Adenoid cystic carcinoma of the skull base: results with an aggressive multidisciplinary approach

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OBJECTIVE Adenoid cystic carcinoma (ACC) is a locally aggressive tumor of salivary gland origin. Little data exist to guide treatment when this tumor extends to involve the structures of the skull base.

METHODS Fifty-one patients with a diagnosis of ACC affecting the skull base were identified from a prospective database at MD Anderson Cancer Center (from 1992 to 2010).

RESULTS Median follow-up for study patients was 6.75 years. The 5- and 10-year overall survival (OS) rates were 78% and 50%, respectively. Sixty-six percent of patients had progression of their disease. The 5- and 10-year progression-free survival (PFS) rates were 46.7% and 21.0%, respectively. Gross-total resection was achieved in 75% of patients, with 49% having microscopically negative margins at the time of first operation. On univariate analysis, resections with microscopically negative margins were associated with a significant OS advantage (20.1 ± 3.3 years) compared with resections that left residual disease, even if microscopic (10.3 ± 1.6 years, $p = 0.035$). In patients who underwent reoperation, the effect persisted, with improved OS in those with negative margins (21.4 ± 0.0 vs 16.7 ± 4.0 years, $p = 0.06$). The use of adjuvant radiotherapy was associated with an OS advantage (16.2 ± 2.5 vs 5.5 ± 2.2 years, $p = 0.03$) at initial diagnosis and improved PFS (7.8 ± 1.0 vs 2.1 ± 0.62 years, $p = 0.005$), whereas repeat irradiation provided no benefit. The use of adjuvant chemotherapy at diagnosis or at recurrence was not associated with any significant advantage. Multivariate analysis revealed margin-negative resection at initial operation and at recurrence retained OS significance, even after controlling for age, radiation therapy, and T stage.

CONCLUSIONS ACC of the skull base is best treated with a multidisciplinary approach aimed at maximal, safe resection. Adjuvant radiotherapy should be offered, whereas chemotherapy does not confer benefit.

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KEY WORDS adenoid cystic carcinoma; radiation; skull base; bifrontal craniotomy; lateral rhinotomy; endonasal endoscopy; neuro-oncology; oncology

ADENOID cystic carcinoma (ACC) is a locally aggressive salivary gland malignancy prone to perineural invasion and metastasis. Local recurrences often involve the skull base, whereas distant metastases most frequently involve the lung, bones, and liver.^{3,4,27,43,45} Standard therapy for this malignancy has most commonly included a strategy of local resection followed by adjuvant radiation therapy.^{6,13,16,17,23,24,28,30,35,38,39,43,46,47,52} Chemotherapy using agents such as carboplatinum and paclitaxel has been used, but with limited results.^{2,11,12,15,26,27,36,41,44,48–50}

ACC can arise in any salivary gland, both major and

minor. Consequently, these tumors can be located in the tongue, trachea, palate, larynx, and paranasal sinuses.²⁷ Tumors in the sinonasal cavity can remain undetected for long periods of time with minimal symptoms. Only after sufficient soft-tissue involvement, bone destruction, or cranial nerve involvement does the malignancy become manifest. Therefore, a strategy of maximal resection with minimal morbidity often presents a substantial therapeutic challenge given the complex anatomy of lesions that involve the paranasal sinuses and extend intracranially into the anterior or middle fossa.

ABBREVIATIONS ACC = adenoid cystic carcinoma; EGFR = epidermal growth factor receptor; ICA = internal carotid artery; OS = overall survival; PFS = progression-free survival; VEGF = vascular endothelial growth factor.

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In this study, we report the largest experience to date of patients with ACC involving the skull base wherein an aggressive, multidisciplinary approach was undertaken.

Methods

From 1992 to 2010, 51 consecutive patients (27 males, 24 females) with a pathologically confirmed diagnosis of ACC involving the skull base were identified from a prospectively maintained database at the MD Anderson Cancer Center (Table 1). Patients were seen in a multidisciplinary setting involving neurological surgery, head and neck surgery, plastic surgery, ophthalmology, medical oncology, and radiation oncology. Thirty-two percent of patients had at least 2 operative interventions for their tumor, and 65% had their first operation and received the entirety of their care at MD Anderson Cancer Center. The remaining patients had their first operation elsewhere and underwent their second operation and the remainder of their care at MD Anderson Cancer Center.

Data Analysis

Data analysis was performed via standard statistical software (SPSS, IBM Inc.) using the Kaplan and Cox regression methods.^{10,32} Multivariate analysis was performed, but was limited given the sample size.

TABLE 1. Characteristics of 51 patients with ACC*

Characteristic	Value
Sex	
Male	27 (53%)
Female	24 (47%)
Age at diagnosis, yrs*	48.1 ± 1.83
Average follow-up, yrs*	8.2 ± 0.91
Progression of disease	66.7%
Average time to progression, yrs*	4.4 ± 0.53
Adjuvant chemotherapy at diagnosis	13.7%
Adjuvant radiotherapy at diagnosis	88.3%
Adjuvant chemotherapy at recurrence	30.1 %
Adjuvant radiotherapy at recurrence	62.5%
Complete resection (>90%) at initial op	75.0%
Negative margins at initial op	48.9%
Complete resection at recurrence	70%
Negative margins at recurrence	47.3%
Persistent complication rate at initial op	2.7%
Pts who underwent ≥2 resections	32%
Pts requiring free myocutaneous flap	39.2%
Pts with metastatic disease	43.0%
Average time to develop metastatic disease, yrs*	4.4 ± 0.67
Cavernous sinus involvement	46%
Perineural invasion	47.0%
T stage at diagnosis	
T2	20%
T4b	80%

Pts = patients.

* Data are presented as ± SEM.

Radiation

Adjuvant radiotherapy was given to the vast majority of patients following the initial operation (88%). In those cases, external beam radiotherapy with a dose of 6000 cGy was most commonly used, with boosts (6600 cGy) given to at-risk areas.^{8,22,39} Gamma Knife stereotactic radiosurgery (n = 11) was most commonly used for small residual disease or for limited new disease (22%).

Operative Considerations

The primary goal of surgery was to achieve a margin-negative total resection of the tumor without subjecting the patient to unreasonable potential morbidity (i.e., carotid injury, need for bypass, stroke, orocutaneous fistulas, and malocclusions). In patients with subdural invasion, piecemeal resection was unavoidable but has been previously shown not to negatively influence outcomes in skull-base malignancies.¹⁷ More recently, where appropriate, patients have also been offered endoscopic approaches, with similar oncological results.²⁸ This strategy has been applied to the 3 most common tumoral locations as follows.

Primary Orbit (Lacrimal Gland)

In these patients, tumors involved the orbital contents and bone, with or without involvement of the superior orbital fissure. Treatment consisted of frontotemporal craniotomy with orbitectomy. Where possible, the superior orbital fissure is transected at a point with negative margins.¹⁶ An extradural, extracavernous dissection allows for the transection of the superior orbital fissure just anterior to the anterior loop of the cavernous internal carotid artery (ICA).

Primary Anterior Cranial Base/Sinonasal Cavity

In these patients, tumors involved the sinonasal cavity and extended into the anterior cranial base. Surgical approaches have included the benchmark bifrontal craniotomy/transfacial approach; purely transcranial, transfacial, or endoscopic approaches; and transcranial approaches combined with endoscopic resection of the sinonasal component of the tumor.

Primary Maxillary/Infratemporal/Pterygopalatine Fossa Tumors

In these patients, the epicenter of the tumor typically originates in the maxilla/palate and involves extensive soft-tissue and bone disruption with tumor extending intracranially via perineural extension through the maxillary, mandibular, or vidian nerves. Additionally, tumors might extend intracranially via orbital involvement with compromise of the superior orbital fissure, or through the infratemporal fossa with extension into the middle cranial base. Approaches consisted of open maxillectomy with or without craniotomy, depending on the tumor extent. If the soft-tissue and bony disease of the skull base could be safely resected without a craniotomy, a single transfacial approach was preferred. This was extended intracranially to resect perineural extensions of tumor along the superior orbital fissure (in combination with orbitectomy), maxillary nerve, mandibular nerve, or vidian nerve by removing the anteromedial wall of the middle cranial fossa.¹³

Limited anterolateral cavernous sinus involvement was resected, but cavernous sinus resection or ICA sacrifice was not performed. There were no planned or unplanned carotid bypass procedures.

Results

Patient characteristics and operative outcomes are displayed in Tables 1 and 2. The mean follow-up for study patients was 8.2 years (median 6.75 years). The average overall survival (OS) and progression-free survival (PFS) were 15.6 years (95% CI 10.8–20.3) and 7.3 years (95% CI 5.6–8.9). The 5- and 10-year overall survival (OS) rates were 78% (95% CI 72–84) and 50% (95% CI 40–60), respectively. Sixty-six percent of patients had progression of their disease, with mean time to progression of 4.4 ± 0.53 years. The 5- and 10-year PFS rates were 46.7% and 21.0%, respectively. Gross-total resection was achieved in 75% of patients, with 49% having microscopically negative margins at time of first operation. The 2- and 5-year local control rates were 86% and 82% (of those who survived 5 years), respectively.

On univariate analysis, resections with negative margins were associated with a significant OS advantage (20.1 ± 3.3 years) compared with resections that left residual disease, even if microscopic (10.3 ± 1.6 years, $p = 0.035$) (Fig. 1). In patients who underwent reoperation, the effect persisted, with improved OS in those with negative margins (21.4 ± 0.0 vs 16.7 ± 4.0 years, $p = 0.06$). The use of adjuvant radiotherapy was associated with an OS advantage (16.2 ± 2.5 vs 5.5 ± 2.2 years, $p = 0.03$) at initial diagnosis and improved PFS (7.8 ± 1.0 vs 2.1 ± 0.62 years, $p = 0.005$), but had no impact when used at time of recurrence. Of those patients who underwent stereotactic radiosurgery, 73% demonstrated local control for treated areas. The use of adjuvant chemotherapy at diagnosis or at recurrence was not associated with any significant advantage. The presence of perineural invasion imparted a significant OS disadvantage of nearly 50%. There was no perioperative mortality. The temporary complication rate (within 60 days) was 14.8% and included temporary postoperative respiratory failure ($n = 2$), neck hematoma requiring evacuation ($n = 1$), epidural hematoma ($n = 2$), CSF leak requiring lumbar drain treatment ($n = 2$), and infection ($n = 6$). The persistent complication rate was 2.7% and included enophthalmos ($n = 1$) and malocclusion of mandible ($n = 1$). Forty-three percent of patients developed metastatic disease. Of those patients, 60% died an average of 2.2 years after the appearance of metastasis, while the remainder survived with stable disease with an average follow-up of 7.7 ± 1.54 years. The average number of operative interventions performed at the primary site of disease was 1.41 ± 0.12 .

In multivariate analysis, margin-negative resection at initial operation and at recurrence retained OS significance, even after controlling for age, radiation therapy, and T stage.

Discussion

Adenoid cystic carcinoma is an aggressive salivary gland tumor known for local and lymphovascular inva-

TABLE 2. Factors influencing OS in 51 patients with ACC*

Variable	OS Values (yrs)	p Value
Margins at initial op		0.035
Negative	20.1 ± 3.3	
Positive	10.3 ± 1.6	
HR	2.8	
95% CI	1.03–8.0	
Margins at 2nd op		0.06†
Negative	21.4 ± 0.0	
Positive	16.7 ± 4.0	
HR	6.7	
95% CI	0.9–50	
Adjuvant radiation after 1st op		0.03
Yes	16.2 ± 2.5	
No	5.5 ± 2.2	
HR	3.4	
95% CI	1.1–10.5	
Adjuvant radiation after 2nd op		0.76
Yes	16.2 ± 4.1	
No	13.1 ± 1.9	
HR	1.2	
95% CI	0.43–43.2	
Adjuvant chemo at 1st op		0.14
Yes	7.3 ± 2.1	
No	16.3 ± 2.6	
HR	0.44	
95% CI	0.14–1.3	
Adjuvant chemo at 2nd op		0.18
Yes	7.1 ± 1.8	
No	16.1 ± 2.7	
HR	0.47	
95% CI	0.16–1.43	
Up-front radiation therapy w/o op		0.07†
Yes	6.6 ± 1.5	
No	16.6 ± 2.6	
HR	2.9	
95% CI	0.84–10.2	
Presence of metastatic disease		0.05
Yes	10.3 ± 2.0	
No	20.7 ± 3.9	
HR	0.42	
95% CI	0.17–1.0	
Cavernous sinus invasion		0.16
Yes	11.44 ± 20.2	
No	20.2 ± 3.9	
HR	0.53	
95% CI	0.22–1.3	
Perineural invasion		0.01
Yes	9.2 ± 1.5	
No	20.7 ± 3.3	
HR	0.27	
95% CI	0.09–0.75	

Chemo = chemotherapy; NS = not significant.

* Data are presented as $\pm$ SEM.

† NS but strong trend.

FIG. 1. Kaplan-Meier curve demonstrating improved OS for patients with negative margins ($p = 0.035$). Cum = cumulative. Figure is available in color online only.

sion, perineural extension, and association with delayed metastases.^{19,24,29,33} Histologically, these tumors are subclassified into 3 categories: tubular, cribriform, and solid. However, sharp demarcation among these categories is difficult because different regions of a single tumor may have a different preponderance of one category versus another.^{5,24,53,54} Molecularly, epidermal growth factor receptor (EGFR), c-kit, and vascular endothelial growth factor (VEGF) have been associated with ACC, although a recent study found no correlation between EGFR, c-kit, and VEGF with respect to prognosis or recurrence.³⁴

Here we report the largest and longitudinally most complete series (8.2 years mean follow-up) to date regarding ACC of the skull base. We have described 3 patterns of skull-base presentation with respect to the orbit, the anterior cranial base, and the lateral cranial base, with the maxilla as the epicenter. Of note, the location of the tumor's epicenter was not associated with differing survival, implying that a maximal resection strategy is applied equally regardless of tumor location (Fig. 2). A focus on the skull base is important because ACC that traverses the skull base by erosive disease or perineural extension is known to negatively influence oncological outcomes.

Our 5- and 10-year OS rates were 78% and 50%, respectively, with an average OS of the study population of 15.6 ± 2.4 years and an average PFS of 7.3 ± 0.85 years. This is significantly better than in previously published smaller series, where focus on the skull base was inconsistent (OS range 4–8 yrs).^{9,23,24,42,51,53} Moreover, the 5-year local control rate of 82% approaches the rates (94%) seen in ACC not involving the skull base.³⁹ Our results indicate that 2 factors may influence a potentially dramatic improvement in OS. These include resections with negative microscopic margins (including exploration and resection of involved cranial nerves¹³) and the use of adjuvant radiotherapy, which demonstrated statistical significance even in multivariate analysis.³⁸ Adjuvant radiation also seemed to triple PFS. On the other hand, the use of primary radiation therapy without surgery resulted in significant survival

FIG. 2. Location of tumor epicenter did not alter the OS of study patients ($p = 0.74$). Figure is available in color online only.

al disadvantage. Of note, margin-negative resections did not significantly alter time to progression (Table 3). This probably reflects the variability in manner of progression (local vs distant metastasis). This comports with our data demonstrating mean time to progression and mean time to metastatic disease in relevant patients to be similar at 4.4 years. That said, the mean time to progression among those who progressed in our study was significantly improved

TABLE 3. Factors influencing time to progression in 51 patients with ACC*

Factor	Time to Progression (yrs)	p Value
Margins		0.99
Negative	7.3 ± 1.2	
Positive	7.4 ± 1.2	
HR	0.98	
95% CI	0.5–1.99	
Adjuvant radiation at 1st op		0.005
Yes	7.8 ± 1.0	
No	2.1 ± 0.62	
HR	4.4	
95% CI	1.6–12.0	
Adjuvant chemo at 1st op		0.52
Yes	5.3 ± 2.0	
No	7.5 ± 0.90	
HR	1.4	
95% CI	0.53–3.66	
Cavernous sinus invasion		0.40
Yes	6.4 ± 1.1	
No	8.0 ± 1.2	
HR	1.3	
95% CI	0.69–2.6	
Perineural invasion		0.03
Yes	5.2 ± 0.90	
No	9.4 ± 1.3	
HR	0.46	
95% CI	0.23–0.93	

* Data are presented as $\pm$ SEM.

compared with previous literature, where mean survivals were approximately an average of 2 years.^{25,27,39} Of note, repeat radiation given at time of recurrence and the use of chemotherapy were not associated with improved OS or time to progression in our series. Furthermore, stereotactic radiosurgery provided local control in > 70% of cases. In addition, we confirmed previous data showing that chemotherapy does not alter outcome in patients with ACC.³⁸ Finally, the presence of perineural invasion was a significant, negative prognostic factor; its presence significantly impacted survival by > 50%.

These improvements in oncological outcomes for patients with ACC involving skull base extension are a result of incremental progress over the last 4 decades. These improvements are attributable to more effective craniofacial resection strategies involving multidisciplinary teams, improved reconstruction options with vascularized flaps, recognition that piecemeal resections with negative margins afford oncological results similar to en bloc resections, and more effective adjuvant therapy including conformal radiation therapy.^{7,17,21,28,40} Endoscopic approaches have gained traction in recent years. Although further data are needed, it appears that oncological outcomes do not appreciably suffer after endoscopic resections as compared with traditional, open craniofacial resections as long as oncological principles are upheld.²⁸ That said, this study describes patients who predominately received open craniofacial approaches given the advanced T stage of their disease (75% of patients receiving endoscopic treatment required conversion to open surgeries). Another key advance in the treatment of ACC has been the recognition of perineural extension as a harbinger of poor outcome.^{7,13,16,18,20,23,24,31} As such, our strategy has been to maximally resect all perineural disease until negative margins are obtained or the risk of neurological complications (via carotid injury) precludes further resection.^{13,46,47} Finally, the importance of bony resection cannot be underestimated, as ACC involving the lacrimal gland is best treated with orbitectomy rather than local resection.¹⁶ Our study confirmed the relative inefficacy of chemotherapy regimens in altering disease progression. It is worth noting that chemotherapy was generally deployed when bulky disease remained after surgery, or in circumstances of disease progression despite previous treatments of maximal cytoreductive surgery and conformal radiotherapy. Regardless, in no instance did chemotherapy halt disease progression. It should be noted, however, that chemotherapy can offer symptomatic relief without objective tumor response.^{1,14,37}

Our surgical strategy resulted in no mortality and minimal lasting morbidity across > 70 procedures. Complications ranged from temporary postoperative respiratory failure, neck hematoma requiring evacuation, enophthalmos, to infection. There were no strokes or other vascular complications, reflecting our avoidance of aggressive manipulation or sacrifice of the ICA (18% in another small skull-base study²⁴). In fact, our average length of hospital stay was only 6.7 ± 0.80 days, which mostly reflects standard monitoring after free flap placement.

Our study limitations include its retrospective nature at a single institution. Moreover, the population reflects mostly patients with aggressive disease, although our re-

sults should apply across the spectrum of ACC. Although this study represents the largest skull-base experience in the literature, the study population is still relatively small at 51 patients, preventing additional meaningful multivariate analysis. Additionally, quality-of-life measures were not performed in this study but are important in patients who undergo aggressive surgery, particularly for those procedures involving significant cosmetic deformity.³⁵ It has been previously noted that the pathological subtypes of cribriform, solid, and tubular components can influence outcome. However, the vast majority of the patients in our series were mixed pathologically without a standardized methodology of quantifying the solid component of tumor, thus rendering statistical analysis unreliable.³⁸ Finally, the availability of molecular status on these tumors was inconsistent, making inferences regarding molecular influence impossible.

Conclusions

Adenoid cystic carcinoma is an aggressive disease, with added complexity when involving the skull base. A strategy of maximal resection with adjuvant radiotherapy should be used to optimize survival. Chemotherapy does not appear to confer benefit.

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