Laryngeal Dysplasia, Demographics, and Treatment
A Single-Institution, 20-Year Review

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IMPORTANCE Laryngeal dysplasia is a common disease entity that remains clinically frustrating because functional outcomes are balanced against oncologic results. Understanding evolution in dysplasia demographics, treatment, and progression rates may inform better therapy in the future.

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.

DESIGN, SETTING, AND PARTICIPANTS In this retrospective medical record review, patients with laryngeal dysplasia treated at an academic medical center were identified on review of pathology records.

INTERVENTIONS Patients were organized by date of dysplasia diagnosis, divided into 2 groups (group 1, January 1, 1993, through December 31, 2002; group 2, January 1, 2003, through December 31, 2012), and compared against one another.

MAIN OUTCOMES AND MEASURES Age at diagnosis, sex, type of treatment, and progression to malignant disease were analyzed from one period to the next.

RESULTS A total of 107 patients were identified through review of pathology databases. Progression of dysplasia to cancer remained roughly stable across periods, at 8.8% and 8.0%, respectively. Mean age at diagnosis decreased from 68.7 to 61.7 years over time, with a statistically significant trend toward presentation at younger ages. The male to female ratio was 3.75 in group 1 and 3.17 in group 2, with a trend toward a greater proportion of females over time that did not reach statistical significance. Use of radiotherapy remained stable across groups, with increased use of microflap excision techniques and laser treatment (especially photoangiolytic lasers) in group 2.

CONCLUSIONS AND RELEVANCE Overall, progression of laryngeal dysplasia to cancer has remained stable during the past 20 years at a rate of approximately 8%. Although laryngeal dysplasia remains a disease predominantly found in males, there is a demographic trend toward diagnosis at earlier ages. Treatment choices may slowly be changing over time, although multi-institutional studies may be required to better categorize this shift.
Laryngeal keratosis occurs with an estimated annual incidence in the United States of 10.2 lesions per 100,000 males and 2.1 lesions per 100,000 females, respectively. In a single-institution review of laryngeal leukoplakia and a subsequent comprehensive literature review, Isenberg and colleagues found that more than half of these hyperkeratotic vocal fold lesions might not contain dysplasia; however, even lesions that did not contain dysplasia on initial biopsy had a risk of progression to malignant disease. Overall estimates of progression of laryngeal dysplasia to invasive laryngeal cancer vary widely, with estimates as low as 1.7% and as high as 46.3%; a meta-analysis of 940 cases of laryngeal dysplasia revealed a pooled malignant transformation rate of 13.6%, with severe dysplasia and carcinoma in situ having a higher rate of malignant transformation than mild or moderate dysplasia. Genomic analysis on an individual dysplastic lesion might someday allow better prognosis of which particular patients might have a risk of progression to invasive malignant disease, but to date there is no compelling evidence for use of this technology in routine clinical practice.

While awaiting further technological advances that allow for more individualized management of patients with laryngeal dysplasia, physicians are challenged by the care of patients with vocal fold leukoplakia. In clinical practice, there is concern that not doing enough may allow for progression of a premalignant process to cancer, whereas doing too much may risk creation of vocal fold scar and subsequent vocal deterioration for what at that time remains a noninvasive process. As a consequence of this clinical dilemma and because treatment technologies and paradigms are ever changing, there is a wide variety of approaches to management of laryngeal dysplasia, including expectant observation, vocal cord stripping, phonosurgical excision with cold instruments, laser excision, and radiotherapy. Among these, vocal fold stripping best highlights the dilemma in the management of this premalignant disease because it can cause scarring far beneath the anatomical level of the diseased tissue. As such, it is described as “a procedure that has no place in modern laryngological practice.” With the goal of preserving the voice while allowing for treatment of leukoplakia and dysplasia, emerging techniques of microflap excision and pulsed laser therapies have been described. To date, the transition over time from one set of techniques to the other has not been explored relative to outcomes such as oncologic efficacy and voice quality.

To address the diversity of practice patterns in the management of laryngeal dysplasia, consensus panels have advocated retrospective and prospective studies evaluating epidemiology, diagnosis, treatment, and voice outcomes. To provide data that highlight transitions in leukoplakia presentation and care over time, this study provides a retrospective review of 20 years of laryngeal dysplasia at a single institution, with comparison of the first 10-year period and the second 10-year period to identify changes in patient demographics, categorize treatment approaches, and review rates of progression to cancer over time. Our hypothesis is that demographics and treatment choices for care of laryngeal dysplasia are changing over time and that comparison of our study periods will reveal this evolution.

Methods

Institutional review board approval was obtained for retrospective review of medical records; no informed consent was required. The pathology database was searched with anatomic (larynx, laryngeal, vocal fold, and vocal cord) and histopathologic (dysplasia, keratosis, parakeratosis, hyperkeratosis, carcinoma in situ, carcinoma, and atypia) keywords to identify possible cases of laryngeal dysplasia or carcinoma in situ identified on biopsy from January 1, 1993, through December 31, 2012. To ensure accuracy of diagnosis, all patients had biopsies performed or had review of outside biopsy results at this institution; cases of dysplasia or carcinoma in situ referred from outside institutions were not included without confirmation of pathologic diagnosis at this institution. Among possible cases, more detailed medical record review was performed to confirm accuracy of this diagnosis. Any patients with a subsequent diagnosis of invasive cancer within 3 months were excluded from analysis, with the thought that the initial biopsy specimen may have been too shallow to identify what might already have been invasive carcinoma. Similarly, patients with pathology reports reading “at least carcinoma in situ,” patients with a history of irradiation for head and neck cancer, and patients with dysplasia in the setting of recurrent respiratory papillomatosis were excluded from analysis because they did not represent the patient cohort of primary laryngeal dysplasia or carcinoma in situ desired for this study.

Among included patients, medical records were reviewed for demographic information, smoking history, type of treatment, and clinical course, including the presence or absence of progression to cancer. Patients were organized by date of dysplasia diagnosis and were divided into 2 groups (group 1, January 1, 1993, through December 31, 2002; group 2, January 1, 2003, through December 31, 2012). Age at diagnosis, sex, and smoking history were compared between the 2 groups. Treatment modalities were grouped as radiation, biopsy without complete excision, and complete excision. For statistical purposes, we included all patients treated with a carbon dioxide laser, potassium titanyl phosphate (KTP) laser, or cold instrument surgery, with or without microflap excision in the complete excision group irrespective of operative technique, as long as the aim of the surgeon was to accomplish gross removal of all visualized disease. Total number and modality of treatments each patient had undergone was noted and compared for the 2 groups. Patients who received radiation therapy as the definitive treatment immediately as their next treatment after initial biopsy diagnosis were coded as having received radiotherapy as their primary treatment; for patients who did not receive radiotherapy, the primary treatment was categorized as biopsy without complete excision or as complete excision based on description available within the operative note.

Statistical analysis was performed using STATA statistical software, version 12 (StataCorp). Comparisons of continuous variables between the 2 groups were made with the unpaired t test, whereas comparison of categorical variables between the 2 groups used χ² analysis. Results were considered statistically significant at P < .05.
Results

A total of 107 patients were identified; 57 were in group 1 (1993-2002) and 50 in group 2 (2003-2012). Demographics are listed in Table 1. Sex in each group was similar, with males representing 45 (78.9%) of 57 patients in group 1 and 38 (76.0%) of 50 patients in group 2. Age at presentation was different between the 2 groups, with a mean age of 68.7 years (range, 46-87 years) in group 1 and 61.7 years (range, 31-81 years) in group 2 (P = .001). When analyzing patients in each period by age at presentation (≥65 years and <65 years), patients with dysplasia were significantly younger in the more recent period (P = .02). Smoking history did not differ significantly between the 2 periods, with data analysis limited by imprecise recording of smoking status in the group 1 medical records, resulting in approximately one-fourth of this cohort being categorized as having an unknown smoking history. Severity of dysplasia, taken directly from pathology reports, is shown in the Figure, with most patients in each period having severe dysplasia or carcinoma in situ rather than mild to moderate dysplasia. Patients with mild dysplasia were a higher proportion of the group 2 cohort than in the group 1 cohort (26.0% vs 7.0%, P = .007), whereas carcinoma in situ comprised a higher proportion of patients in group 1 than in group 2 (63.2% vs 32.0%, P = .002). Anatomical distributions of the lesions by patient in group 1 were as follows: unilateral true vocal cord (TVC), 48 (84.2%); bilateral TVC, 5 (8.8%); anterior commissure, 2 (3.5%); and epiglottis, 2 (3.5%). In group 2, anatomical distribution was as follows: unilateral TVC, 39 (78%); bilateral TVC, 9 (18%); aryepiglottic fold, 1 (2%); and anterior commissure, 1 (2%).

As it related to progression of cancer and in light of sample size in each period, treatments were split simply into categories of radiation therapy, biopsy without complete excision, and complete excision. With the use of this classification schema, no statistically significant difference was found between the group 1 and group 2 cohorts in overall choice of primary treatment modality (P = .39) (Table 2). Complete excision was used in most patients, and its overall use was similar between the groups: 33 (57.9%) of 57 patients in group 1 and 31 (62.0%) of 50 patients in group 2. In total, 11 patients (10.3%) underwent radiotherapy. Regarding the severity of the disease, 9 (81.8%) of the 11 patients had carcinoma in situ (including all patients undergoing radiotherapy in the second period); in the first period, one patient had bilateral TVC involvement with mild dysplasia, and another had moderate dysplasia with anterior commissure involvement. Although the proportion of patients who underwent radiation therapy revealed a decrease over time (14.0% in group 1 vs 6.0% in group 2), this finding did not reveal statistical significance between treatment modalities in the 2 study groups. Among surgical treatments, use of the KTP laser with microflap excision increased over time. Whereas none of the patients in group 1 had microflap resection with the KTP laser treatment, 7 patients (14.0%) in group 2 were managed with these techniques (P = .003). Although this finding was not statistically significant, there was decreasing use of carbon dioxide laser treatment over time: 7 patients (12.3%) in group 1 were managed with the carbon dioxide laser, whereas 2 patients (4.0%) in group 2 were managed with this technique (P = .17).

In the overall study population, 9 of 107 patients with laryngeal dysplasia had progression to cancer for a malignant transformation rate of 8.4%. This rate of progression to cancer was not statistically significant between the 2 study groups (8.8% in group 1 vs 8.0% in group 2, P = .59). Risk of progression to cancer was analyzed as a function of severity of dysplasia (Table 3), and with consideration of 4 grades of severity as taken directly from pathology reports (mild, moderate, severe, and carcinoma in situ), there was no effect of severity
of dysplasia on malignant transformation rate \( (P = .83) \). Similarly, treatment modality \( (\text{Table 4}) \) did not reveal statistical significance in malignant progression in both groups \( (P = .91) \). In addition, after losses to follow-up were accounted for, comparison of the 9 patients with malignant progression and the 91 patients without malignant progression did not yield any statistically significant differences in age or sex \( (\text{Table 5}) \), although no nonsmokers had progression to cancer, and there was a trend toward smokers having a higher risk of malignant transformation \( (P = .08) \).

### Discussion

The current study is one of the longest single-institution studies on dysplasia to be presented in the literature and has the benefit of categorizing demographics, treatment, and progression to laryngeal cancer of a cohort of patients with laryngeal dysplasia that spans the transition in treatment approaches that has occurred in the past several years. A similar review\(^2\) from the University of Wisconsin published in 2008 encompassed 15 years of review, whereas 2 reviews\(^{12-13}\) from Inverness, Scotland, and Paisley, Scotland, encompassed 15 years and 10 years, respectively. In addition to encompassing a long time frame, this series also documents 107 patients with laryngeal dysplasia, a number that compares well with other published series in the literature. In a meta-analysis,\(^3\) aside from a single 1989 study\(^4\) that discussed 317 patients, included studies had between 26 and 116 patients. To encompass this number of years and patients, the present study went as far back as could be accomplished within limitations of the pathology database and electronic medical records. We divided our study period into two 10-year periods because this seemed to be long enough to study the evolution in management and left us an appropriate number of patients in each group.

The overall rate of progression of laryngeal dysplasia to malignant disease within this review is 8.4%, slightly beneath the pooled rate of malignant transformation of 13.6% and within the 95% CI of 8% to 22% found in the meta-analysis.\(^3\) This finding may be a reflection of low sample size, with 9 patients progressing to malignant disease. In addition, perhaps because of the sample size, despite best efforts to generate the largest single-institution database possible, this study was not able to have statistically meaningful associations between grade of dysplasia and progression to malignant disease. This is an association that has been revealed in the literature, with higher rates of progression to cancer among patients with severe dysplasia or carcinoma in situ than among patients with mild or moderate dysplasia.\(^2-3\) This study similarly did not find any statistically significant differences among the 3 primary treatment categories of radiotherapy, biopsy without complete excision, and complete excision as predictors of progression to malignant disease. This finding is not too surprising because even the largest currently available meta-analysis could not find statistically significant differences in rates of progression to malignant disease between the biopsy without com-

### 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>

### Table 5. Age, Sex, and Smoking Status in Patients With and Without Malignant Progression

<table>
<thead>
<tr>
<th>Demographic</th>
<th>No Malignant Progression (n = 91)</th>
<th>Malignant Progression (n = 9)</th>
<th>Lost to Follow-up (n = 7)</th>
<th>Total (N = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at diagnosis, y</td>
<td>65.6</td>
<td>64.1</td>
<td>64.1</td>
<td>83 (77.6)</td>
</tr>
<tr>
<td>Male sex</td>
<td>71 (78.0)</td>
<td>7 (77.7)</td>
<td>5 (71.4)</td>
<td>83 (77.6)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>66 (72.5)</td>
<td>6 (66.7)</td>
<td>4 (57.1)</td>
<td>76 (71.0)</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>14 (15.4)</td>
<td>0</td>
<td>0</td>
<td>14 (13.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (12.1)</td>
<td>3 (33.3)</td>
<td>3 (42.9)</td>
<td>17 (15.9)</td>
</tr>
</tbody>
</table>

\(^*\) Data are presented as number (percentage) of patients unless otherwise indicated.
complete excision and complete excision groups, partly because meta-analysis is sometimes limited in its ability to determine what intervention might have been performed for any particular patient with progression to cancer. As called for in a consensus panel on laryngeal dysplasia, continued aggregation of retrospective data and pooled prospectively collected data will be necessary to demonstrate best practices in the care of laryngeal dysplasia moving forward. These studies will need to be well coordinated to reduce variances caused by variations in histopathologic grading and surgical treatment.

Although overall comparison among the 3 primary treatment choices of radiotherapy, biopsy without complete excision, and complete excision did not reveal any differences in frequency of use between the 2 study periods, a closer look at microflap excision and pulsed laser photoangiolysis indicates that they have been used uniformly within the second 10-year period (2003-2012). This temporal trend toward emergence of microflap excision and pulsed laser photoangiolysis reached statistical significance. Changes in treatment modality are heavily dependent on physician preference, experience, and technical equipment provided by the hospital; surgeon preference clearly plays a large role in choice of treatment and may explain this difference. However, use of a pathology database extending for 20 years and accrual of patients from many different surgeons may somewhat mitigate the effect that any single surgeon’s treatment choice might have on these results. Along with surgeon preference, these results may also indicate emerging trends in care of this disease.

The emerging trends in care of laryngeal dysplasia also include transition of patients with recurrent leukoplakia from the operating room to the office, which is certainly a technique used by the authors. Current practice patterns among the laryngologists at Johns Hopkins University include initial management in the operating room to completely remove and stage the disease, then transitioning patients with recurrent leukoplakia to the office for photoangiolytic treatment as necessary. For purposes of the current study, however, identification of patients through the pathology database limited our patient population to those treated in the operating room, and comparisons of trends over time were made only for operating room interventions. Office-based laser therapy at Johns Hopkins University began with arrival of one of the authors (L.M.A.) late in the overall study period, and no patients are treated in the office without first having had evaluation of their pathologic diagnosis and complete treatment in the operating room. Although an important technique for future care of these patients, office-based care did not bias identification of patients in either period. The effect of emerging treatment paradigms on voice outcomes was not an end point of this study, and with low numbers of overall progression to cancer, this study cannot offer any meaningful conclusions on the oncologic safety of one approach relative to another. Over time, further prospective studies may offer documentation of the voice outcomes and malignant transformation rates achieved with these modalities.

This article is unique in its evaluation of temporal trends in laryngeal dysplasia presentation and management. In addition to finding emerging use of microflap excision and pulsed laser photoangiolysis, this study found another temporal trend in laryngeal dysplasia—over time, patients are presenting younger and with a higher percentage of milder dysplasia. These trends may be linked because higher-quality office endoscopy, including high-definition digital images and narrow-band imaging, may allow patients to be identified at earlier stages of disease and at younger ages than had been possible earlier. It could also be that the dynamics of laryngeal neoplasia are themselves changing; review of National Cancer Institute data suggests that although overall incidence of laryngeal cancer remains higher in those 65 years or older than in those younger than 65 years, the overall decrease in incidence for this older group is occurring more rapidly than is the decrease in the younger age groups. As this trend continues, patients with laryngeal cancer may, on the whole, have slowly decreasing age at diagnosis. A similar national trend with laryngeal cancer is present for sex, in which incidence over time is decreasing more quickly for men than for women, such that over time women are becoming a larger relative proportion of patients with laryngeal cancer. Although the male to female ratio of the patients with laryngeal dysplasia was not statistically different in this study between the 2 study groups, the change in the male to female ratio of 3.75 in group 1 to 3.16 in group 2 reveals a trend toward increasing proportion of females.

This article adds meaningfully to the series of patients with laryngeal dysplasia described in the literature and is the first, to our knowledge, to identify temporal trends in laryngeal dysplasia demographics and treatment. These trends include younger age at diagnosis, less severe grade at diagnosis, and emerging use of microflap excision and pulsed laser photoangiolysis. Even as more is learned about laryngeal dysplasia, the dilemma of balancing oncologic safety with functional outcomes, such as voice quality, persists for patients with laryngeal dysplasia. As noted in a previous study and as seen in the patient population presented in this article, even patients with no or mild dysplasia can progress to cancer, and therefore treatment is warranted. However, overall, only a small proportion of patients with laryngeal dysplasia will progress to cancer. For many patients, this remains a superficial process for which superficial treatment that preserves the functional anatomy of vocal fold vibration is warranted. Better understanding of laryngeal dysplasia in general and temporal trends in its presentation and management in particular may offer insights that better allow for improved management of this disease process. Ultimately, knowledge of risk factors and epidemiology of dysplasia may allow for otolaryngologists to identify these patients before disease progression, whereas prospective evaluation can allow for balance of oncologic efficacy and functional outcomes.

Conclusions

In this 20-year, single-institution review of laryngeal dysplasia, 8.4% of patients had dysplasia that progressed to cancer. This rate remained stable when compared between the 2 study groups. In this series, treatment type, sex, smoking, and grade of dysplasia were not related to progression of dysplasia to cancer. There were statistically significant temporal trends over
time toward younger age at diagnosis and less severe grade at diagnosis. Although overall use of radiotherapy vs biopsy without complete excision vs complete excision were not different between the study periods, further analysis of the types of surgery being performed reveal emerging use of microflap excision and pulsed laser photoangiolysis in the more recent cohort. Temporal trends in laryngeal dysplasia demographics and treatment deserve further study, along with prospective evaluation of emerging treatment paradigms that seek to balance oncologic efficacy with voice preservation.

ARTICLE INFORMATION

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Author Contributions: Drs Karatayli-Ozgursoy and Akst had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Karatayli-Ozgursoy, Pacheco-Lopez, Hillel, Akst. Acquisition, analysis, or interpretation of data: Karatayli-Ozgursoy, Best, Bishop, Akst.

Conflict of Interest Disclosures: None reported.


