LARYNGEAL DYSPLASIA

Tomas Fernandez M; 3rd year ENT resident, Son Espases University Hospital
✓ Laryngeal cancer constitutes 1-2% of all malignancies diagnosed worldwide

✓ Survival is related to stage of the disease...
   ✓ It is essential to concentrate on the initial steps in tumor development
     ✓ Early detection
     ✓ Implementation of suitable therapy

✓ Review points on laryngeal dysplasia
   ✓ Current terminology and classification systems
   ✓ Current and alternative management strategies
### NORMAL HISTOLOGY

<table>
<thead>
<tr>
<th>Nonkeratinized stratified squamous epithelium</th>
<th>Pseudostratified ciliated columnar epithelium + globet cells</th>
<th>Seromucinous glands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior epiglottic surface</td>
<td>Ventricular folds</td>
<td>Posterior epiglottic surface</td>
</tr>
<tr>
<td>Upper half of the posterior epiglottic surface</td>
<td>Ventricle</td>
<td>False cords</td>
</tr>
<tr>
<td>Superior margin of A-E folds</td>
<td>Saccule</td>
<td>Ventricle</td>
</tr>
<tr>
<td>Vocal cords</td>
<td>Subglottic region</td>
<td>Saccule</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subglottis</td>
</tr>
</tbody>
</table>
Nonkeratinized epithelium of the vocal cord

Pseudostratified ciliated columnar epithelium

NORMAL HISTOLOGY
Leukoplakia

- **CLINICAL TERM:** any white lesion on a mucous membrane
- **NO HISTOLOGICAL IMPLICATIONS**
- **NO SYNONYMOUS WITH “CANCER”/“MALIGNANCY”**

Erythroplakia

- **CLINICAL TERM:** any reddish plaque on the mucosal surface
- **Epithelial atypia and invasive carcinoma presence is not uncommon**

Erythroleukoplakia
Laryngeal leukoplakia caused by parakeratosis

Laryngeal leukoplakia caused by candidiasis

https://medicine.uiowa.edu/iowaprotocols
HISTOPATHOLOGICAL TERMINOLOGY

SQUAMOUS METAPLASIA

✓ Replacement of normal respiratory epithelium by stratified squamous epithelium
✓ Can follow persistent trauma or chronic irritation
✓ No evidence it predisposes to malignancy

SQUAMOUS CELL HYPERPLASIA

✓ BENIGN AND REVERSIBLE CHANGE
✓ Epithelium becomes thicker without cellular atypia
HISTOPATHOLOGICAL TERMINOLOGY

PSEUDOEPITHELIOMATOUS HYPERPLASIA

- Exuberant reactive or reparative overgrowth of squamous epithelium with extension of bulbous rete processes into the lamina propria
- May simulate well-differentiated SCC --- no evidence it is a potentially malignant lesion
- Absence of epithelial cellular atypia
- Inflammatory infiltrate
KERATOSIS/ORTHOKERATOSIS/PARAKERATOSIS

- Abnormal change resulting from the production of keratin on the surface of the epithelium
- Orthokeratosis --- prominent granular layer, without nuclei
- Parakeratosis --- prominent granular layer, with nuclei
- CELLULAR ATYPIA IS ABSENT + CORRECT MATURATION SEQUENCE OF THE CELLULAR LAYERS
- NOT REGARDED AS A PRECANCEROUS LESION
LARYNGEAL INTRAEPITHELIAL NEOPLASIA, DYSPLASIA AND ATYPIA

- Describe the presence of atypical cytologic features in the laryngeal squamous epithelium
  - Atypia --- individual cellular changes
  - Dysplasia --- altered (atypical) epithelium and disordered epithelial maturation

- Some authors believe the term “dysplasia” should be replaced by “intraepithelial neoplasia”
  - 3 classification grading systems
Friedman & Ferlito have used the term LARYNGEAL INTRAEPITHELIAL NEOPLASIA (LIN)

LIN I (mild/minimal dysplasia)

- Stratification is preserved and cellular layers in the more superficial 2/3 show cytoplasmic differentiation.
- Cellular and architectural atypia occur in the lower third
  + “nuclear crowding” + cellular and nuclear pleomorphism + increased nuclear/cytoplasmic ratio
Friedman & Ferlito have used the term LARYNGEAL INTRAEPITHELIAL NEOPLASIA (LIN)

**LIN II (moderate dysplasia)**

- ✓ Histologic changes similar to LIN I, but abnormalities extend to 2/3 of the thickness of the epithelium
- ✓ Differentiation and stratification still seen in superficial 1/3
- ✓ Mitotic features are more numerous
- ✓ Common to find 2 different grades of dysplasia within single high-power visual field
Friedman & Ferlito have used the term LARYNGEAL INTRAEPITHELIAL NEOPLASIA (LIN)

LIN III (severe dysplasia and carcinoma in situ)

- Non-stratified, undifferentiated cells occupy from >2/3 up to the full thickness of the epithelium
- Nuclear pleomorphism —— bizarre large nuclei
- Mitotic figures >>> %
- No keratinization in majority of cases
- LESION IS ALWAYS CONTAINED BY THE BASAL LAMINA!
HISTOPATHOLOGICAL TERMINOLOGY

Severe dysplasia

Carcinoma in situ
<table>
<thead>
<tr>
<th>Benigne</th>
<th>Grad I: Plattenepithel-hyperplasie</th>
<th>Simple squamous cell hyperplasia</th>
<th>Simple hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Präkanzeröse Läsion mit mäßigem Risiko der Karzinomentwicklung</td>
<td>Grad II: mäßige oder mittelgradige Dysplasie</td>
<td>Mild dysplasia</td>
<td>Abnormal hyperplasia (Basal/parabasal cell hyperplasia)</td>
</tr>
<tr>
<td>Präkanzeröse Läsion mit hohem Risiko der Karzinomentwicklung</td>
<td>Grad III: schwere Dysplasie</td>
<td>Severe dysplasia</td>
<td>Atypical hyperplasia</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>Carcinoma in situ</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Normal appearing epithelium → Hyperplasia → Mild dysplasia → Severe dysplasia or carcinoma in situ → Invasive carcinoma

Carcinogen exposure
- 9p21 deletion
- p16/p14 inactivation

Genetic changes
- 3p deletions
- TP53 mutations
- Tetraploidy

Epigenetic aberrations
- Telomerase activation
- 11q13
- 13q21
- 8p deletion
- Aneuploidy
- Cyclin D1 amplification
- 18q deletion
- 10q23
- 3q26
- PTEN inactivation

Genomic instability

Head and neck cancer; Athanassios Argiris, Michalis V Karamouzis, David Raben, Robert L Ferris; Lancet 2008; 371: 1695-709
DEVELOPMENT OF INVASIVE CANCER

✓ Widely varying differences with respect to the probability of malignant progression in mild, moderate and severe dysplasia

✓ Meta-analysis of 940 cases, Weller et al demonstrated
  ✓ **Overall malignant transformation rate of 14%**
  ✓ **Mean time to malignant transformation of 5.8 years**
  ✓ >>> with increased severity of dysplasia
    ✓ **30.4% for severe dysplasia**
    ✓ **10.6% for mild/moderate dysplasia**

✓ No good evidence for the use of biomarkers in predicting the future behavior of laryngeal dysplastic lesions
The risk and interval to malignancy of patients with laryngeal dysplasia; a systematic review of case series and meta-analysis

Weller, M.D.,* Nankivell, P.C.,* McConkey, C.,† Paleri, V.‡ & Mehanna, H.M.*

*Institute of Head and Neck Studies and Education, University Hospitals Coventry and Warwickshire, Coventry, UK,
§Clinical Trials Unit, University of Warwick, Coventry, UK, and ‡Freeman Hospital, Newcastle upon Tyne, UK

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Malignant transformation and intervention type

The variety of interventions reported and the lack of clarity regarding interventions and follow-up regimes made it difficult to extract data on intervention type. The studies were subdivided into two groups, namely those where formal surgical excision had been performed in an attempt to excise the lesion, (using either cold steel or LASER) and a ‘non-excision’ group where only a biopsy had been performed or the modality of treatment was not made clear. When these two groups were analysed, the MTR was 15% (12%, 18%) for the surgical group (752 patients) and 21% (CI – 16%, 27%) for the ‘non-excision’ group (188 patients). This did not reach statistical significance even after adjustment for grade ($P = 0.12$).

Effect of treatment modality

The data shows lesions treated by surgical excision have a lower MTR than those that have not. This was not statistically significant, however, and therefore, it is not possible to make strong recommendations regarding the role of surgery in this condition. However, this provides a good basis for further research, enabling sample size calculations to be performed.
Laryngeal Dysplasia, Demographics, and Treatment
A Single-Institution, 20-Year Review

Selmin Karatayli-Ozguroy, MD; Paulette Pacheco-Lopez, MD; Alexander T. Hillel, MD; Simon R. Best, MD; Justin A. Bishop, MD; Lee M. Alst, MD


OBJECTIVES To review laryngeal dysplasia cases at a single institution during the last 20 years and identify changes in patient demographics, categorize treatment approaches, and review rates of progression to cancer.

Table 1. Demographics of the Study Participants

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(n = 57)</td>
<td>(n = 50)</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>36 (63.2%)</td>
<td>20 (40.0%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (78.9%)</td>
<td>38 (76.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (21.1%)</td>
<td>12 (24.0%)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35 (61.4%)</td>
<td>41 (82.0%)</td>
</tr>
<tr>
<td>No</td>
<td>8 (14.0%)</td>
<td>6 (12.0%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>14 (24.6%)</td>
<td>3 (6.0%)</td>
</tr>
<tr>
<td>&gt; 30 Pack-years</td>
<td>13 (22.8%)</td>
<td>20 (40.0%)</td>
</tr>
</tbody>
</table>
For mild dysplasia, the difference in the study periods is statistically significant at $P = .007$; for carcinoma in situ (CIS), the difference in the study periods is statistically significant at $P = .002$. 
Overall, 8.4% of PT had a malignant transformation

**Table 3. Cancer Progression According to Severity of Dysplasia**

<table>
<thead>
<tr>
<th>Severity of Dysplasia</th>
<th>No Cancer Progression (n = 91)</th>
<th>Cancer Progression (n = 9)</th>
<th>Lost to Follow-up (n = 7)</th>
<th>Total (N = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>14 (15.4)</td>
<td>1 (11.1)</td>
<td>2 (28.6)</td>
<td>17 (15.9)</td>
</tr>
<tr>
<td>Moderate</td>
<td>10 (11.0)</td>
<td>2 (22.2)</td>
<td>1 (14.3)</td>
<td>13 (12.1)</td>
</tr>
<tr>
<td>Severe</td>
<td>23 (25.3)</td>
<td>1 (11.1)</td>
<td>1 (14.3)</td>
<td>25 (23.4)</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>44 (48.4)</td>
<td>5 (55.6)</td>
<td>3 (42.9)</td>
<td>52 (48.6)</td>
</tr>
</tbody>
</table>

**Table 4. Cancer Progression According to Treatment Modality**

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>No Cancer Progression (n = 91)</th>
<th>Cancer Progression (n = 9)</th>
<th>Lost to Follow-up (n = 7)</th>
<th>Total (N = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>10 (11.0)</td>
<td>1 (11.1)</td>
<td>0</td>
<td>11 (10.3)</td>
</tr>
<tr>
<td>Biopsy without complete excision</td>
<td>27 (29.7)</td>
<td>3 (33.3)</td>
<td>2 (28.6)</td>
<td>32 (29.9)</td>
</tr>
<tr>
<td>Complete excision</td>
<td>54 (59.3)</td>
<td>5 (55.6)</td>
<td>5 (71.4)</td>
<td>64 (59.8)</td>
</tr>
</tbody>
</table>
"Obtaining images of high quality and resolution, revealing the detailed morphology of the glottal structures, is one of the main tasks in laryngeal imaging."

**WHICH ARE THE CURRENT LARYNGEAL DIAGNOSTIC SYSTEMS?**

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

First described in 1979 by Hamou, offers additional in vivo diagnostic procedure based on the staining of the superficial mucosal layer and direct in vivo and in situ examination of the epithelial cells.

Technique: staining of the superficial cells with 1% MB before the magnification of the suspected areas through the direct contact of the tip of the endoscope.

- High magnification --- cells + blood vessels
- False negatives...
  - Due to incomplete penetration of the stain
  - Carcinoma in situ --- absence of angioneogenesis does not exclude the possibility of IC
- Reliability --- 75% to 88%
Enhanced Contact Endoscopy for the Detection of Neangiogenesis in Tumors of the Larynx and Hypopharynx

Roberto Puxeddu, MD, FRCS; Sara Sionis, MD; Clara Gerosa, MD; Filippo Carta, MD

### TABLE II.
Enhanced Contact Endoscopy Vascular Patterns.

<table>
<thead>
<tr>
<th>Vascular Pattern</th>
<th>Diagnosis</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 0</td>
<td>Normal mucosa</td>
<td>Thin-end regular subepithelial vessels connecting with a thicker and deeper arborescent vascular network running parallel to the epithelium.</td>
</tr>
<tr>
<td>Type I</td>
<td>Inflammation</td>
<td>The subepithelial vessels are increased in number and size, with irregular and sometimes crossing directions.</td>
</tr>
<tr>
<td>Type II</td>
<td>Hyperplasia</td>
<td>When the hyperplasia is at the initial stage, intra-CLs are visible running toward the surface. In this phase, CLs are generally still very thin and short, arising from the underlying inflammatory vasculature, with a scattered distribution, but in case of mature hyperplasia, the deeper inflammatory vascular network is not visible, and only the elongated CLs can be easily seen. In the case of vegetating keratosis, the deeper inflammatory vascular network is often not visible, and the elongated CLs are difficult to see. A particular type of &quot;bobby-pin&quot; can be seen in laryngeal papillomatosis, where we found the typical papilla encasing the &quot;bobby-pin&quot; inside the papilloma.</td>
</tr>
<tr>
<td>Type III</td>
<td>Mild-moderate dysplasia</td>
<td>Vascular changes become progressively more consistent, with elongated small vessels in the typical &quot;bobby-pin&quot; shape, but some arborescence appears at the end of the CLs.</td>
</tr>
<tr>
<td>Type IV</td>
<td>High-grade dysplasia/carcinoma in situ/invasive carcinoma</td>
<td>The vascularity of the chorion is more evident, and CLs appear significantly dilated, with various shapes and a wide range of vascular architectural changes such as corkscrews or tree-like patterns.</td>
</tr>
</tbody>
</table>

CLs = capillary loops.

![Image](Fig. 4. Patient 31, squamous cell carcinoma. Contact endoscopy + Storz Professional Image Enhancement System-Spectra B mode with 1% methylene blue staining (60×). Type IV alterations of the capillary loops are strongly reliable, with histologic diagnosis of carcinoma. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.] )
Auto fluorescence

- Auto fluorescence is defined as a natural fluorescence emission of tissue arising from endogenous fluorophores after exposure and activation by radiation of a suitable wavelength.
- Fluorophores are present at different concentrations in healthy and neoplastic laryngeal mucosa.

(Wagner et al., 1998). Autofluorescence diagnosis is based on the ability of oxidised flavin mononucleotide (FMN) in the normal cells to emit green fluorescence when exposed to blue light. Nicotinamide adenine dinucleotide plus hydrogen (NADH) and flavin adenine dinucleotide (FAD) are important intracellular fluorophores found in all tissue layers; their concentration is nearly 100 times lower in malignant tissue than in benign tissue (Uppal and Gupta, 2003), therefore, malignant cells do not have fluorescence to the same degree as benign cells (Baletic et al., 2004).
Stepwise protocol used for intraoperative work-up. A: during direct microlaryngoscopy, initial assessment in white light of a suspected left vocal cord SCC staged cT1a; B: the area of excision is marked with several laser spots, maintaining an apparent margin of healthy tissue of approximately 2 mm compared to the visible limits of the suspected neoplastic lesion; C: assessment of field using direct autofluorescence showing an area of surgical excision insufficient compared to that found by autofluorescence in the dark (the histological examination on the surgical specimen and biopsy on the contralateral vocal cord found an invasive SCC in both the site of the clinically visible tumour (red circle) and in the contralateral vocal cord (yellow circle)

UPSTAGING FROM GLOTTIC T1A TO T1B
Flaws on autofluorescence!!!

- Illuminating light does not penetrate through diseased epithelium
- Granulation tissue and telangiectasia produce similar reduction in bright-green fluorescence (attribute to the absorptive properties of heme molecule)
- Scar tissue, necrosis and inflammation can unpredictably alter mucosal fluorescence
Narrow band imaging (NBI)

- Optical image enhancement technology that enhances vessels in the surface mucosa using the characteristics of the light spectrum (Sano et al, 2001)

- NBI system contains a lighting unit with special filters that narrow the frequency range --- 400-430 nm (blue) and 525-555 nm (green) bands

- Since blue light wv (415 nm) is absorbed by hemoglobin the capillary blood vessels are seen brown in the summary picture

- Abnormalities of the intraepithelial papillary loop, located beneath the basement membrane of epithelium, have been found to predict the depth of superficial cancer invasion
Proposal for a descriptive guideline of vascular changes in lesions of the vocal folds by the committee on endoscopic laryngeal imaging of the European Laryngological Society

Christoph Arens¹ · Cesare Piazza² · Mario Andrea³ · Frederik G. Dikkers⁴ · Robin E. A. Tjon Pian Gi⁴ · Susanne Voigt-Zimmermann¹ · Giorgio Peretti⁵

Fig. 1 Laryngoscopic picture (WL and NBI) presenting a normal vascular pattern of vocal folds (thin, parallel running to the medial edge of vocal fold, arising from posterior and anterior blood vessels of vocal folds)
Proposal for a descriptive guideline of vascular changes in lesions of the vocal folds by the committee on endoscopic laryngeal imaging of the European Laryngological Society

Christoph Arens¹ · Cesare Piazza² · Mario Andrea³ · Frederik G. Dickers⁴ · Robin E. A. Tjon Pian Gi⁵ · Susanne Voigt-Zimmermann¹ · Giorgio Peretti⁵

Fig. 12 a-f Typical dots in carcinoma in situ (a, c, e WL and b, d, f NBI, e, f contact endoscopy)
Consensus statement by otorhinolaryngologists and pathologists on the diagnosis and management of laryngeal dysplasia

Mehanna, H.,* Paleri, V.,† Robson, A.,‡ Wight, R.§ & Helliwell, T.†

*Institute of Head and Neck Studies and Education, University Hospitals Coventry and Warwickshire, Coventry, UK, †Freeman Hospital, Newcastle upon Tyne, UK, ‡Dept of Otorhinolaryngology, North Cumbria Acute Hospitals NHS Trust, §Dept of Head Neck surgery, James Cook University Hospital Middlesbrough and †Division of Pathology, University of Liverpool

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clinicians. The aims of the workshop were to develop consensus criteria for the histopathological reporting and clinical management of patients with laryngeal dysplasia/intra-epithelial neoplasia. As a prelude to detailed
Laryngeal dysplasia: an evidence-based flowchart to guide management and follow up

B COSWAY, V PALERI

Department of Otolaryngology, Head and Neck Surgery, Freeman Hospital, Newcastle Upon Tyne, UK

Consider radiotherapy if:
1) 2 or more recurrences
2) Still smoking
3) High anaesthetic risk
4) Patient preference
5) Persistent or recurrent widespread disease (especially in smokers)
Laryngeal dysplasia follow-up post excision

Low risk
1) Mild or moderate dysplasia with no:
   i) smoking
   ii) persistent hoarseness
   iii) visible lesion

Minimum 6 month follow up. Advise to return if change in voice or other "throat" symptoms appear

High risk
1) WHO severe dysplasia or CIS
2) Mild or moderate dysplasia + one or more of:
   i) smoking
   ii) persistent hoarseness
   iii) visible lesion

Year 1: 2–3 monthly
Year 2: 3–4 monthly
Year 3: 3–4 monthly
Year 4: 6 monthly
Year 5: 6 monthly

Residual or Persistent disease (see dysplasia management flowchart)

Minimum follow-up standards:
1) Flexible nasal endoscopy
2) Colour photo documentation filed in patient notes
3) Low-risk lesions can be followed up by general ENT surgeons in peripheral clinics
<table>
<thead>
<tr>
<th>1. Epidemiological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence/natural history</td>
</tr>
<tr>
<td>Progression rate</td>
</tr>
<tr>
<td>Mortality rates/laryngectomy rates</td>
</tr>
<tr>
<td>Response to radiotherapy</td>
</tr>
<tr>
<td>Control for site/selection bias</td>
</tr>
<tr>
<td>2. Diagnostic</td>
</tr>
<tr>
<td>Reproducibility – type of biopsy</td>
</tr>
<tr>
<td>3. Pathogenesis</td>
</tr>
<tr>
<td>HPV</td>
</tr>
<tr>
<td>Cellular mechanism of recurrence</td>
</tr>
<tr>
<td>Biomarkers predicting progression</td>
</tr>
<tr>
<td>Behaviour/mechanism of progressive lesions</td>
</tr>
<tr>
<td>?Animal models/cell lines</td>
</tr>
</tbody>
</table>

4. Treatment

- Effect of radiotherapy on dysplasia (does it get more unstable)
- Are there markers of radioresistance
- Screening for second primaries in lung & oral cavity
- Standardisation of treatment
  - Non-surgical treatment
  - Chemoprevention

5. Follow-up

- Smoking cessation and its effects on natural history
- Triggers for re-biopsy

6. Outcomes

- Voice outcomes
Thank you!