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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Dear Editor,

We write on behalf of those that attended the first consensus meeting on the diagnosis and management of laryngeal dysplasia to communicate with you and your readers our conclusions.

Workshop design

A total of 80 clinicians (40 ENT surgeons and 40 pathologists) attended a national workshop, which was held under the auspices of ENT-UK and the Royal College of Pathologists. Invitation to the workshop was open to all 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 discussions by surgeons and pathologists, a plenary presentation on the use of auto-fluorescence endoscopy in the diagnosis and follow-up of dysplastic lesions was given by Professor Hiltrud Glanz (Giesen, Germany), followed by a presentation by Professor Nina Gale on the Ljubliana classification of laryngeal dysplasia (devised by Kambic and Lenart)[1] in comparison to the World Health Organisation (WHO) classification.[2] Using the Ljubliana classification, the risk of progression to invasive carcinoma was 1% for simple and basal/parabasal hyperplasia and approximately 10% for atypical hyperplasia with a mean follow-up period of 6–7 years. It was noted that vocal cord stripping was the usual treatment for all patients in Ljubliana with a diagnosis of atypical hyperplasia.

Correspondence: H. Mehanna, Institute of Head and Neck Studies and Education, University Hospitals Coventry and Warwickshire, Clifford Bridge Road, Coventry CV2 2DX, UK. Tel: +44 (0)2476 96 5244; Fax: +44 (0)2476 96 6915; e-mail: Hisham.Mehanna@uhcw.nhs.uk

Note: Some parts of the consensus statement have been published as a meeting report in the Bulletin of the Royal College of Pathologists. January 2010; **149**, 74–76.

Pathology working party

The pathology group included similar numbers of oral and laryngeal pathologists. General presentations were given on the reasons for, and principles supporting, grading dysplastic lesions and a summary of problems of classification of oral pre-malignant lesions, emphasising the value (at this site) of taking multiple biopsies in order to map the areas of most severe dysplasia. These were followed by an overview of a proposed research project to evaluate biomarkers for the progression of head and neck carcinomas and dysplasias.

Before the meeting, the attending pathologists were invited to grade 40 biopsies according to the Ljubljana low/high (2 tier) system,[1] WHO system[2] and on a visual analogue scale of 0–7, using digitised images on the web. The preliminary results of this pilot study were presented. The pathology workshop provided an opportunity to discuss a few cases in detail using projected, digitised images and for participants to debate the merits of different approaches, and to agree a consensus approach (detailed below).

Surgical working parties

The group of surgeons considered the results of a systematic review and meta-analysis of publications on the management and follow-up of laryngeal dysplasia. This showed that the available evidence was all level 3 and 4. The meta-analysis reported an overall mean transformation rate from dysplasia to invasive carcinoma of 16.7%, with severe dysplasia/carcinoma *in situ* showing a mean progression rate of approximately 30.4%.[3]

Audits on the management of dysplasia patients between 1999 and 2003 were presented by several units from around the country. The surgical group divided into working parties tasked with formulation of recommendations on investigation and initial management, follow-up strategies, management of recurrent lesions, documentation audit and research.

Consensus formulation

Each surgical workgroup and the pathology group presented their recommendations to a joint plenary session of all the groups, and each group's recommendations were debated and agreed. The draft recommendations were written up by the group facilitators, reviewed by the steering committee and circulated to all attendees of the meeting for comment before the statement was finalised.

Investigation and management of laryngeal leukoplakic lesions at initial presentation

The following is the consensus on the management of laryngeal leukoplakic lesions on first presentation. These lesions have not been previously investigated or treated. It should be noted that in most cases diagnosis and treatment of the leukoplakic lesion will be undertaken as one procedure, that is, resection of the lesion will provide histological diagnosis and will also constitute the initial management of the lesion.

1. Expertise

a. Surgeons managing laryngeal dysplasia and leukoplakia should have had appropriate training in laryngology.
b. We recommend that laryngeal dysplasia should be preferably managed by a member of the head and neck cancer multidisciplinary team and not by a generalist ENT surgeon. There should be a nominated or a defined number of surgeons providing laryngeal dysplasia management within a designated Head and Neck service.

2. Decision making

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

a. Single and multiple foci 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 re-biopsy in the presence of widespread disease.
c. Other factors may be important in deciding management include the patient's general condition and fitness for surgery, physiological age, co-morbidity and the presence of other risk factors.
d. A discussion with the patient should be undertaken to inform them of the potential risks hoarseness and change in voice quality postoperatively, and of the possibility of recurrence.

3. Modality of surgical treatment

a. Cold steel or CO_2 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 photo-documentation prior to histologic processing.

4. Risk factor reduction

a. All patients should be counselled regarding measures to reduce risk factors, especially smoking.
b. Symptomatic patients with laryngopharyngeal reflux should also be counselled about the potential risks, and should be offered treatment.

Pathological diagnosis

The group included pathologists with a range of current practices for the description and grading of squamous intraepithelial lesions of the larynx. There was broad agreement on many issues discussed and that there was currently insufficient evidence to prefer one grading system over another.

1. Natural history

a. There was rarely any demonstrable strict linearity of progression from mild dysplasia, through moderate and severe dysplasia to carcinoma *in situ* and invasive carcinoma.
b. It was accepted that many genetic changes in the epithelium did not result in morphological abnormalities and that, therefore, prediction of the risk of progression using any system was inherently difficult, particularly when using excised epithelium in an attempt to predict the behaviour of residual epithelium.

2. Handling of histological specimens

a. The principles of laboratory handling of laryngeal biopsies were agreed, including the need to consider at least three haematoxylin and eosin stained sections at levels through a block of tissue and to exclude fungal infection when neutrophils were present.
b. It was noted that laryngeal biopsies varied in size and that surgeons should try to take larger biopsies when possible to make orientation and evaluation more reliable, particularly if there were previous difficulties in interpretation of the pathology.

3. Grading systems of dysplasia

a. It was agreed that hyperplastic changes in the laryngeal epithelium, i.e. those lesions that lack nuclear atypia, should not be graded as dysplasia.
b. Most pathologists at the meeting used the WHO grading system to grade dysplasia and it was agreed that it was often appropriate to follow the WHO guidance that severe nuclear atypia should increase the grade of dysplasia.
c. The Ljubliana classification was also acceptable as a grading system for those trained in its use. As there is not a simple translation between WHO and Ljubliana grades, there was agreement that further training would be required before pathologists could implement alternative systems and were able to justify its recommendation to surgeons.
d. There was general agreement to be prepared to discuss developments of grading systems in the future.

4. Interpretation of the histopathology report

a. It is important that the pathology grading of dysplasias is not used in isolation to guide treatment.
b. All cases of severe dysplasia/atypical hyperplasia and carcinoma *in situ* should be discussed in a multidisciplinary setting and clinical data on the extent of the abnormalities and the potential for lifestyle modification would be important considerations in determining treatment and follow-up of the patients.
c. For the purposes of management, severe dysplasia and carcinoma *in situ* should be regarded as synonymous. It was acknowledged that *in situ* carcinoma showed more aberrant cytological features and presumably greater genetic damage than severe dysplasia and hence was likely to have a greater potential for progression to invasive carcinoma.
d. A pragmatic approach suggested that a threshold risk of progression from dysplasia to invasive carcinoma of between 10% and 20% was likely to be a trigger for treatment (following multidisciplinary discussion). Diagnoses of atypical hyperplasia, severe dysplasia or carcinoma in situ would provide this degree of risk and would therefore be proposed as triggers for intervention, acknowledging that the different grading systems did not provide directly comparable predictors of risk and that a very small number of patients might be classified inadequately using this approach.
e. The presence of dysplasia at surgical margins is not considered to be an indication for further excision or biopsy. Lesions that subsequently recur or change in appearance warrant further investigation.

Follow-up strategies

This section deals with routine follow-up protocols. The group considered certain principles, e.g. resource implications, reducing the 'did not attend' rate and the importance of patient involvement in decision making. The group's remit was not to consider extra implications of audit or research.

1. Risk classification for follow-up

For the purpose of follow-up, laryngeal squamous intraepithelial lesions are classified in two clinico-pathological groups:
1. High risk lesions – patients who have:
a. WHO classification severe dysplasia or carcinoma in situ (Ljubliana 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.

2. Low risk lesions – patients who have mild or moderate dysplasia with no visible lesion or hoarseness, or who are not smoking.

2. Follow-up standards

All patients should be followed up with the following standard protocols:

a. Use of a flexible nasendoscope to view the larynx (new technology end digital camera scopes is an aspirational aim).
b. Colour photo-documentation must be done and retained in the notes.
c. Stroboscopy is helpful if available, but is not essential.
d. Place of follow-up and personnel involved.
i. Low risk lesions can be followed up by general ENT surgeons in peripheral clinics.
ii. Other lesions should be followed up by a designated ENT surgeon with a special interest in Head and Neck surgery and/or laryngology.

3. Duration of follow-up:

a. 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.
b. Low risk patients 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 recommended early discharge from clinic, with open or early return should patients develop anxiety, recurrence of their hoarseness, or 'throat symptoms'.

4. Outcomes

a. Outcomes of treatment include recurrence and progression to cancer. Patients who progress to cancer should be highlighted on DAHNO (National comparative Head and Neck Audit in England and Wales).
b. Voice outcomes should also be assessed using a patient-reported voice questionnaire.
c. Timing: assessment should be at baseline, 6 and 12 months.

Management of persistent or recurrent squamous intra-epithelial lesions

All patients must be actively encouraged to stop smoking. Further treatment of persistent or recurrent lesions should be by excisional biopsy, where practical, as previously described under the initial management section.

Further management depends on histology, as follows:

1. Recurrent, focal mild or moderate dysplasia: should be excised if possible.
2. Recurrent, widespread mild or moderate dysplasia: may be observed or excised. Excision should especially be undertaken, if there is a change in:
a. appearance (heterogenous texture; erythroplakia; proliferative features), or
b. symptoms.

Patient factors and the effect of further resections on their voice should also be taken into consideration.

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:
a. patients who have had two or more recurrences,
b. patients who continue to smoke,
c. patients who have a high risk of anaesthetic complications,
d. patients who have access problems for surgery,
e. 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.

Documentation

The following documentation should be undertaken for all white lesions or suspicious lesions of the vocal cords.

1. Pre-treatment

The following should be documented in the notes and/or in clinical correspondence:

a. Demographics and history:
i. NHS number (for linkage of records).
ii. Age and gender.
iii. Duration of dysphonia and other symptoms.
iv. Voice usage and impact of dysphonia on employment/daily living.
v. Co-morbidity and any immuno-suppressive therapy.

vi. Smoking status.
- Never smoked, previous smoker, current smoker.
- Number of cigarettes per day and duration in years).

vii. Inhaled substance abuse.
viii. Alcohol – units/week and current status.
ix. Reflux-record e.g. by Reflux Symptom Index, and whether reflux treated or not.
b. Examination/findings:
i. Document and describe lesions of the vocal cords, with a specific comment on vocal cord mobility.
ii. Palpate the neck and document clinical nodal status and distribution.
iii. Voice quality by GRBAS method, although this may be difficult to implement due to need for training.
iv. Flexible endoscopic image printed in notes.
c. Clinicians should strive to achieve the following, but they are not mandatory:
i. Pre-treatment speech and language assessment.
ii. Assessment by a voice outcome measure such as VOiSS or VHI.
iii. Stroboscopy.

2. In theatre

a. Photograph before biopsy or surgery.
b. Examination findings from:
- Rigid endoscopy (0°/30°/70°).
- A panendoscopy.
- Palpation of the vocal cord.

c. Post-procedure on-table photograph, attached to notes with a copy attached to pathology request form if possible.
d. Details of type of biopsy – state whether incisional or excisional.

If excision has been performed – details should be documented of the technique and extent of resection, and the categorisation of the procedure according to the European Laryngological Society classification.

It should be noted that a documentation classification may need to be devised as, under the European Laryngological Society classification, most resections would be Type 1.

3. Follow-up

The following should be documented in the notes and/or in clinical correspondence:
a. Comment on symptomatic voice change.
b. Smoking status post-procedure and at review and smoking cessation interventions undertaken.
c. Photograph at 6 weeks post-procedure with a copy filed in the notes.
d. Future management plan to be clearly documented in notes, e.g. if not smoking follow for 1year, then if normal discharge.
e. The pathology report should be filed in notes. The group identified the need for agreement on a consensus content and format for the pathology report.

Audit

The following were considered areas that should be audited (priority areas have been highlighted by *):
- *Dysplasia – incidence/prevalence.
- Impact and compliance with smoking cessation programmes, including:
  - o Whether they have been offered.
  - o Who provided them.
  - o The rate of uptake.
- *Documentation – the rate of compliance and quality of documentation.
- There is a need to define standards of care so that they can be audited.
- *Voice quality.
- *Transformation rates at 1 year, and 5 and 10 year rates by matching via NHS number cancer registrations. Definitions to include:
  - o Residual disease – defined as disease apparent in the same area of treatment within 6 months.
  - o Recurrence is defined as disease in the same site appearing after 6 months from treatment.
- *Disease free rates defined as 'normal larynx' except for scar.
- Impact of different management strategies – e.g. auditing outcomes of a biopsy with watch and wait *versus* excision.

Research

1. General principles

a. There was consensus that this is an important area for research due to the significant lack of evidence base and its importance as a pre-malignant, potentially preventable condition. Most research on the topic is level 4 evidence in the form of retrospective case series.
b. It was acknowledged that consensus on terminology and diagnostic criteria should be developed to provide a common basis and starting point for research.
c. It was recommended that consensus criteria for the design and reporting of studies on laryngeal dysplasia should be developed and agreed. This should include a consensus on a minimum dataset, which should

encompass age, gender, smoking status, number and date of biopsies, clarification of excisional *versus* incisional biopsies, grade of dysplasia, type of treatment and longitudinal follow-up.

d. Progression to cancer and recurrence should be the main outcome measures.

2. Discussion forum for pathology

An on-line discussion forum would be hosted by the University of Liverpool to promote further debate and would provide access to the images and assessment criteria to allow further training, as well as providing an easy way to distribute the post-meeting analysis of the scoring of digitised images. [Contact trh@liv.ac.uk for access to the discussion forum].

3. Future research strategies

It was agreed that whilst prospective research is the ideal (See Table 1), there was also a role for retrospective studies of pooled cases and samples.

Table 1. Potential priority areas of research identified by the group

1. Epidemiological
Incidence/natural history
Progression rate
Mortality rates/laryngectomy rates
Response to radiotherapy
Control for site/selection bias
2. Diagnostic
Reproducibility – type of biopsy
3. Pathogenesis
HPV
Cellular mechanism of recurrence
Biomarkers predicting progression
Behaviour/mechanism of progressive lesions
?Animal models/cell lines
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

The following research strategy was recommended:

a. Pooling of retrospective cohorts and cases. Samples from cases with their anonymised minimum dataset would be pooled in a central repository/tissue bank to allow the study and analysis of large sample sizes and the generation of more meaningful results. This design would be especially applicable for studies examining epidemiology, diagnostic criteria and prognostic biomarker studies. The role of Human Papilloma virus (HPV) should also be explored. A project is currently in progress in this field.

b. Setting up of a prospective registration study of a cohort of patients for follow-up to examine the natural history, effects of various treatment modalities and follow-up strategies, examination of the effects of diagnosis with a premalignant condition on psychology and quality of life, and validation of biomarkers identified on retrospective studies. This could be coupled with a national audit on laryngeal dysplasia.

Members of the First Consensus Meeting on the Diagnosis and Management of Laryngeal Dysplasia are:

Pathologists:

Dr Samita Agarwal, Dr Richard Allibone, Dr Bernice Almeida, Dr Muhammed Baber Aslam, Dr Bill Barrett, Dr Timothy Bates, Dr Robert Blahut, Dr Claribel Cardozo, Dr Brendan Conn, Dr David Gouldesbrough, Mr David Grant, Dr David Green, Dr Gillian Hall, Dr Rachel Hall, Dr Tim Helliwell, Dr Laszlo Karsai, Dr Shakir Kendeel, Dr Besim Latifaj, Professor Leslie Michaels, Professor Peter Morgan, Dr Seamus Napier, Professor Edward Odell, Dr Tim Palmer, Dr Malcolm Reed, Dr Ivan Robinson, Dr Simon Rose, Dr Ketan Shah, Dr Jonathan Sheard, Dr Edward Sheffield, Dr Roger Start, Dr Jason Stone, Dr Krishna Suchak, Dr Susanna Szakacs, Professor Nalin Thakker, Dr Jacqueline Van Der Wal, Dr Joanne Wilkinson, Dr Hazel Williams, Dr Julian Woolgar, Dr Andrew Zarod.

Otorhinolaryngologists:

Professor Patrick Bradley, Mr Mike Bridger, Mr Hugh Cable, Mr Peter Clarke, Miss Helen Cocks, Mr Declan Costello, Ms Anne Davis, Stijn Fleskens, Mr Adam Frosh, Mr Nicholas Gibbins, Dr David Gouldesbrough, Mr David Grant, Mr Huw Griffiths, Mr Churunal Hari, Mr Meredydd Harries, Mr Andreas Hilger, Mr Owain Hughes, Mr Andrew Husband, Mr Philip Jones, Mr Wale Larinde.

Dr Wayne Kinsey, Dr Besim Latifaj, Mr Kenneth Mackenzie, Mr Tass Malik, Mr Conor Marnane, Mr Hisham Mehanna, Mr Jim Moor, Miss Julie Morris, Mr Sean Mortimore, Mr Andreas Nicolaides, Mr Vinidh Paleri, Mr

Chris Randall, Mr Stuart Robertson, Mr Andrew Robson, Mr Ricard Simo, Mr Murray Stuart.

Ms Alica Torres, Mr Hugh Wheatley, Mr Richard Wight, Mr Peter Williamson.

Further reading:

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Conflicts of interest

None declared.

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