Adenoid Cystic Carcinoma of the Skull Base: Response to Radiation Therapy and Outcomes in a Retrospective Case Series

Shekhar K. Gadkaree¹ Anuraag S. Parikh¹ Alejandro I. Rodarte¹ Ashton Lehmann¹ Stacey T. Gray^{1,2} Derrick T. Lin^{1,2}

¹ Department of Otolaryngology Head and Neck Surgery, Harvard Medical School, Boston, Massachusetts, United States

² Division of Head and Neck Surgery, Department of Otolaryngology Head and Neck Surgery, Harvard Medical School, Massachusetts Eye and Ear, Boston, Massachusetts, United States

Address for correspondence Shekhar K. Gadkaree, MD, Department of Otolaryngology Head and Neck Surgery, Harvard Medical School, Massachusetts Eye and Ear, 243 Charles Street, Boston, MA 02114, United States (e-mail: shekhar_gadkaree@meei.harvard.edu).

J Neurol Surg B 2020;81:505–510.

Abstract

Objectives The main purpose of this article is to examine a single-center cohort of patients with nasopharyngeal adenoid cystic carcinoma (ACC) for pathologic features, skull base invasion, overall survival, and disease-free survival, with a focus on response to proton beam radiation therapy.

Design, Setting, and Participants Single-center institutional cancer registry was used to retrospectively identify and analyze outcomes for 12 patients treated for ACC of the nasopharynx from 2000 to 2016.

Main Outcomes and Measures Primary outcomes included 5-year overall survival and locoregional control. Statistical analysis was performed using STATA 12.0 (STATA Corp, College Station, Texas, United States). Spearman's rank order correlation was used for ordinal, monotonic variables with *p*-values <0.05 considered statistically significant. Survival analysis was performed by Kaplan–Meier method; comparison between groups was performed using log-rank test.

Results Twelve patients with ACC of the nasopharynx were included. All patients presented with advanced disease and were treated with primary radiation therapy, typically proton beam therapy. Only two underwent a surgical attempt at resection. A majority of cases had a cribriform growth pattern. The 5-year survival was 75% and rate of locoregional control rate at 5 years was 50%, comparable to other ACC cohort studies that included earlier stage tumors in various subsites that were surgically resected.

Conclusions Although ACC is traditionally noted to be radioresistant, ACC of the nasopharynx was responsive to radiotherapy in our cohort, despite advanced stage and skull base invasion. Reasons for this improved survival are unclear and suggest the need for further pathologic and genetic characterization of nasopharyngeal ACC.

Keywords

- ▶ nasopharyngeal malignancy
- ▶ adenoid cystic carcinoma
- ▶ skull base
- ▶ radiation therapy
- ▶ outcomes

Introduction

Adenoid cystic carcinoma (ACC) is rare, accounting for less than 2 to 4% of nasopharyngeal carcinoma and of ~4% of head

and neck ACC.¹ Typically, ACCs are known for slow growth rates, high rates of distant metastasis, and high likelihood of perineural spread. Nasopharyngeal ACC (NACC) has been previously described with a 5 to 20% incidence of skull

received

April 4, 2019

accepted after revision

July 28, 2019

published online

September 18, 2019

© 2020 Georg Thieme Verlag KG
Stuttgart · New York

DOI <https://doi.org/10.1055/s-0039-1696706>.
ISSN 2193-6331.

base invasion.² In the nasopharynx specifically, these tumors typically have a low rate of lymphatic metastases, slow growth, and a relatively high rate of local invasive spread.³

Treatment for NACC, given the location, is limited to either radical surgical resection or, more commonly, radiation therapy.^{3–5} Traditionally, ACC has been presumed to be radioresistant in previous studies, but NACC, given its challenging location, has been treated primarily by radiation.^{6–9} Given the rarity of these tumors, few studies have examined the treatment and survival of high-grade invasive NACC of the skull base. However, skull base involvement, tumor recurrence, perineural invasion, bone invasion, and lymphovascular invasion have been shown to lead to increased incidence of recurrence and decreased survival.¹⁰

Characterizing survival outcomes can be difficult in these tumors due to their indolent course, low incidence, and variable staging at the time of presentation, with the average onset of symptoms estimated at 3 to 5 years after suspected presence of disease.^{3,7} Particularly for NACC at the skull base, tumors present following extensive invasion of surrounding structures due to their typical asymptomatic initial presentation.

Methods

Patient Selection and Recorded Variables

Institutional Review Board approval was obtained prior to beginning this study. The institutional cancer registry was used to retrospectively identify and analyze outcomes for twelve patients treated for ACC of the nasopharynx and skull base from 2000 to 2016. Patient demographics were recorded. Location of tumor, treatment modalities, pathology report findings including tumor subtype, histology, staging, perineural and lymphovascular invasion, and invasion into surrounding structures were recorded. Type of radiation, chemotherapy, overall survival, locoregional recurrence, and distant metastasis were all recorded.

Primary Outcomes and Statistical Analysis

Primary outcomes included 5-year overall survival and locoregional control. Spearman’s rank order correlation was used for ordinal, monotonic variables with *p*-values <0.05 considered statistically significant. Survival analysis was performed by Kaplan–Meier method. All statistical analysis was performed using STATA 15.0. (STATACorp, College Station, Texas, United States). Chi-squared tests were used for normally distributed categorical variables. Analysis of variance (ANOVA) tests were used to compare parametric continuous variables and Kruskal–Wallis one-way ANOVA was used for nonparametric variables. Kaplan–Meier curves were used to model overall survival and locoregional recurrence. *p*-values of less than 0.05 were considered statistically significant.

Results

Twelve patients with NACC of the skull base were included. Study characteristics are shown in ►Table 1. Ten of the twelve patients presented with advanced stage (T3 or T4)

Table 1 Clinical characteristics of study population (n = 12)

Gender, n (%)	
Male	3 (25)
Female	9 (75)
Age	
> 60	5 (42)
< 60	7 (58)
Skull base invasion, n (%)	
Yes	12 (100)
No	0 (0)
Cavernous sinus involvement, n (%)	
Yes	6 (50)
No	6 (50)
Predominant pathologic subtype, n (%)	
Solid	1 (8)
Tubular	2 (17)
Cribriform	2 (17)
Mixed/indeterminate	7 (58)
Treatment, n (%)	
Radiation alone	4 (33)
Radiation + chemotherapy	6 (50)
Chemotherapy + radiation + surgery	2 (17)
Stage	
Tx, T1, T2	2 (17)
T3, T4	10 (83)

disease (83%) and all were treated with radiation therapy, typically proton beam therapy. ►Table 2 shows the treatment courses for each patient, histology, and presence of treatment toxicity. ►Fig. 1 demonstrates an example of advanced stage NACC included in the study population. Four patients (33%) were treated with radiation alone, whereas six patients (50%) were treated with radiation and chemotherapy. Only two (17%) received surgery followed by radiation therapy. Three patients had perineural invasion; none had lymphovascular invasion; and two had metastases to the neck. Both patients with neck metastases were managed with radiation alone without surgical neck dissection. Of those with perineural invasion, one died and the other two others survived at 5 years with no evidence of locoregional recurrence. Of those with surgery, one had positive margins but did not recur following radiation and the other had a recurrence following radiation and died, though initial margin status following surgery was unavailable. The 3-year and 5-year survival was 83 and 75%, respectively (►Fig. 2), while the 3-year and 5-year locoregional control rate was 83 and 50%, respectively (►Fig. 3). Of the five patients followed for 10 or more years, two (40%) died. Immunohistochemical staining information was available for five patients in the study.

Table 2 Treatment algorithms for 12 patients with adenoid cystic carcinoma of the skull base

Patient number	Presenting stage (advanced or early)	Initial therapy	Secondary treatment	Neck metastasis	Histology	Molecular markers	Type of radiation	Radiation therapy dose	Fractions	Chemotherapy	Treatment toxicity	5 Years survival
1	Early	Radiation		No	Tubular	CK17 (CD117) positive	Proton	76 Gy	38	No	None	Yes
2	Advanced	Radiation		No	Mixed		Proton	76 Gy	44	No	None	No
3	Advanced	Radiation		Yes	Solid		Unspecified	50 Gy	Unspecified	No	None	No
4	Advanced	Surgery	Radiation + chemotherapy	No	Mixed	Keratin, epithelial membrane antigen	Proton	70 Gy	35	Carboplatin	None	Yes
5	Early	Surgery	Radiation + chemotherapy	No	Tubular		Proton	66 Gy	33	No	None	Yes
6	Advanced	Radiation + chemotherapy		Yes	Mixed		Proton	76 Gy	38	Cisplatin	Osteoradionecrosis of mastoid	Yes
7	Advanced	Radiation + chemotherapy		No	Cribiform		Proton	70 Gy	35	Carboplatin, taxol	None	Yes
8	Advanced	Radiation + chemotherapy		No	Mixed	Keratin (AE1/AE3/ CAM5.2), CD117 (c-kit), S100, neuron-specific enolase, p53, CK7	Proton	70 Gy	35	Carboplatin, taxol	Spinal fractures from radiation	Yes
9	Advanced	Radiation + chemotherapy		No	Cribiform	p63, CEA, AE1/AE3, Vimentin, CD117, MSA, S100	Proton	70 Gy	35	Carboplatin, taxol	None	Yes
10	Advanced	Radiation + chemotherapy		No	Mixed	CK7, p40, p63, CD117	Proton	76 Gy	38	Carboplatin, taxol	None	Yes
11	Advanced	Radiation		No	Mixed		Unspecified	Unspecified	Unspecified	No	None	Yes
12	Advanced	Radiation		No	Mixed		IMRT	72 Gy	47	No	None	Yes

Abbreviations: CEA, carcinoembryonic antigen; IMRT, intensity-modulated radiation therapy; MSA, muscle-specific actin.

Fig. 1 Initial imaging of T4 nasopharyngeal adenoid cystic carcinoma with skull base invasion treated with partial resection, proton beam therapy, and carboplatin, leading to locoregional control and survival at 5 years post-treatment.

Fig. 2 Nasopharyngeal adenoid cystic carcinoma locoregional recurrence-free survival curve.

Discussion

Our data suggest that advanced NACC with skull base involvement treated primarily with radiation therapy may have a high 5-year survival rate, suggesting a radio-responsiveness that is not associated with ACC of other subsites.^{7–9,11} NACC has previously been hypothesized to have unique biologic behavior with a propensity to spread along the orbital cavity or cranial nerves and avoid cervical lymph nodes.^{1,3,5} There is an estimated prevalence of 30% of distant metastasis in NACC, though the spread specifically for NACC of the skull base has not been explored, and was lower in this study.⁵ There was a similar 5-year survival for NACC at the skull base as overall NACC (50–75%),^{1,3} despite advanced tumor stages, and involvement of the orbit, cavernous sinus, or palate for a majority of patients.

All patients received standard recommended radiation doses for NACC between 55 and 80 Gy.³

The radiosensitivity of NACC at the skull base is notable given that ACC overall is considered to be resistant to radiotherapy.^{1,8,9} Current treatment paradigms for nasopharyngeal ACC generally include initial surgical resection if the lesions are amenable.^{6,12,13} However, in this study, which focuses on NACC involving the skull base, the close proximity of critical structures makes surgical intervention much more morbid. Radiation therapy for skull base NACC currently is the primary modality of therapy with surgical therapy reserved for unique cases that are amenable despite skull base invasion. In this study, only two cases of skull base invasion were first treated surgically. Even in cases of ACC where the tumor is completely resected, there is a high rate

Fig. 3 Nasopharyngeal adenoid cystic carcinoma overall survival curve.

of distant metastasis; however, this study shows a decreased propensity for distant metastases with only one patient experiencing lung metastases.¹³ Survival and locoregional outcomes in NACC have been shown to be similar regardless of the aggressiveness of treatment modalities.^{6,13} Radiotherapy alone has shown reduction in tumor volume in greater than 90% of treated patients; however, surgery should still be offered when possible, as the rates of locoregional recurrence with radiation alone are relatively high.^{14,15} Of the two patients who underwent surgical resection and the patients who treated with radiation or chemotherapy and radiation alone, the rate of recurrence at 5 years was 50%.

Immunohistochemistry is valuable for diagnosis and several markers are currently used for staining to establish diagnosis.¹⁰ In the nasal cavity, for example, an entity of human papillomavirus (HPV)-associated carcinoma with ACC-like features has been recently described and shown to have favorable prognosis.^{16,17} If any of the cases in this study had a similar pathology, it could potentially explain the high survival rates seen in this study. With this in mind, adequate biopsy tissue for HPV testing is important in diagnosis, even if nonsurgical treatment is anticipated. MYB overexpression on immunohistochemical staining has been shown to be associated with cribriform-type architecture and an improved prognosis, again highlighting the importance of better characterizing these lesions and stratifying patients before treatment. In the limited sample size of those who did not survive in this study, solid type pathology was predominant. Given limited tissue available for most patients, neither HPV testing nor MYB staining was reported in any of the cases. Further staining and examining prognosis and response to radiation remain an area of future study, given the preliminary relationship between tumor biology and prognosis.

This study had several limitations. As a retrospective study, it was inherently limited in its ability to determine causation. The study was relatively small in sample size, due to the rarity of the disease and the specific inclusion criteria of NACC at the skull base. As with other studies that necessarily span several years, subtle advances in targeted radiation therapy and treatment modalities may have evolved throughout the study period resulting in altered survival, though the overall treatment modality NACC has remained fairly consistent throughout the last 20 years. Further examining tumor biology and cell markers for the variations in response to treatment was not able to be tested in this study but remained an area of future study.

Conclusion

ACC of the nasopharynx is responsive to radiation therapy with reasonably high survival rates despite high-grade, invasive tumors invading into skull base. Surgery can be useful in appropriately selected tumors, but locoregional recurrence rates at 5 years remain relatively high. Further studies examining tumor biology may be necessary to account for differential response rates to radiation therapy.

General Disclosures

The authors have not received financial assistance related to this manuscript.

Funding/supporting organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

These results of this study were presented at the North American Skull Base Society Annual Meeting in February, 2019 in Orlando, FL.

Conflict of Interest

None.

References

- 1 Afani L, Errihani H, Benchafai I, Lalami Y. [Nasopharyngeal adenoid cystic carcinoma, a rare but highly challenging disease with unmet therapeutic needs: a case-report and review of the literature]. *Cancer Radiother* 2016;20(05):400–404
- 2 Ryckman JM, Kusi Appiah A, Simone CB II, Verma V. Treatment approaches for nasopharyngeal adenoid cystic carcinoma. *Acta Oncol* 2018;57(07):995–1001
- 3 Liu T-R, Yang A-K, Guo X, et al. Adenoid cystic carcinoma of the nasopharynx: 27-year experience. *Laryngoscope* 2008;118(11):1981–1988
- 4 Spiro RH, Koss LG, Hajdu SI, Strong EW. Tumors of minor salivary origin. A clinicopathologic study of 492 cases. *Cancer* 1973;31(01):117–129
- 5 Shotton JC, Schmid S, Fisch U. The infratemporal fossa approach for adenoid cystic carcinoma of the skull base and nasopharynx. *Otolaryngol Clin North Am* 1991;24(06):1445–1464
- 6 Alleyne CH, Bakay RA, Costigan D, Thomas B, Joseph GJ. Intracranial adenoid cystic carcinoma: case report and review of the literature. *Surg Neurol* 1996;45(03):265–271
- 7 Cao C-N, Luo J-W, Xu G-Z, Gao L, Xu Z-G, Tang P-Z. Management of nasopharyngeal adenoid cystic carcinoma. *J Oral Maxillofac Surg* 2013;71(04):e203–e209
- 8 Zielke-Temme B, Wannenmacher M. Adenoid cystic carcinoma (cylindroma) in the head and neck. A clinical review of 82 cases. *Acta Radiol Oncol Radiat Phys Biol* 1978;17(05):401–413
- 9 Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million RR. Management of minor salivary gland carcinomas. *Int J Radiat Oncol Biol Phys* 1996;35(03):443–454
- 10 Liang Y-F, Kong B, Xiang W-Y, et al. Nasopharyngeal adenoid cystic carcinoma: a case report and review of the literature. *Int J Clin Exp Pathol* 2014;7(07):4516–4518
- 11 Khan AJ, DiGiovanna MP, Ross DA, et al. Adenoid cystic carcinoma: a retrospective clinical review. *Int J Cancer* 2001;96(03):149–158
- 12 Lee DJ, Smith RR, Spaziani JT, Rostock R, Holliday M, Moses H. Adenoid cystic carcinoma of the nasopharynx. Case reports and literature review. *Ann Otol Rhinol Laryngol* 1985;94(03):269–272
- 13 Gormley WB, Sekhar LN, Wright DC, et al. Management and long-term outcome of adenoid cystic carcinoma with intracranial extension: a neurosurgical perspective. *Neurosurgery* 1996;38(06):1105–1112, discussion 1112–1113
- 14 Soprani F, Armaroli V, Venturini A, Emiliani E, Casolino D. A rare case of adenoid cystic carcinoma of the nasopharynx manifesting as Horner's syndrome: discussion and review of the literature. *Acta Otorhinolaryngol Ital* 2007;27(04):216–219
- 15 Vikram B, Strong EW, Shah JP, Spiro RH. Radiation therapy in adenoid-cystic carcinoma. *Int J Radiat Oncol Biol Phys* 1984;10(02):221–223
- 16 Bishop JA, Ogawa T, Stelow EB, et al. Human papillomavirus-related carcinoma with adenoid cystic-like features: a peculiar variant of head and neck cancer restricted to the sinonasal tract. *Am J Surg Pathol* 2013;37(06):836–844
- 17 Chung AM, Sun DI, Jung ES, Lee YS. Human papillomavirus infection-associated adenoid cystic carcinoma of the hard palate. *J Pathol Transl Med* 2017;51(03):329–331