low-threshold for rebiopsy should be the practice in the event of a new lesion or change in appearance of preexisting lesion. The management of patients with atypical hyperplasia/severe dysplasia and CIS should ideally be discussed at a multidisciplinary meeting.

Although the rate of MTR has been documented to be lower in patients undergoing surgical excision 15% (CI, 12–18%) compared to patients in the ‘non-excision’ group 21% (CI, 16–27%) this result could not reach statistical significance (p = 0.12) despite adjustment for grade, and therefore a precise distinction and superiority of either treatment modality has not be made thus far.\textsuperscript{5}

The concordance of NBI endoscopy findings with histopathological results of vocal fold leukoplakic lesions has been proven to be statistically significant with a kappa index of 0.77, (p <0.001).\textsuperscript{16} The use of NBI is advocated when available for its superior quality in highlighting neovascularization and the ability to delineate more precise margins of a vocal fold lesion, especially in the follow-up setting.

**FOLLOW-UP RECOMMENDATION**

Laryngeal dysplasia is classified into 2 categories, i.e high risk and low risk lesions for the purpose of follow-up as per the consensus statement.\textsuperscript{11,15} The low risk category consists of mild/moderate dysplasia
in the absence of smoking, persistent hoarseness or visible lesion. These patients must be followed-up for a minimum period of 6 months and advised to return in the event of new ‘throat’ symptoms or change in voice. Severe dysplasia/CIS as per WHO grading or, mild/moderate dysplasia with presence of either smoking, persistent hoarseness or visible lesion are categorized as high risk. It is this group that must be followed up as per T1 laryngeal carcinoma protocol.

Flexible nasendoscopy and colour photo-documentation are the basic requirements during each visit. A recent secondary analysis of preexisting data by Paleri et al. has highlighted the benefits and role of NBI on follow-up of patients with laryngeal dysplasia. The treating physician is 4 times less likely to miss a malignant transformation with the use of NBI during follow-up in the case of severe dysplasia. Hence, a negative finding on NBI would allow monitoring the patient in an outpatient setup, and
negate the necessity for unnecessary repeated biopsies, and subsequent worsening of voice quality.\textsuperscript{17}

Although full thickness biopsies are essential for diagnosis, a recent longitudinal retrospective analysis demonstrated that repeated full-thickness excisions/biopsies do not confer therapeutic regression of dysplasia in terms of reversal of progression or downgrading of severity,\textsuperscript{6} contrary to that previously reported.\textsuperscript{18} In fact, the odds of dysplasia worsening had increased by 4\% with each additional excision.\textsuperscript{6} The aforementioned findings reinforce the use of NBI in surveillance and surgery, to cautiously avoid over-zealous treatment.

**MANAGEMENT OF RECURRENT/PERSISTENT DISEASE**

Severe dysplasia/CIS must be managed as per T1 laryngeal carcinoma. Management of mild/moderate dysplastic lesions again depends on whether they are focal or widespread. Focal lesions should be excised where possible, whereas cohesive lesions may be excised or observed. Excision in this case is recommended when patients are symptomatic or there is evidence of change in the appearance of the lesion.\textsuperscript{11,15}

Radiotherapy may be considered in active smokers, patients with 2 or more recurrences, patients with high anaesthetic risks, widespread persistent/recurrent disease especially so in smokers or if radiotherapy is the patient’s modality of choice.\textsuperscript{11,15}

**SURGICAL PROCEDURES AND LASERS**

Serial microflap excision has been the practice norm and believed to have significant benefits with regard to oncologic outcome,\textsuperscript{18} till recently challenged by a longitudinal study.\textsuperscript{6} Serial excisions however result in poorer voice quality. A recent single-stage excision method of combining submucosal infusion technique with microflap excision described by Kono et al., has demonstrated safe oncologic clearance with satisfactory vocal function,\textsuperscript{19} however, this would require further research.

Besides providing increased precision and an unobstructed view of the surgical field compared to microflap surgery, lasers minimize tissue manipulation, intraoperative bleeding and surrounding tissue damage.\textsuperscript{20} Carbon dioxide (CO\textsubscript{2}) laser has long been the workhorse of laryngeal surgery in general, and for laryngeal dysplasia specifically. In recent times, pulsed dye laser (PDL) and potassium titanyl phosphate (KTP) lasers have gained their respective roles in laryngeal surgery. They not only photoangiolyse the microvasculature of the superficial lamina propria (SLP), but affect the extracellular matrix and connective tissue, and therefore are able to target vascular lesions while preserving the surface epithelium.\textsuperscript{21} The characteristics of various lasers as described by Yan et al.\textsuperscript{21} are summarized in Table 1.

The preferential use of PDL over KTP in laryngeal dysplasia might be guided by the fact that PDL does not only create a cleavage plane between the basement membrane and SLP, but penetrates deeper than KTP, conferring an advantage in thick lesions.\textsuperscript{21,22} Lesions in the non-phonatory region of the vocal fold are better off treated with PDL as the basement membrane and SLP remain unaffected.\textsuperscript{21}

While serial in-office use of lasers for leukoplakic lesions might control disease effectively, minimize

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**Table 1:** Types of lasers utilized in laryngeal surgery and their characteristics

<table>
<thead>
<tr>
<th>Laser type/Characteristics</th>
<th>CO\textsubscript{2}</th>
<th>KTP</th>
<th>PDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigid</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fiber-optic transmission</td>
<td>Yes (flexible type)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Office use (LA)</td>
<td>Yes (flexible type only)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Operating theater use (GA)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Wavelength (nm)</td>
<td>10,600</td>
<td>532</td>
<td>585</td>
</tr>
<tr>
<td>Target chromophore</td>
<td>Water</td>
<td>Hemoglobin</td>
<td>Hemoglobin</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Cutting/ablating</td>
<td>Photoangiolytic</td>
<td>Photoangiolytic</td>
</tr>
<tr>
<td>Specific characteristics</td>
<td>Continuous mode preferred for coagulative property</td>
<td>Allows for contact/non-contact mode</td>
<td>Allows for contact/non-contact mode</td>
</tr>
<tr>
<td></td>
<td>Pulsed mode preferred for incisions</td>
<td>Better hemostatic effect than CO\textsubscript{2}</td>
<td>Better hemostatic effect than CO\textsubscript{2}</td>
</tr>
<tr>
<td></td>
<td>Minimal surrounding tissue damage</td>
<td>Wide pulse width</td>
<td>Short pulse width</td>
</tr>
<tr>
<td></td>
<td>More focused than KTP/PDL</td>
<td>Slower heating</td>
<td>Risk of vessel wall rupture prior to completion of hemostasis</td>
</tr>
</tbody>
</table>
morbidity and preserve voice quality, simultaneously reducing cost from operating theatre charges and hospitalization fees, judicious patient selection is crucial in minimizing complication rates and repeated procedures. Earlier operative intervention might benefit patients who require repeated six-monthly in-office procedures. Nevertheless, selection of one laser type over the other ultimately boils down to the principle of balancing thermal damage and its efficacy on target tissue, availability of the equipment and trained personnel and preference of the surgeon.

**BIOMARKERS**

Biomarkers are genes or proteins detected in precancerous or malignant lesion and have a crucial role in predicting malignant transformation. Although the scoring systems for biomarker staining vary widely among studies, presence of cortactin, cyclin D1 and Ki67 from individual studies have demonstrated statistically significant progression to malignancy when these biomarkers were positive. The wide heterogeneity in scoring systems and published results of these biomarkers have made attempts at meta-analysis not possible or the results of such attempts insignificant.

The presence of p53 on the other hand is inversely related to malignant transformation. The results of a pooled meta-analysis on p53 proved to be statistically insignificant in predicting malignant transformation. In conclusion, there is insufficient evidence on the role of biomarkers to predict malignant transformation of laryngeal precancerous lesions at present.

**RISK FACTOR REDUCTION AND CHEMOPREVENTION**

The detection of human papilloma virus (HPV) load depends on the processing method, i.e., polymerase chain reaction, in situ hybridization or immunohistochemistry staining. Several small cohorts have failed to demonstrate a positive association between HPV with laryngeal premalignancy. There is a need for substantial high quality evidence to demonstrate either a causal effect or negative relationship between HPV and laryngeal dysplasia.

The carcinogenic properties of alcohol, although not fully understood, is thought to arise from the effect exerted by acetaldehyde; a metabolite of alcohol, onto epithelial cells or due to direct contact of alcohol with surface epithelium. A recent meta-analysis by Bagnardi et al. demonstrated a pooled relative risk of 2.65 of developing laryngeal cancers in heavy drinkers as compared to occasional and non-drinkers; with a positive dose-risk relationship.

A small retrospective analysis has described that continuation or cessation of smoking does not influence the progression of laryngeal dysplasia to malignancy. This perhaps could be attributed to the irreversible genetic and morphologic changes incurred by smoking. Although tobacco smoking is an established risk factor for laryngeal cancers and produces a synergistic effect with alcohol in carcinoma formation, current knowledge as demonstrated in a meta-analysis by Weller et al. dictates that there is insufficient evidence to conclude on the harmful effects of smoking or alcohol on malignant transformation of laryngeal dysplastic lesions.

Beside the free radical action and direct insult on laryngeal mucosa, hydrochloroletic complex, the main active component of gastric acid secretion, exerts its damaging effect at the junctional intercellular structures, resulting in increased permeability, raised intercellular acidity, osmotic disruption and subsequent cell necrosis. Inactivated trypsin, a component of duodenalgastric reflux, exerts its proteolytic effect by breaking down cell connection. A statistically significant association is noted in reflux being a risk factor for precancerous and squamous malignancies of the laryngo-pharyngeal complex; especially so with prolonged exposure of over 20 years. A direct causal-effect relationship of acid reflux and formation of cancer has yet to be demonstrated probably due to the simultaneous presence of smoking and alcohol consumption as confounding risk factors in studied patients.

It is nevertheless sensible to advocate cessation of smoking and drinking, as well as place patients on anti-reflux therapy, as recommended in the consensus statement. Enrolment into smoking cessation programs should be offered to patients who face difficulty in dropping this habit.

The natural course of normal cells evolving to cancerous cells is determined by the effect of field cancerization and multistep carcinogenesis. These in turn are influenced by genetic instability (loss of heterozygosity in 9p and 3p) and environmental exposure of carcinogens. These neoplastic principles form the fundamentals for chemoprevention intervention and development of targeted therapies.

Folate deficiency causes genetic instability by breakage of DNA as a result of assimilation of uracil within DNA, and in turn promoting carcinogenesis. Primary chemoprevention with oral folic acid supplement might be beneficial in halting the progression of laryngeal precancerous lesion, but further controlled trials are required to establish its role. At present, smoking cessation is the best intervention to prevent recurrences. The limited number of chemoprevention trials in laryngeal dysplasia might be attributed to the limitations in
accessibility and monitoring of lesion within the larynx; in contrast to oral precancerous lesion, that are conveniently accessed and well researched.

LIMITATIONS

Meta-analyses and systematic reviews of either management strategies or biomarkers were mostly of level 3 and 4 evidence consisting of retrospective studies and case series, except for one prospective study in Weller’s systematic review and the various prospective studies on NBI. Nevertheless, the pooled MTR and time to malignant transformation were statistically significant. Further well planned prospective trials and future research into the role of biomarkers and genetic analysis would shed light on new pertinent information in formulation of future guidelines to direct more appropriate management of laryngeal dysplasia. Comparative studies on the efficacy of various treatment modalities, influence of smoking and alcohol consumption on malignant transformation, and role of chemoprevention is a scope to consider as well.

CONCLUSION

The challenge in the management of laryngeal dysplasia remains in finding the balance between achieving oncologic clearance and acceptable functional outcome. The natural course of the disease is nonlinear. Severe dysplasia and CIS demonstrate a higher rate of malignant transformation. Grade of dysplasia still dictates treatment decision and every effort possible should be made to reduce observer variability. Narrow band imaging has an established role in follow-up of patients. Smoking cessation must be advocated to prevent recurrence.

REFERENCES

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