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Adenoid Cystic Carcinoma of the Major Salivary Glands Treated with Surgery and Radiation

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Objective: **To examine patient characteristics, pathologic features, and treatment outcomes of adenoid cystic carcinoma of the major salivary glands.** ***Study Design:*** **Retrospective review of patients in an academic medical center.** ***Method:*** **Review of medical records regarding demographics, extent of tumor, stage, histologic characteristics, and treatment outcomes of patients treated with surgery and postoperative radiation.** ***Results:*** **Of the 33 patients, 19 (58%) were male, and 14 (42%) were female. The average age of presentation was 49 (range 22–81) years. Of the 29 patients fully staged at the time of diagnosis, 7 (24%) presented at American Joint Committee on Cancer stage I, 9 (31%) at stage II, 4 (14%) at stage III, and 9 (31%) at stage IV. The cribriform histologic subtype was predominant (64%). The majority originated in the parotid gland (21, 64%), with the remaining originating in either the submandibular gland (10, 30%) or the sublingual gland (2, 6%). Local control was 94% at 5 years and 73% at 10 years. Metastatic control was 82% at 5 years and 63% at 10 years. Four patients failed locally and nine failed distally. Overall survival was 85% at 5 years and 69% at 10 years, with a median of 12.9 years.** ***Conclusion:*** **Surgical excision with postoperative radiation provides a long period of disease-free survival. Patients were more likely to fail with metastases than with local recurrence.** ***Key Words:*** **Adenoid cystic carcinoma, postoperative radiation, major salivary glands.**

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INTRODUCTION

Adenoid cystic carcinomas of the head and neck are relatively rare tumors, consisting of approximately 10% of all salivary gland neoplasms.[1] They are derived from mucus-secreting glandular cells of the foregut. Adenoid cystic carcinomas are found both in the major salivary glands (parotid, submandibular, and sublingual glands) and in the minor salivary glands located in the palate, nasal cavity, paranasal sinuses, trachea, and lacrimal gland. These tumors are characterized by slow, local growth and rarely spread to local lymph nodes. Unfortunately, they tend to metastasize distally. Size of original tumor, presence of perineural invasion, and positive margins have been suggested to make local and distal control challenging in the long term for this malignancy.[2–6]

This study reviews a 42 year experience at the University of California-San Francisco of patients with adenoid cystic carcinoma of the major salivary glands who have been treated with surgical resection and postoperative radiation therapy. Given that a small number of patients are diagnosed with this disease worldwide, this retrospective analysis further characterizes factors that affect both local and distant control as well as overall survival.

MATERIALS AND METHODS

Between November 1958 and May 2000, 33 consecutive patients with adenoid cystic carcinoma of major salivary glands (parotid, submandibular, or sublingual gland) underwent both surgery and radiation therapy with curative intent at the University of California–San Francisco. Patient characteristics, pathologic findings, and treatment modalities were obtained from a retrospective medical record review of both paper and electronic documentation. Complete data of all factors analyzed were not always obtainable and has been noted appropriately. Only initial information was available for two patients in the population, so they were not included in analysis of outcome. Staging was based on the American Joint Committee on Cancer (AJCC) 1997 system when sufficient information was documented at time of presentation. Exact dates of death were also searched for and confirmed by using the U.S. Social Security database.

The mean age of presentation in this series was 48.7 years and ranged from 22 to 81 years of age (Table I). Fourteen (42%) were female, and 19 (58%) were male. The majority of patients were white (25, 76%). Other ethnicities represented include Hispanic (4, 12%), black (2, 6%), and Asian (2, 6%).

Of the 33 patients identified with adenoid cystic carcinoma of the major salivary glands, 21 (64%) originated from the parotid, 10 (30%) originated from the submandibular gland, and 2 (6%) originated from the sublingual gland (Table I). AJCC staging

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TABLE I.
Patient Population (n = 33).

Variable	No. of Patients (%)
Primary site	
Parotid gland	21 (64)
Submandibular gland	10 (30)
Sublingual gland	2 (6)
Stage (n = 29)	
I	7 (24)
II	9 (31)
III	4 (14)
IV	9 (31)
Sex	
Male	19 (58)
Female	14 (42)
Mean age (years)	48.7
Range	22–81
Margins (n = 26)	
Positive	13 (50)
Microscopically positive	6 (23)
Negative	7 (27)
Presence of extracapsular invasion (n = 29)	
Perineural invasion	18 (62)
Perivascular invasion	5 (17)
Muscle or tissue invasion	15 (52)

was available for 29 patients (Table I); of these, there were 7 (24%) stage I patients, 9 (31%) stage II patients, 4 (14%) stage III patients, and 9 (31%) stage IV patients.

The histologic subtype, when noted (14 patients), was most often cribriform (64%). Other subtypes present in the study include cystic, trabecular, glandular, tubular, and solid. Some specimens were found to have a combination of subtypes consisting of two of the following: cribriform, tubular, solid, and glandular.

Twenty-six patients had pathology reports that specifically documented the margin status (Table I). Most margins were found to be either positive or microscopically positive in 13 (50%) and 6 (23%) patients, respectively. Seven patients had negative surgical margins (27%).

Perineural invasion was noted in 18 of the 29 (62%) pathology reports in which this characteristic was addressed (Table I). Of the tumors that demonstrated perineural invasion, four (22%) were of identifiable, named nerves. Also, perivascular invasion was identified in 5 (17%), and invasion into muscle or surrounding tissue was identified in 15 (52%).

All patients studied underwent total gross surgical resection and postoperative radiation therapy. Information regarding postoperative radiation therapy was available for 32 of the 33 patients. Three patients elected to pursue radiation therapy at an outside institution. The range of dose for patients who completed a course of postoperative radiation therapy ranged from 5,040 to 7,989 cGy. Sixty-six percent of these patients received greater than 6000 cGy. Three patients discontinued postoperative radiation therapy prematurely at 900, 4,080, and 2,604 cGy.

Descriptive statistics were calculated to characterize the patient sample because of the number of evaluable patients, n = 31. The Kaplan-Meier product limit method was used to estimate the probability of local control, metastatic control, disease-free survival, and overall survival. All durations were measured from diagnosis. The date of last contact was the endpoint if the patient did not fail when calculating the time to recurrence or if the patient was still alive when calculating the survival duration.

RESULTS

Patient outcomes of 31 evaluable patients were analyzed for local and distant control as well as disease-free and overall survival. Median follow-up on all patients was 6.5 years, ranging from 0.4 to 30.8 years. Median follow-up for survivors was 10.6 years. Seven patients have been followed for at least 14.8 years.

Local Control

Four of the 33 patients failed locally (Fig. 1A). The 5, 10, and 15 local control rates were 94%, 73%, and 73%, respectively (Table II). Of note, the median had not been achieved yet in this population, and therefore the 15 year local control rate is of limited significance. The mean time to local failure was 6.5 (range 4.8–7.5) years.

The four patients who failed locally had disease of the parotid in origin and were diagnosed at stages II, III (2 patients), and IV. Margin status was available for three of the four local failures, and all margins were positive. In comparison with patients with documented margin status who did not fail, the majority (64%) also had positive or microscopic positive margins. One patient was noted to have involvement of a named nerve. All four local failures underwent postoperative radiation (5,400–6,500 cGy). Of these four local failures, one patient subsequently developed a distant metastasis to the brain 1.8 years after the local failure.

Distant Control

A total of 10 patients developed metastatic disease (Fig. 1B). One of the 10 had documented metastases at the time of diagnosis. The 5, 10, and 15 year metastatic control rates are 82%, 63%, and 54%, respectively (Table II). Among those developing metastatic disease, the mean time until diagnosis of a metastasis was 3.4 years after initial diagnosis and ranged from 0 to 12.3 years.

Full pathologic reports were available for eight of the patients who developed metastatic disease. Six patients had positive or microscopic positive margins. Seven had documented perineural invasion, and three of these were of a named nerve. All underwent radiation therapy (5,040–7,989 cGy). Only four presented at an advanced stage (stage III or IV). The lung was the most common site of metastasis (5), followed by bone (4), brain (2), and skin (2). Three of the 10 patients had multi-organ metastasis (lung/skin, bone/skin, and lung/bone/skin).

Disease-Free and Overall Survival

The 5, 10, and 15 year - survival probability estimates were 74%, 41%, and 24%, respectively (Fig. 1C) (Table II). The median disease-free survival was 7.4 years. Nine of the 31 patients died after recurrent disease.

The 5, 10, and 15 year overall estimates of survival are 85%, 69%, and 35%, with a median overall survival was 12.9 years (Fig. 1D) (Table II). Fifteen of 31 patients

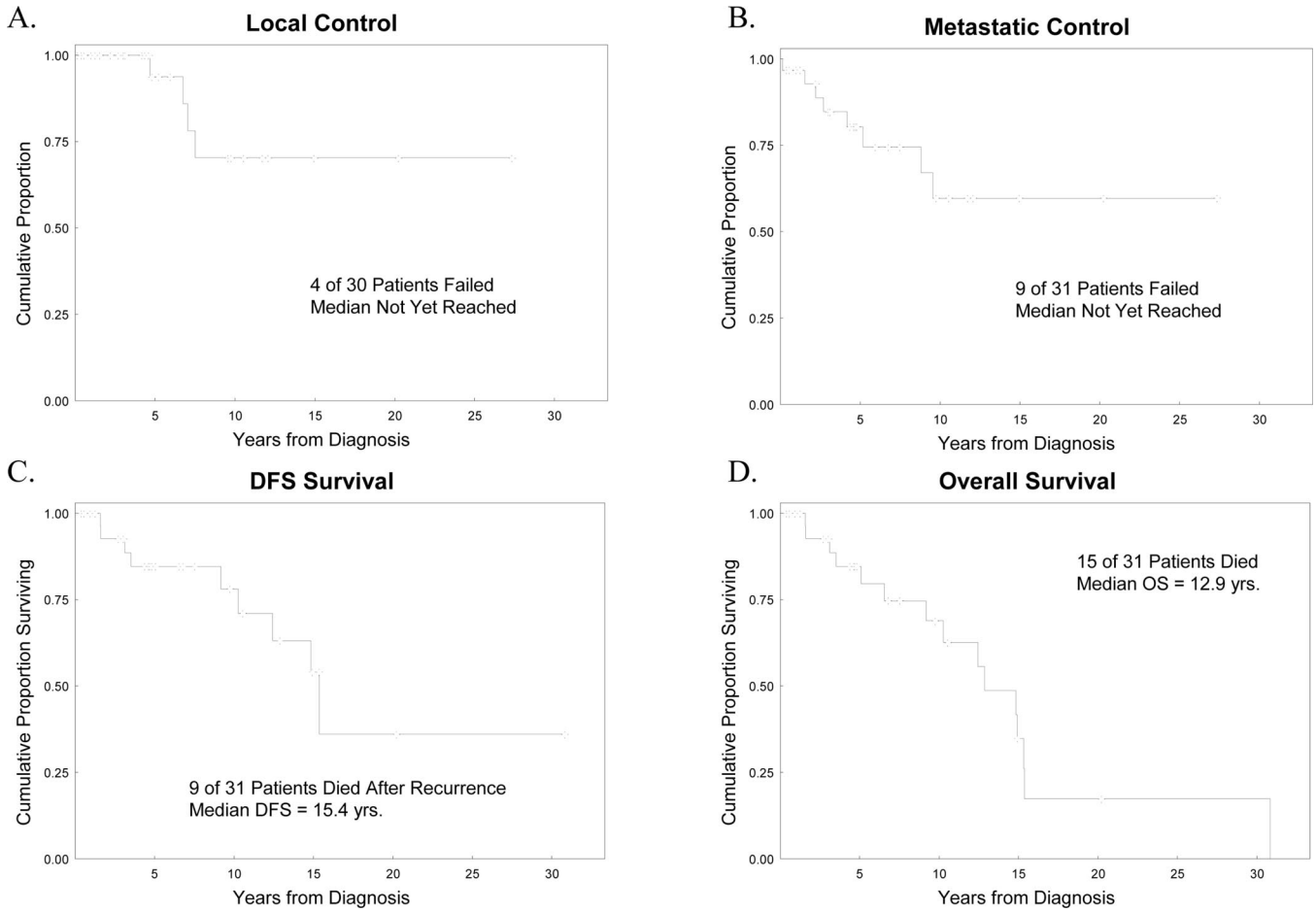

Fig. 1. Kaplan-Meier survivorship curves of patients with adenoid cystic carcinoma of the major salivary glands treated with surgery and radiation therapy. (A) Local control; (B) distant control; (C) disease-free survival (DFS); (D) overall survival (OS).

died by their last follow-up. Nine had metastatic disease before death. Four of the remaining six deaths occurred without evidence of recurrence and likely were caused by other factors.

Sex, age, early (stage I or II) versus late (stage III or IV), gland of origin, margin status, and perineural invasion did not statistically correlate with local or metastatic control, nor did disease-free or overall survival in this series.

TABLE II.
Kaplan-Meier Probability Estimates.

	Years from Diagnosis		
	5	10	15
Number at risk	17	11	7*
Local control	94%	73%	73%
Metastatic control	82%	63%	54%
Overall survival	85%	69%	35%
Disease free survival (failure or death)	74%	41%	24%
Death after failure	85%	78%	54%

*Follow-up at least 14.8 years.

DISCUSSION

This single academic institution retrospective study represents one the largest series of patients with adenoid cystic carcinoma of the major salivary glands. Adenoid cystic carcinoma is a challenging disease to study because it is an uncommon entity and is associated with an overall long survival. This retrospective review focuses on patient characteristics, pathologic features, and survivorship outcomes.

Adenoid cystic carcinoma is usually treated with a combination of both surgery and postoperative radiation. The general consensus is that postoperative radiation therapy improves local control and overall survival.[1,3,7,8] The management of these patients at our institution is aligned with this approach, and this study examines patients treated with both treatment modalities.

Although the majority of the patients in this study underwent conventional radiation therapy, some of the patients in the last 5 years of this retrospective study underwent intensity-modulated radiation therapy (IMRT). Given the long-term disease-free and overall survival, it is too early to say whether IMRT will be additionally beneficial. However, treatment with this modality will benefit the patient by sparing more normal tissue than conventional methods.

There is also suggestion in the literature that fast neutron beam therapy is as effective in achieving local control as conventional radiation therapy; however, a survival benefit has not been demonstrated.[9]

For patients who are not surgical candidates, radiation therapy and chemotherapy are two possible treatment modalities. Neutron beam therapy may be beneficial in unresectable, locally advanced, grossly margin positive disease or recurrent disease.[10,11] Chemotherapy is sometimes used in recurrent or metastatic adenoid cystic carcinoma to delay progression or for palliation.[12] There is some hope that molecular analysis will allow identification of tumor subsets that may be chemotherapy sensitive.[1]

Patients with adenoid cystic carcinoma of the major salivary glands treated with surgery and radiation have excellent overall control rates. The 5 and 10 year local control rates of 94% and 73% compare favorably with other reports.[2,10] This is encouraging because a third of patients had advanced (stage III or IV) disease, and over half had positive margins. Direct comparisons with other published reports are limited; other studies published group major and minor salivary gland origins, combine surgery alone with surgery and postoperative radiation, study histologic subtypes other than adenoid cystic alone, and vary in duration of follow-up. Nevertheless, the encouraging overall control rates may suggest a more favorable prognosis for patients with adenoid cystic carcinoma of the major salivary glands.

If patients fail treatment, they are more likely to fail with distant metastases. Even so, this can be a late occurrence. In this study, 5 and 10 year metastatic control rates are 82% and 63%, respectively. The median time to distant metastasis is 2.7 years; however, metastasis can occur as late as greater than 12 years after diagnosis. This demonstrates the need for long-term surveillance of patients with adenoid cystic carcinoma. Given the propensity for these patients to develop distant metastases many years after initial diagnosis, ultimate survival remains guarded for most patients.

Because local and metastatic control is often achieved initially, patients with adenoid cystic carcinoma of the major salivary glands treated with surgery and postoperative radiation also experience high overall likelihood of survival. The 5 and 10 year overall survival for patients in this series is 85% and 69%, respectively. These compare favorably with other reports in the literature.[3,4,6,10]

The majority of the tumors (64%) in this study originated in the parotid gland rather than in the submandibular or sublingual gland. Some reported populations also find that the parotid is the most frequent major salivary gland of origin.[3] Yet other reports find adenoid cystic carcinoma of the major salivary glands to more frequently originate in the submandibular and sublingual glands.[2,10,13] Taken together, it appears that the most frequent gland of origin varies among different patient populations.

It is often said that tumors of the parotid are more likely to be benign than malignant, and with decreasing size of salivary gland of origin, tumors are more likely to be malignant than benign. In this study, the major salivary gland of origin did not statistically correlate with outcome. It may indeed be that adenoid cystic carcinoma behaves similarly among major salivary gland of origin or that the population size was not sufficiently large enough to demonstrate a statistically significant difference between the major salivary glands of origin.

Many attempts have been made to correlate patient characteristics or pathologic features with long-term prognosis. Inconsistently throughout the published literature, T stage, histologic features such as solid subtype, perineural invasion (both microscopic and clinical), and margin status have been correlated with prognosis. Which, if any, of these disease characteristics correlates with improved local or distant control remains controversial because none are clearly or consistently correlated with outcome. For example, some authors have found that perineural or neural invasion of a clinically named nerve portends a worse prognosis;[2,3,10] however, others have found that perineural involvement does not impact outcome.[5] Some reports suggest that tumor size and stage correlate with control,[3,10] whereas others have not found a significant difference.[4,5,8] Similar differences are noted when evaluating margin status.[2,5,10]

In our study, analysis of age, sex, stage, gland of origin, margin status, and perineural invasion did not demonstrate a statistically significant association with survival. This is likely caused by three factors. First, because adenoid cystic carcinoma is an uncommon tumor of the head and neck, it is difficult for a single institution to cull a patient population size large enough to demonstrate statistical significance in outcomes. Second, the analysis of outcomes for adenoid cystic carcinoma requires long-term follow-up to track local and distant recurrences long after initial diagnosis. The requisite length of follow-up is challenging to obtain in retrospective studies. Finally, direct comparison of this study with others is limited because other published studies group together other histologic subtypes, major and minor salivary glands, and combinations of treatment modalities.

The challenge in investigating the relationship between various disease characteristics and survival may reflect the nature of this disease as both rare and with long-term survival. It is difficult to obtain large patient populations for statistical analysis and is challenging to maintain long-term follow-up to explore survival. These questions may be better addressed with a larger multicenter study with persistent long-term follow-up to better analyze disease characteristics and their association with disease outcome.

CONCLUSION

Patient characteristics and pathologic features of adenoid cystic carcinoma of the major salivary glands treated with surgery and postoperative radiation therapy were studied. Overall, patients have relatively long overall survival but are at risk for failure, especially from distant metastases, in the long term. Larger studies with longer follow-up may be needed to correlate disease characteristics with outcome.

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