


Laryngeal dysplasia: a 10-year review of rates of progression to invasive carcinoma and treatment-specific outcomes in a regional ENT department in Northern Ireland

G Donaldson¹ , L McCadden¹, S Napier² and T J Tan³

Departments of ¹Otolaryngology and Head & Neck Surgery, and, ²Pathology, Royal Victoria Hospital, Belfast, Northern Ireland and ³Institute of Cardiovascular Science, University College London, UK

Main Article

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Author for correspondence:

Dr Gavin Donaldson, Department of Otolaryngology and Head & Neck Surgery, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA, Northern Ireland, UK
E-mail: gdonaldson06@qub.ac.uk

Abstract

Background. Laryngeal dysplasia represents a complex pre-malignant condition characterised by a spectrum of mucosal changes, with a reported malignant transformation rate from dysplasia to invasive carcinoma of 14.0 per cent.

Objective. To identify whether increasing glottic dysplasia severity is associated with higher local malignant transformation rates or adverse clinical outcomes.

Methods. This retrospective cohort study identified 125 patients with any histopathological grade of glottic dysplasia over a 10-year period who were followed up for a standardised 10-year period.

Results. The malignant transformation rate was 21.8 per cent over 10 years, demonstrating a statistically significant greater risk with increasing dysplasia severity. The mean time to transformation was 52 months, with time to transformation statistically associated with increasing dysplasia severity. Rapid progression to carcinoma within 12 months occurred in 40 per cent of cases, and 58 per cent of subsequently diagnosed laryngeal squamous cell carcinomas were tumour stage T₁.

Conclusion. Laryngeal dysplasia carries a significant malignant potential, appearing greatest within 12 months of diagnosis and with increasing severity of dysplasia.

Introduction

Laryngeal dysplasia represents part of a spectrum of mucosal changes, characterised by a variable clinical course and a propensity for squamous cell carcinoma (SCC) development. Efforts have been directed towards correlating histopathological grade to clinical outcomes, particularly conversion to malignancy. A meta-analysis of 940 patients in 2010 reported an overall mean transformation rate from dysplasia to invasive carcinoma of 14.0 per cent.¹ The histopathological grade of dysplasia clearly correlates with malignant transformation rates, with the risk increasing three-fold between mild or moderate (10.6 per cent) and severe or carcinoma in situ (CIS) (30.4 per cent) cases.¹ The mean time to transformation is approximately 5.8 years, but there is considerable worldwide variation.^{1–5}

Although laryngeal dysplasia represents a series of mutational changes occurring within the overlying stratified squamous epithelium in the larynx,⁴ there is a paucity of evidence to demonstrate that sequential epithelial changes occur in a linear fashion.⁵ The progression to laryngeal carcinoma has been shown to relate directly to cigarette smoking, alcohol abuse and exposure to other extrinsic irritants that trigger pathways of genetic events. Cigarette smoking and heavy alcohol consumption are both independent and synergistic risk factors for laryngeal cancer.⁶ Despite the conclusive evidence demonstrating the role of human papilloma virus (HPV) in the aetiopathogenesis of oropharyngeal cancer, the significance of this infection in laryngeal cancer needs further evaluation,^{7,8} with studies suggesting that the prevalence of high-risk HPV genotypes in laryngeal SCC shows considerable variation, ranging from 5 to 60 per cent.^{9–11}

In 2017, the World Health Organization (WHO) updated the classification system of laryngeal dysplasia into a two-tier system, low and high grade, in view of reported inter- and intra-observer variability and lack of standardisation.^{12–14} A study by Sannino *et al.* demonstrated that rates of progression to carcinoma for mild and moderate grades of laryngeal dysplasia were 7.7 per cent and 19.8 per cent, respectively.¹⁵ This raised concerns that the treatment and need for follow up of the newly termed 'low-grade lesions' would be crudely underestimated.

The survival rate for non-metastasised laryngeal carcinoma is 90 per cent, reducing to approximately 63 per cent in cases with dissemination to regional lymph nodes, with minimal improvement in these figures over time despite the introduction of novel treatment options.¹⁶ A consensus statement by UK ENT surgeons in 2010 outlined the management of the first presentation of laryngeal dysplasia. Cold steel or carbon dioxide (CO₂) laser is

recommended in the first instance, with radiotherapy reserved for small numbers in rare circumstances such as poor access for resection in a high-grade lesion.¹⁷

Given that dysplasia is regarded as a precursor to invasive malignancy, early recognition and characterisation of these lesions could represent a potentially curative stage of the disease. With this in mind, a treatment dilemma exists: oncological safety needs to be balanced with functional outcomes.¹⁸

Aim and hypothesis

This study aimed to identify whether patients with a histopathological diagnosis of high-grade laryngeal dysplasia have a higher rate of progression to carcinoma compared to patients with low-grade dysplasia during a follow-up period of 10 years at a single tertiary ENT department.

Materials and methods

A retrospective cohort review was conducted of all patients with a histopathological diagnosis of any grade of dysplasia (mild, moderate, severe and CIS), according to the WHO 2005 classification system, affecting the glottis area of the larynx, over a 10-year period from 1 January 2000 to 31 December 2009.

The histopathology database was trawled for the key words of dysplasia affecting the ‘vocal cords’ or ‘larynx’. Data were retrieved by a computer-assisted search of the Systematized Nomenclature of Medicine classification codes for the specific sites of the vocal folds, larynx and laryngeal commissures (classification codes: T24100, T24400, T24410, T24420 and T24471). We identified all grades of laryngeal dysplasia, including those specimens coded as ‘not otherwise specified’, affecting this anatomical region (classification codes: M74000, M74001, M74002, M74003, M74410, M74412 and M80102).

Outcome measures

Patient records were reviewed, and the following data were collected using a pre-defined proforma with Microsoft Excel® spreadsheet software: patient demographics, including age, gender and smoking status at time of diagnosis (smoker, ex-smoker, never smoked, unknown); histopathological findings of laryngeal biopsy, anatomical site and the specific grade of dysplasia; time to diagnosis of SCC from dysplasia during a 10-year follow-up period; and treatment modality for dysplasia (CO₂ laser, cold steel excision, radiotherapy, ‘watch and wait’ or other). We also recorded the tumour (T) stage, prior and follow-up biopsy results, 10-year all-cause mortality rates, and requirement for total laryngectomy.

In order to ensure the validity of the results, the primary author reviewed each pathology report on the LabCentre laboratory information management system to confirm accurate coding and consistency of data collection. For cases with multiple grades of dysplasia, the most severe grade was included for analysis. We have categorised severe dysplasia and CIS together as ‘severe’ dysplasia in an attempt to standardise our results with other major studies, including the UK laryngeal dysplasia consensus statement. We have not included hyperplasia or hyperkeratosis cases. Mortality rates are described as either related or unrelated to the underlying laryngeal pathology.

Exclusion criteria

The exclusion criteria were: the presence of simultaneous pharyngeal or laryngeal carcinoma not confined to the glottis; prior laryngeal carcinoma or previous head and neck radiotherapy before the time of the initial biopsy; inappropriately or wrongfully coded sites; and patients with a subsequent diagnosis of SCC within three months, with the rationale that a tissue sampling error may have prevented the identification of invasive carcinoma.

Ethical considerations

This study constituted a retrospective review of local practice; therefore, formal ethical committee approval was not required. This study was registered with the local standards quality and audit department.

Statistical analysis

Data were entered into IBM SPSS® Statistics software, version 26, where all statistical analyses were performed. A Shapiro–Wilk test was conducted to assess normality, in order to determine whether a parametric or non-parametric test should be conducted. Pearson chi-square tests were conducted on parametric categorical variables, and a Fisher’s exact test was used for non-parametric categorical variables. Results with a *p*-value lower than 0.05 were considered statistically significant.

A logistic regression analysis was used to ascertain the effect of dysplasia severity on the likelihood of malignant transformation. A Kaplan–Meier curve was constructed, and a log rank test was performed to determine whether there were differences in the mean length of time to malignant transformation (in months) for different grades of dysplasia.

Results

Data for a total of 317 biopsies from 177 patients were included. Fifty-two patients had a histopathological diagnosis of SCC based on their primary biopsy, leaving 125 patients with any severity of dysplasia (Figure 1). Of the 125 patients with laryngeal dysplasia, the mean average age was 62.8 years (median of 62 years, interquartile range = 56–73 years). The male to female ratio was 2.7:1, including 91 male and 34 female patients.

Table 1 outlines the patient demographics of this cohort analysed according to gender. Despite a larger number of male patients within this sample, there was no difference between the mean and median ages of the two groups. The graphical representation of age appears normally distributed with few major outliers.

Following the exclusion of 6 patients who underwent ‘rapid progression’ to carcinoma within three months, our analysis examined the remaining 119 patients. Two cases are described as dysplasia ‘not otherwise specified’, as the severity was not specified in the pathology report. The severity of dysplasia is displayed in Figure 2.

The overall malignant transformation rate from dysplasia to invasive SCC was 21.8 per cent. This represented 26 of all 119 dysplasia cases. When analysing the effect of histological grade, the malignant transformation rate over 10 years was found to be 10.8 per cent for mild dysplasia, 24.0 per cent for moderate dysplasia and 34.6 per cent for severe dysplasia.

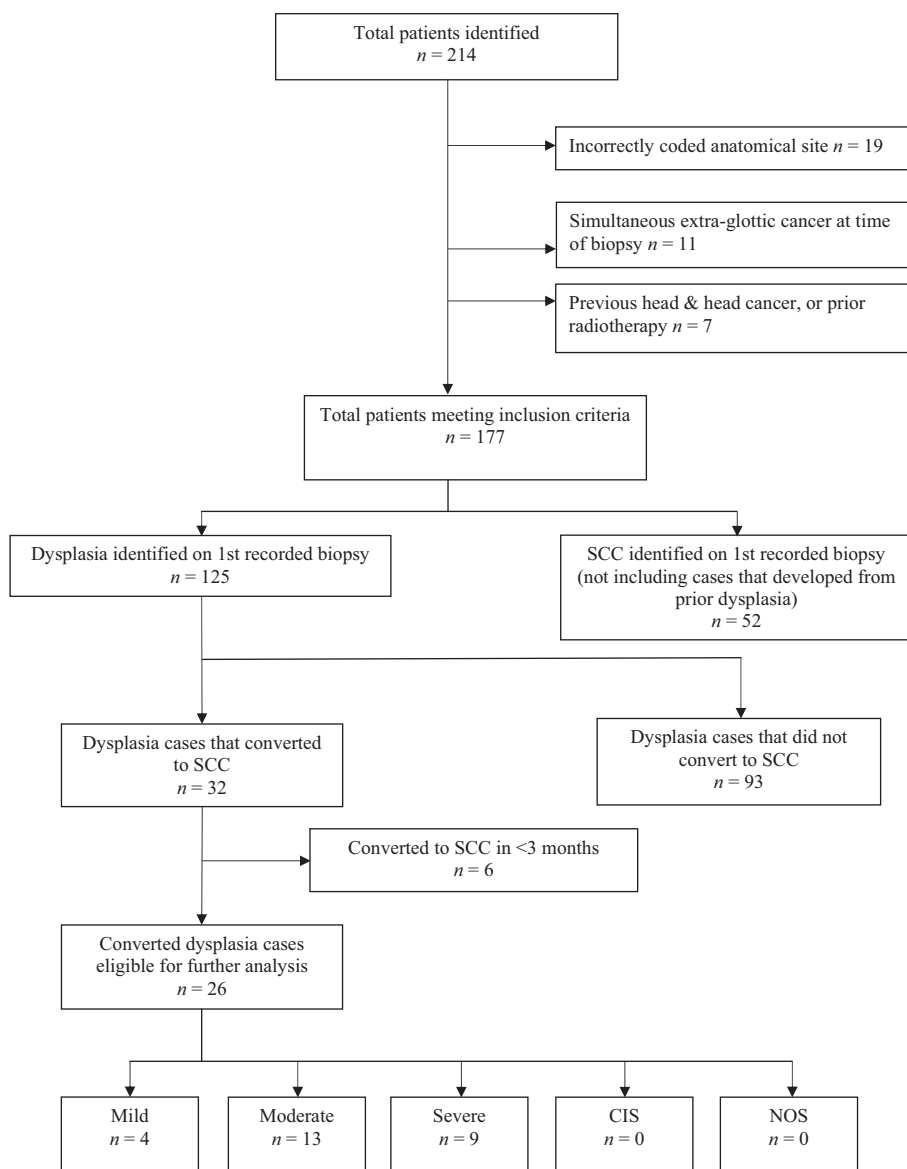


Fig. 1. Flowchart demonstrating the selection of eligible patients for analysis. SCC = squamous cell carcinoma; CIS = carcinoma in situ; NOS = not otherwise specified

Table 1. Demographics of patients diagnosed with dysplasia on index biopsy according to gender

Parameter	Female	Male	Total
Gender (n)	34	91	125
Age group (n)			
- <40 years	0	2	2
- 40–49 years	2	8	10
- 50–59 years	11	21	32
- 60–69 years	12	29	41
- 70–79 years	8	25	33
- 80–89 years	1	6	7
Mean age (years)	63.6	63.3	62.8
Median age (years)	62.0	62.0	62.0
Age range (years)	41–84	29–89	29–89
Age IQR (years)	57–73	56–73	56–73

IQR = interquartile range

The mean time to transformation was 52 months, with the time to conversion reducing with increasing dysplasia severity, as shown in Table 2.

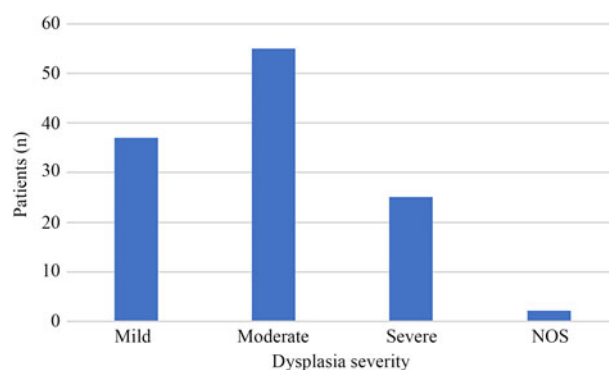


Fig. 2. Distribution of dysplasia cases of differing severity. NOS = not otherwise specified

Both patients in whom dysplasia was classified as ‘not otherwise specified’ had conversion to malignancy within three months. Consequently, this severity of dysplasia was not analysed any further in respect to malignant transformation cases. Of the 32 patients in whom malignant transformation occurred at any stage, 13 patients (40.1 per cent) had transformation within 12 months and 23 patients (71.9 per cent) within 60 months. Excluding those who had rapid

Table 2. Distribution of all dysplasia cases undergoing malignant transformation

Dysplasia grade	Female (n)	Male (n)	Total (n)	Gender difference p-value	Malignancy conversion rate (%)	Mean time to malignant transformation (months)
Mild	1	3	4	1.000	10.8	101
Moderate	2	11	13	0.710	24.0	52
Severe	3	6	9	0.667	34.6	28
Overall	6	20	26	-	21.8	52

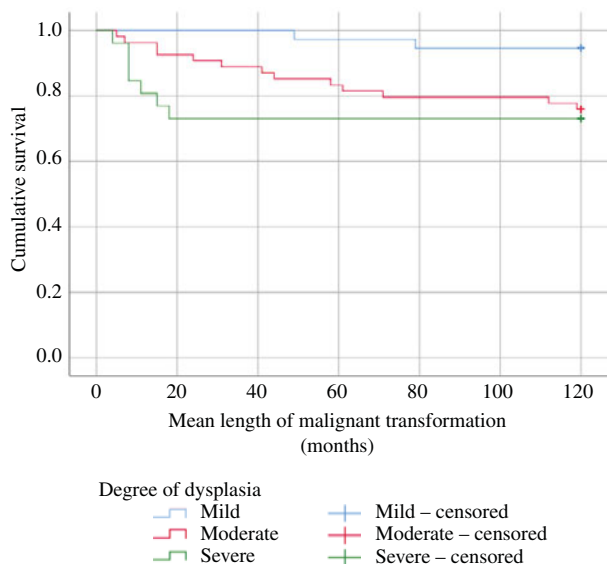


Fig. 3. Kaplan–Meier survival curve demonstrating time to malignant transformation of mild, moderate and severe dysplasia cases.

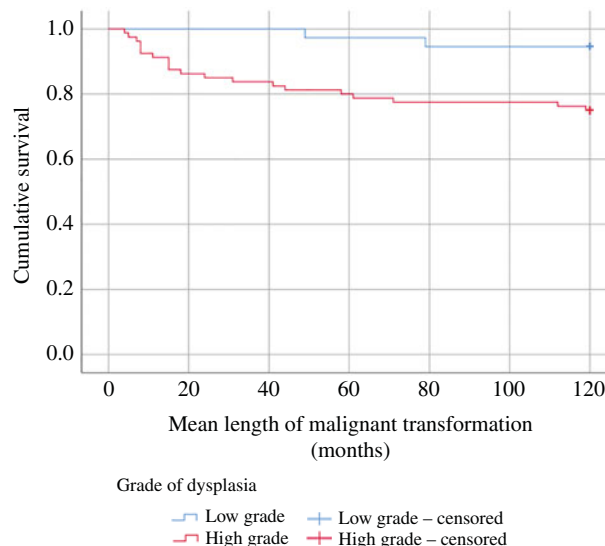


Fig. 4. Kaplan–Meier survival curve demonstrating time to malignant transformation of low- and high-grade dysplasia cases.

progression to carcinoma, occurring within 12 months, 19 of the remaining 112 patients with initial dysplasia (16.9 per cent) had conversion to invasive malignancy within 10 years.

In this study, mild, moderate and severe dysplasia appeared to behave as three separate entities with respect to malignant transformation rate. Particularly, we identified that moderate dysplasia had a considerable malignant transformation rate, closer to severe than mild. When the moderate and severe dysplasia groups were combined into a ‘high-grade dysplasia’ group, conversion to malignancy represented 85 per cent (22 out of 26) of all malignant transformations. The remaining four ‘low-grade lesions’ represent all those specimens reported as mild dysplasia. The malignant transformation rate for high-grade lesions was found to be 27.5 per cent over 10 years, compared with 10.8 per cent for low-grade lesions. The Pearson chi-square test revealed a significant difference ($p = 0.043$) in the rate of malignant transformation when low and high grades of dysplasia were classified in this way.

When the time to malignant transformation was plotted on a Kaplan–Meier survival curve, a log rank test demonstrated that the mean length of time (in months) was statistically different when comparing mild, moderate and severe dysplasia ($p = 0.037$) (Figure 3), as well as high- versus low-grade dysplasia ($p = 0.012$) (Figure 4). Additionally, there was a statistically significant difference between the mean length of time to malignant transformation for the three grades of dysplasia, mild, moderate and severe, as determined by one-way analysis of variance (64 ± 21.2 months, 46.4 ± 37.1 months and $10.3 \pm$

4.8 months, respectively; p -value = 0.031). A Tukey post-hoc test revealed that the time to malignant transformation was statistically significantly lower in patients with severe dysplasia (10.3 ± 4.8 months; $p = 0.048$) compared with patients with moderate dysplasia (46.4 ± 37.1 months).

The 10-year all-cause mortality rate was higher for the malignant transformation group compared with the non-transformation group (46 per cent vs 15 per cent). Salvage total laryngectomy was performed in 30 per cent of malignant transformation cases. Important clinical outcome measures, including mortality rates and salvage laryngectomy rates, are described in Table 3.

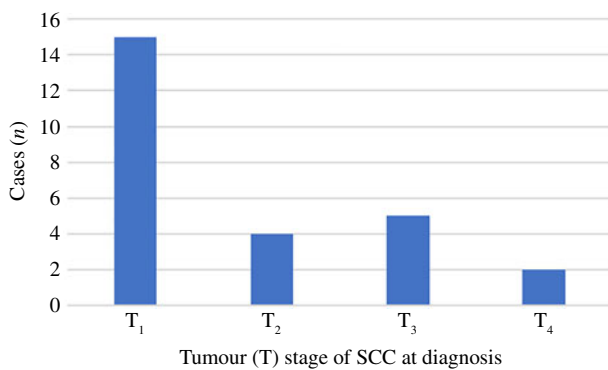
Data on the T stage of the subsequent developing cancer are shown in Figure 5, demonstrating that 58 per cent of subsequently diagnosed cancers were stage 1. The timescale of malignant transformation was highly variable for each stage, with no discernible relationship. The mean time to diagnosis of SCC for each T stage, T₁ to T₄, was 43 months, 29 months, 102 months and 33 months, respectively.

The details of the treatment modality are displayed in Table 4. Radiotherapy was utilised in two cases: one because of difficult access to the anterior commissure with laser and the other as the outcome of multidisciplinary team discussion.

In an attempt to aid our understanding of risk factors for progression to invasive carcinoma, we noted the treatment modality used in each grade of dysplasia that subsequently converted. These data are displayed in Table 5. The Fisher’s exact test indicated no significant difference between the treatment type and the chance of malignant transformation ($p = 0.171$).

Table 3. Demographics and secondary outcome measures for all malignant transformation cases

Dysplasia grade	Lesions undergoing malignant transformation (n)	Mean age (years)	Positive smoking history (active & ex-smokers) (%)	10-year all-cause mortality (n (%))	Requirement for salvage total laryngectomy (n (%))
Mild	4	67.1	100	2/4 (50)	3/4 (75)
Moderate	13	69.1	85	7/13 (54)	3/13 (23)
Severe	9	68.7	89	3/9 (31)	2/9 (22)
Overall	26	67.7	88	12/26 (46)	8/26 (30)

**Fig. 5.** Squamous cell carcinoma (SCC) stage at time of diagnosis in patients with prior dysplasia of any severity.

Discussion

This regional retrospective cohort study is one of the largest studies of laryngeal dysplasia in the UK, including 119 patients with a histopathological diagnosis of dysplasia affecting the glottis. An important observation identified during data collection was the high rate of synchronous head and neck cancers. Eleven patients were diagnosed with a synchronous tumour, and seven had evidence of a previous head and neck cancer or local radiotherapy. This should highlight the spectrum of mucosal changes that can occur along the entire upper aerodigestive tract.

Our results agree with other major studies and cancer incidence data indicating that laryngeal cancer predominantly affects male patients.^{19,20} There is a widely reported malignant transformation rate of laryngeal dysplasia ranging between 2 and 74 per cent. Our results show an overall malignant transformation rate of 21.8 per cent, and demonstrated a higher risk and shorter mean time to transformation with increasing dysplasia severity. This would seem to disagree with the finding of a meta-analysis by Weller *et al.* in 2010, which concluded that the transformation time was not dependent on the grade of dysplasia.¹ When considering each grade of dysplasia, our results showed that mild dysplasia was associated with a low rate of progression to carcinoma of 10.8 per cent, very similar to the value of 10.6 per cent reported by Weller *et al.*¹ The same meta-analysis combined moderate and severe lesions, producing a transformation rate of 30.4 per cent, similar to 27.5 per cent as shown in this study. A similarly sized study in Paisley, Scotland showed a transformation rate of 16 per cent, with a mean time to diagnosis of 43 months.³ A further study based in Newcastle with 113 patients demonstrated a transformation rate of 24 per cent, with 75 per cent occurring within 12 months.²¹ A very recent publication from Denmark showed a transformation rate of 18.3 per cent among 965 patients with laryngeal dysplasia.

When considering all 125 cases of dysplasia, 40 per cent of patients proceeded to have invasive carcinoma diagnosed on

subsequent biopsies within 12 months and 72 per cent within 60 months. This high number of patients within a 'rapid progression to carcinoma' group may represent those with very unstable mucosal changes at high risk of subsequent invasion, or is perhaps a consequence of tissue sampling errors. Our study design excluded those patients in whom SCC was diagnosed within three months of their primary biopsy. The rationale for this was two-fold: firstly, this was a standard adopted by many of the other major studies in this area and thus would allow comparison of results; and secondly, the diagnosis of dysplasia could represent a tissue sampling error. Consequently, clinicians should carefully follow up all patients with dysplasia, particularly within the first year, with a low threshold for repeating biopsy or instigating appropriate treatment.

An interesting finding within the biopsy samples of all 76 cases of SCC is that co-existing epithelial dysplasia was reported for at least 74 per cent of samples, with the reports for the remaining samples not explicitly recording this. This is not insignificant, considering that a tissue sampling error could have resulted in a biopsy that missed the invasive cancer and only captured an area of dysplasia. A large meta-analysis also concluded that laryngoscopy is inadequate for the detection of dysplastic and malignant lesions, in that only 47.1 per cent of clinical leukoplakia revealed dysplasia.²² These findings reaffirm the concerns of reliance on histopathological reports.

All grades of dysplasia – mild, moderate and severe – appeared to behave as separate entities, with increasing rates of progression to carcinoma noted as dysplasia severity increased. Moderate dysplasia was the most commonly identified degree of dysplasia, representing 46 per cent of all biopsies. This finding may reflect our arbitrary application of a distinct classification system to a spectrum of mucosal changes, meaning that most biopsies will contain changes that lie somewhere in the middle. There has been much debate about the malignant potential of moderate dysplasia. Our results would tend to agree with Luers *et al.*,²³ who concluded in 2014 that moderate dysplasia confers a significant conversion risk. In our study, 24.0 per cent of moderate dysplasia cases progressed to invasive cancer, which clearly represents a significant risk.

When moderate and severe dysplasia groups were combined into a 'high-risk' group, this constituted 85 per cent of all patients who subsequently developed SCC. Combining these two groups would certainly identify the majority of lesions at higher risk of SCC on future biopsies. If this more heterogeneous group were recognised, it might harmonise these high-risk lesions, so as to minimise the worry of over-treating and to negate the concern of inter-observer variability in reporting. Combining the classification system of dysplasia from four tiers to two, and in certain circumstances three, was the recommendation of the WHO in 2017.²⁴ Our results would appear to support that decision. Our findings would also support the use of more aggressive treatment of patients

Table 4. Treatment modality utilised following initial histopathological dysplasia diagnosis

Dysplasia grade	Total patients (n)	Treatment modality (n)				
		Laser	Cold steel excision	Radiotherapy	'Watch & wait'	NOS
Mild	37	14	8	0	15	0
Moderate	54	30	9	1	13	1
Severe	26	15	2	1	6	2
NOS	2	0	0	0	0	2
Total	119	59	19	2	34	5

NOS = not otherwise specified

Table 5. Treatment modality used in dysplasia cases that subsequently developed into invasive cancer

Dysplasia grade	Total patients (n)	Treatment modality (n)			
		Laser	Cold steel excision	Radiotherapy	'Watch & wait' or conservative management
Mild	4	4	0	0	0
Moderate	13	10	2	1	0
Severe	9	5	0	0	4
Total	26	19	2	1	4

with severe dysplasia, as 34.6 per cent had subsequent evidence of invasive carcinoma within a mean time frame of 28 months.

Our results showed a statistical difference in the mean time to malignant transformation for both the two-tier and the three-tier classification system. The mean time for high-grade lesions was 43 months, compared with 101 months for low-grade lesions. Although there were only four patients within the low and mild dysplasia groups, the earliest point at which one of these patients had further evidence of SCC was after four years. High-grade lesions seem to confer a higher risk within a shorter time period. The SCC was diagnosed between 4 and 132 months after the index biopsy showing dysplasia. This clear variability highlights the difficulty for clinicians in planning the duration of surveillance.

There was no apparent association between the initial grade of dysplasia and the T stage of the subsequently diagnosed SCC. This would support the general principle that dysplasia in itself is a precursor to malignancy, but not in a reproducible pattern.

Our study demonstrates the preferential use of CO₂ laser over other modalities for managing high-grade dysplasia. Although this study showed a tendency to use laser therapy, there was no significant difference between treatment modalities in terms of the risk of malignant transformation. The wide variation of treatment protocols limits direct comparison between studies.

- Laryngeal dysplasia confers a considerable malignant potential
- The malignant transformation rate rises with increasing dysplasia severity
- Each degree of dysplasia severity appears to behave as a separate entity, with moderate dysplasia conferring a higher potential malignant risk than previously described
- By classifying dysplasia into a two-tier classification system of high- and low-grade dysplasia, prognostic information can be improved, but this risks including more heterogeneous patient groups
- Duration and frequency of surveillance should consider dysplasia severity in addition to recognised patient and disease risk factors

Our results showed that mild dysplasia tends to progress to invasive carcinoma over a long period of time (mean of 101

months), which may not be served well by rigorous invasive monitoring in the short term. However, the possibility of tissue sampling errors always merits consideration. Our results show a significant malignant potential of moderate dysplasia (24.0 per cent), a risk that should not be considered inconsequential. Ultimately, we cannot lose sight of the clinical aspects of this disease. There is currently insufficient evidence to suggest that symptom recurrence correlates with presentation at an early stage; therefore, there appears to be a lack of evidence to advocate the early discharge of patients with low-grade dysplasia.

Conclusion

Laryngeal dysplasia carries a significant risk of malignant transformation. This risk appears to increase with dysplasia severity. This study advocates the combination of moderate and severe dysplasia into a high-grade group. In this study, the high-grade group demonstrated a higher malignant transformation rate (27.5 per cent vs 10.8 per cent; $p = 0.043$) and shorter mean time to transformation (43 months vs 101 months; $p = 0.012$), when compared with low-grade or mild dysplasia. There is a high rate of malignant progression within the first 12 months of initial diagnosis, but transformation can still occur late. Mild, moderate and severe dysplasia appear to behave as separate entities, with a statistical difference identified in their mean time to transformation (101 months, 52 months and 28 months, respectively; $p = 0.037$). This study does not conclude that one particular treatment modality confers a higher cure rate or survival rate for laryngeal dysplasia.

Laryngeal dysplasia, specifically affecting the glottis, is a multifactorial process, influenced by a plethora of confounding factors, some of which, such as smoking and male gender, have been demonstrated within this study. A diagnosis of laryngeal dysplasia carries a high morbidity and mortality rate. There is a well-recognised rate of tissue sampling error and inter-observer variability that should lead to caution when interpreting a histopathological report without sufficient

clinical information. We must highlight the crucial role of the multidisciplinary team approach and allow for patient autonomy when deciding upon the appropriate treatment and surveillance of this complex patient group.

Competing interests. None declared

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