ADENOID CYSTIC CARCINOMA OF THE LARYNX: A 40-YEAR EXPERIENCE

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Abstract: Background. Laryngeal adenoid cystic carcinoma (ACC) is a rare disease. We reviewed our experience at the Princess Margaret Hospital (PMH) with its treatment.

Methods. This is a retrospective chart review of 15 cases treated at PMH between 1963 and 2005.

Results. The mean age was 48.6 years. There was no sex predilection. The subglottis was the most common subsite involved. Only 2 patients had regional metastasis. Local or regional recurrence was noted in 5 patients (33.3%). The distant metastasis rate was 66.7% and involved the lungs. The median follow-up time was 6.9 years. The 5- and 10-year overall and disease-specific survival rates were 64% and 46%, and 69% and 49%, respectively.

Conclusion. Laryngeal ACC is a rare disease with a high rate of distant recurrence. Its management should emphasize maximizing local and regional disease control by surgery followed by radiotherapy with distant disease failure eventually dictating survival.

Keywords: larynx; adenoid cystic carcinoma; outcome; treatment; survival

Adenoid cystic carcinoma (ACC) of the head and neck is a well-recognized pathologic entity usually arising in the major salivary glands and the minor salivary glands of the oral and sinonasal cavities.1 Robin and Laboulbene were the first to describe the histopathology of what they termed “tumeurs heteradentique” or “heteradenic tumors.” However, it was Billroth in 1856 who coined the term “cylindroma,” which became a widely accepted term for this tumor. Other terms which have been applied to describe this entity include basalioma, adenocarcinoma of the cylindromatous type, adenocarcinoma of the mixed type, and ACC.2

Laryngeal ACC is extremely rare. A review of 1342 cases of laryngeal tumors treated at the Institut Gustave Roussy identified only 5 cases of laryngeal ACC.3 This tumor arises from the glandular elements4 that are known to be present in the larynx.

In addition to the relative rarity of this malignancy, other factors that contribute to the difficulty in studying this disease are the lack of
uniformity in reporting the cases as ACCs and the fact that the same patients have been described in different reports and series.

In the absence of large, prospective multi-institutional studies to identify rare head and neck malignancies, guidance on therapeutic approach and treatment must rely on institutional case series. The objective of this article was to review our long-term experience at the Princess Margaret Hospital (PMH) with treating ACC of the larynx.

PATIENTS AND METHODS
A retrospective chart review of all adult patients treated for ACC of the larynx at the PMH, Toronto between 1963 and 2005 was performed. Patients were identified through the PMH Cancer Registry. Patients with ACC of the trachea were excluded. A total of 15 patients were eligible for chart review. Approval was obtained from the institution’s Research Ethics Board.

Demographic, clinical, and pathologic data were obtained from the hospital records. The diagnosis was confirmed before treatment by a head and neck pathologist at the PMH.

Statistical analysis was performed using the SAS v11 software. Demographic and pathologic data were summarized using descriptive statistics. The main endpoints assessed were overall and disease-specific survival and local, regional, and distant recurrence rates. Overall and disease-specific survival were calculated from the date of diagnosis to the event of interest. Kaplan-Meier estimates were used to calculate the survival curves.

RESULTS
Thirty-seven patients were identified in the registry with ACC of the larynx or trachea. The larynx was the primary site of involvement in 15 patients. The mean age at diagnosis was 48.6 years, with a range of 26 to 71 years. There was no sex predilection, with 8 patients being males and 7 females. Forty percent of the patients were non-smokers, 53.3% of the patients were smokers, and 6.6% were not specified.

Dyspnea was the most commonly reported presenting symptom, followed in frequency of occurrence by hoarseness and dysphagia. Presenting symptoms are listed in Table 1. Duration of symptoms before presentation ranged from 2 to 40 months, with an average of 10.1 months.

Vocal cord fixation or impaired mobility was noted in 46.6% of patients. Three patients presented with a neck mass, 2 of which were found to be due to direct tumor extension, with only 1 patient presenting with nodal metastases.

The subglottis was the most common laryngeal subsite involved. Table 2 lists the frequencies as related to site distribution within the larynx. The subglottis was involved alone in 60% of the cases, while another 20% had actual extension to the subglottis in addition to a supraglottic or glottic involvement.

Pathologic subtyping in this patient population determined that 1 patient had a solid pattern, while the remaining patients were distributed equally between the cribriform (46.6%) and the mixed patterns (46.6%). Cartilage invasion was documented in 33.3% of patients.

Only 1 patient had regional metastasis upon presentation (6.6%). Another was found to have it by pathologic inspection of the surgical specimen. Two patients (13.3%) had distant metastatic disease to the lungs upon presentation.

Treatment details and outcomes are presented in Table 3. The treatment strategies included radiation therapy alone in 2 patients. One patient was treated with radiation therapy and chemotherapy. Three patients were treated surgically with no radiotherapy delivered. The remaining 9 patients (60%) received combined-modality treatment with surgery and radiation, with 1 patient having preoperative radiotherapy. Of the 2 patients treated with radiotherapy alone, 1 was found to have persistent disease on follow-up but

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<th>Table 1. Presenting symptoms.</th>
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<th>Table 2. Distribution by site.</th>
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refused surgical salvage. The other was found to have recurrent disease and underwent salvage surgery with a total laryngectomy procedure. Resection with clear margins was achieved in only 5 of the 12 patients who underwent surgery. Patients who underwent a total laryngectomy had a 50% positive margin rate compared with patients who underwent a conservative laryngectomy approach, who had a 75% positive margin rate.

Recurrence. Only 3 patients remained free of disease after treatment; however, 2 died of other causes. Local or regional recurrence after treatment was noted in 33.3% (n = 5) of the patients. One patient was confirmed to have residual disease after radiotherapy (RT) but refused salvage laryngectomy. Two patients developed local recurrence, and another 2 developed regional recurrence. Only 1 of the 9 patients who were treated with combined-modality therapy had locoregional failure. Distant metastasis occurred in 66.7% (n = 10) of the patients, with 2 patients having it upon presentation. The lungs were the predominant site of distant metastasis (Table 4).

Follow-Up, Survival, and Vital Status. The median follow-up time was 6.9 years, with a range of 1.3 to 22.3 years. At last follow-up, 6 patients were alive; of these, only 1 was free of disease. Seven patients died from their disease, and 2 died from other causes. Table 4 summarizes the failure pattern and illustrates the time to failure and length of life after failure. The 5- and 10-year overall survival rates were 64% and 46%, respectively. The 5- and 10-year disease-specific survival rates were 69% and 49%, respectively. The Kaplan-Meier curves are illustrated in Figure 1.

**DISCUSSION**

Sialogenic laryngeal neoplasms account for less than 1% of all laryngeal tumors. The overall density of minor glands in the larynx is between 23 and 47 glands/cm². The laryngeal glands are of the exocrine compound tubuloalveolar type and are known to be mixed seromucinous glands. The gland count decreases as one moves from the supraglottis to the glottis and subglottis. The mucous glands are also known to be numerous in the area of the false cords and immediately inferior to the anterior commissure.

Many previously reported series showed ACC to be the most common type of malignant minor salivary gland tumors of the larynx. However, a review by Spiro et al on 20 cases of sialogenic laryngeal tumors in 1976 showed that adenocarcinoma was more frequent than ACC. It is possible that many tumors that were previously considered under the heading of adenocarcinoma would be reclassified with immunohistochemical staining techniques.
The subglottis appears to be the most common site of origin. Sixty percent of our patients had isolated subglottic tumors, and an additional 20% of patients had extension of their tumor from the supraglottis or glottis to the subglottis. Batsakis et al reported that two thirds of laryngeal ACCs arise in the subglottis. Similar findings were noted by Ganly et al and Whicker et al.

Patients present with the usual complaints associated with laryngeal carcinomas, the spectrum of which depends upon the extent of the tumor and its anatomic location. Pain may be present, and this could be related to the propensity of this tumor for perineural spread. The duration and progression of symptoms can be quite variable, as evidenced by our series, and this depends most likely on the biologic behavior of the tumor. However, unlike the more common laryngeal squamous cell carcinoma (SCC), there was no predilection in our series to male sex and there appears to be no association with smoking as a risk factor. ACC’s propensity for subglottic involvement is another difference.

ACC generally behaves in an indolent manner. However, some patients are also observed to have aggressive tumors with rapidly progressive disease. The predilection for laryngeal glandular carcinomas to spread submucosally may account for the fact that most patients actually present with locally advanced tumors and would also account for the high incidence of positive margins on surgical specimens. Fordice et al reviewed their experience with ACC of the head and neck at The University of Texas M. D. Anderson Cancer Center. They looked into the prognostic factors and the predictors of mortality and morbidities associated with ACC. They commented that perineural invasion, positive margins, and solid histologic variants predicted treatment failures, while nodal metastases, neural invasion, the presence of more than 4 symptoms, and solid features negatively affected survival.

Our results indicate that laryngeal ACC is associated with a behavior similar to ACC in other
head and neck sites with a long period of survival with recurrent disease and frequent development of late distant metastases.

The analysis of survival in this group of patients shows a 5-year overall survival rate of 64\%, 5,8,10,13 The 5-year actuarial survival in the University of California-Los Angeles (UCLA) series was 75\% (for 5 patients).9 Cohen et al15 found a 42.8\% 5-year survival rate in their series of laryngeal sialogenic tumors. The discrepancy in survival rates between reported series could be related to a difference in the treatment approach or to the fact that the small number of patients in all series does not allow for a fair comparison. It is also to be noted, however, that the 5-year survival figure may not reflect the actual long-term survival, because even patients with adequate local control could develop recurrence many years after treatment.14

Most of our patients were treated with a combined-modality approach. With this approach, we were able to achieve an excellent local control rate. It is difficult to formulate an optimal treatment protocol for laryngeal ACC because all previous reports, including ours, are limited by their retrospective design, varied treatment regimens, and small subject numbers. However, we can also rely on our experience with treatment for ACC at other sites in the head and neck.

Chen et al15 reviewed their experience at the University of California-San Francisco (UCSF) with treatment for ACC of the head and neck. They found that omission of postoperative radiotherapy and, when delivered, a dose less than 60 Gy, were independent predictors of local recurrence. The 5- and 10-year local control rates were 92% and 84%, respectively, for combined-modality treatment patients compared with 80% and 61% for those who did not receive radiation therapy. They recommended a combined-modality therapy with surgery followed by radiation therapy to an excess of 60 Gy as a treatment for ACC of the head and neck.

In our series, we observed that 2 of our patients who were treated with primary radiotherapy developed local recurrence. Another observation was that 2 of 3 patients who were treated only with surgery and did not receive radiotherapy developed locoregional recurrence.

In view of the submucosal pattern of spread of this tumor, a partial or a total laryngectomy procedure may result in positive margins. We were able to achieve free margins in only 1 of our 4 patients who had conservative surgery. The rate of positive margin with the total laryngectomy group was high as well (50\%). Still we were able to control the disease locoregionally for many years in many of the patients who had positive margins (in both groups, partial and total). While we realize that a negative margin is the ideal goal to achieve for maximal control, we recognize from our results that it is often not possible and therefore we must balance the treatment goals with the quality of life. Conservative resection is possible only in selected cases, particularly when radiotherapy is given postoperatively. This should be dictated on an individualized basis, taking into consideration the age, the impact on the quality of life, and the preference of the patient as well as the extent of disease on presentation. As with ACC at other head and neck sites, the goal is to achieve local and regional disease control as these patients can live for a long period of time. Currently, we advocate surgical resection with postoperative radiotherapy to allow for maximal locoregional control of this malignancy.

Only 1 of our patients had regional metastasis at the time of presentation. Another was found to harbor regional metastasis in the surgical resection specimen. Lymph nodes could be involved by direct extension. However, true embolic metastases cannot be excluded.16 Conley and Dingman17 considered that neck dissection is not perceived as an integral part of the treatment unless the patient has a clinically or histologically confirmed nodal metastasis. This observation was also reported by Ferlito et al16 and Ganly et al.9

In our series, the rate of distant metastasis was 66.7\% percent, and distant metastasis occurred up to more than 11 years posttreatment. The lungs were the predominant site of distant metastases in all of our cases. However, ACC shows a very slow growth pattern, and the patients can survive for many years even in the setting of distant metastases. In fact, some of our patients survived for much more than 10 years with the disease.

In addition, it is important to note that the presence of lung metastases at the time of presentation should not prevent surgical resection of the tumor for local control, because patients could still live for a long time with the disease, as evidenced by our series.

**CONCLUSION**

ACC of the larynx is a rare entity. However, the diagnosis should always be considered in case of a submucosal mass in the larynx. Most patients present with an advanced stage. It is associated with a high rate of local disease control through a planned combined-treatment protocol with surgi-
cal resection followed by postoperative radiotherapy. Laryngeal preservation surgery may be possible in selected cases. Laryngeal ACC has a low incidence of regional metastases. However, a neck dissection should be performed in the setting of a clinically or radiologically positive neck. Disease in most patients recurs, often at a distant site and predominantly in the lungs. It is also important to note that distant recurrence may occur many years after treatment. However, this tumor shows a slow growth rate, with many patients surviving for a prolonged period of time with the disease. To conclude, we can say that the key to care of a patient with laryngeal ACC is to maximize local disease control, with distant disease failure eventually dictating overall survival.

REFERENCES