Adenoid Cystic Carcinoma of the Nasal Cavity and Paranasal Sinuses: A Meta-Analysis

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Abstract

Keywords

- adenoid cystic carcinoma
- paranasal sinuses
- skull base
- meta analysis
- survival

Objectives To identify independent predictors of outcome in patients with adenoid cystic carcinoma (ACC) of the paranasal sinuses and skull base.

Design Meta-analysis of the literature and data from the International ACC Study Group.

Setting University-affiliated medical center.

Participants The study group consisted of 520 patients, 99 of them from the international cohort. The median follow-up period was 60 months (range, 32 to 100 months).

Main Outcome Measures Overall survival (OS) and disease-specific survival (DSS).

Results The 5-year OS and DSS of the entire cohort were 62% and 67%, respectively. The local recurrence rate was 36.6%, and the regional recurrence rate was 7%. Distant

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metastasis, most commonly present in the lung, was recorded in 106 patients (29.1%). In the international cohort, positive margins and ACC of the sphenoid or ethmoidal sinuses were significant predictors of outcome ($p < 0.001$). Perineural invasion and adjuvant treatment (radiotherapy or chemoradiation) were not associated with prognosis.

Conclusion Tumor margin status and tumor site are associated with prognosis in ACC of the paranasal sinuses, whereas perineural invasion is not. Adjuvant treatment apparently has no impact on outcome.

Introduction

Adenoid cystic carcinoma (ACC) accounts for 3 to 5% of all head and neck malignancies.¹ It is characterized by an intermediate growth rate, low probability of lymphatic spread, and frequent lung metastases.² The overall survival (OS) rate of localized ACC that originates in the major salivary glands and minor oral cavity salivary glands are 93.9% and 92.4%, respectively, whereas survival rates for metastatic disease are 43.3% and 55.4%, respectively.¹ However, ACC of the paranasal sinuses and skull base represent a pathology with distinct clinical implications.³ Those tumors are typically diagnosed late, and their proximity to vital structures (e.g., dura, brain, orbit, and central nerves) makes adequate oncological resection less likely.⁴ Another characteristic of ACC of the paranasal sinuses is perineural spread, with an incidence of over 50%.³ Due to the high propensity of local invasion to adjacent vital anatomical structures (i.e., cranial nerves) and late diagnosis, ACC is associated with poor prognosis, intracranial extent, and positive surgical margins.⁵ The mainstay of treatment of ACC is surgery; adjuvant radiation therapy is reserved in case of positive margins or advanced stage.^{6–8}

Due to its rarity, there is some controversy over the clinical and histological factors that affect the survival of patients with ACC of the paranasal sinuses and skull base. Perineural invasion, efficacy of adjuvant treatment, and the site of origin were found to be significant prognostic factors by some authors, whereas others found that they had no impact on survival.^{6,9–11} Since most of the reports on ACC of the paranasal sinuses are based on small cohorts and on studies that also included tumors from other anatomical locations, information on predictors of outcomes in this specific population is sparse.

We performed a meta-analysis of the published pathologic and clinical data on ACC of the paranasal sinus and anterior skull base. Our aims were (1) to assess clinical and histological characteristics of this population, (2) to characterize the outcome of these patients, and (3) to identify independent predictors of outcome. Recognition of the biologic behavior of this tumor and the clinical predictors of survival may have implications for the treatment and prognosis of patients and may play a role in planning the extent of surgery and the surgical approach. To the best of our knowledge, this study represents the first meta-analysis of patients with ACC of the skull base and paranasal sinuses.

Materials and Methods

Meta-Analysis Search Strategy and Selection Criteria

During October 2012, we conducted a systematic electronic literature database search of PubMed, CINAHL, Cochrane Central Register of Clinical Trials, and Google from 1975 to 2012. The searches were conducted using the Medical Subject Heading (MeSH) terms (*adenoid cystic*) AND (*carcinoma* OR *cancer*) AND (*skull base* OR *paranasal sinuses* OR *sinonasal*) and limited to *human*. Reference lists of retrieved manuscripts were hand-searched for additional publications. Publications in a language other than English that could not be translated because of resource constraints were excluded. Two reviewers (M.A. and Z.G.) independently screened all available titles, as well as abstracts that were identified by the electronic search strategies. Articles were rejected at the initial screening if their titles or abstracts showed that they were clearly irrelevant. The full text of potentially relevant articles was reviewed to assess their suitability for inclusion in this meta-analysis. The study selection process is described in **Fig. 1**. According to the study design, the inclusion criteria were randomized controlled trials, prospective and retrospective cohorts, case-control study designs, case reports, and case series. Criteria for study population inclusion were histopathologic diagnosis of ACC involving the paranasal sinuses or the orbit, > 6 months follow-up or earlier death, and available outcome data, including survival or recurrence. The included studies are listed in **Table 1**. Two independent reviewers assessed both their quality and risk of bias of the included publications. They were not blinded to publication details, but measures were taken to obscure outcome assessment by using an identical abstraction form to record the collected data, thereby avoiding the description of incomplete outcome data, and to assess the risk of selective outcome reporting. The two authors independently checked each case, and all available specific data and end points were recorded for each cohort in the selected studies. Discrepancies between the two reviewers were resolved by discussion and consensus.

Patients

The International Study Group of the ACC cohort included 99 patients treated for ACC of the paranasal sinuses between 1985 and 2011 in nine cancer centers worldwide. The study was approved by the local institutional review board

Fig. 1 Flowchart of the study selection process. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.

committees of the participating centers. The patients ranged in age from 20 to 91 years (median 55 years) and included 44 males (44%). Their follow-up ranged from 2 to 240 months (median 41 months). All patients underwent primary sur-

gery, with or without adjuvant radiotherapy or chemoradiation. The tumors were evaluated by a certified head and neck pathologist in each center according to current guidelines for the histopathological assessment of head and neck cancer

Table 1 Studies Included in the Meta-analysis

Author	Number of patients	Stage (T1–2/T3–4)	Treatment		
			Surgery	Surgery followed by RT/ChRT	Primary RT/ChRT
Lin et al. 2012 ²⁰	25	6/19	21	0	4
Strick et al. 2004 ²⁴	7	0/7	0	7	0
Bhattacharyya 2003 ¹⁸	64	n/a	n/a	n/a	n/a
da Cruz Perez et al. 2006 ²¹	18	2/16	3	8	7
Douglas et al. 2000 ²²	30	n/a	0	32	0
Pitman et al. 1999 ⁸	35	0/35	0	35	0
Qureshi et al. 2006 ²⁵	8	2/6	n/a	n/a	n/a
Resto et al. 2008 ²⁶	20	n/a	0	11	9
Vedrine et al. 2009 ¹⁵	4	0/4	0	3	1
Lupinetti et al. 2007 ⁶	105	26/79	11	60	34
Schramm et al. 2001 ²⁷	11	0/11	2	9	0
Rhee et al. 2006 ¹⁹	35	10/25	3	24	8
Doerr et al. 2003 ²⁸	14	n/a	3	10	1
Pommier et al. 2006 ⁷	23	n/a	0	12	11
Kim et al. 1999 ¹¹	22	4/18	3	10	9
Amit et al.	99	31/68	28	71	0
Total	520	81/288	74	282	84

Abbreviations: ChRT, chemoradiation therapy; n/a, not available; RT, radiotherapy.

carcinoma.¹² Of the 99 patients, 60 (60%) died during follow-up, and 18 (18%) had distant metastases.

Statistical Analysis

Five-year OS, disease-specific survival (DSS), and disease-free survival (DFS) rates were calculated using the Kaplan-Meier method, and the difference in survival rate was assessed by the log rank test. OS was measured from the date of surgery to the date of death or last follow-up. The DSS for patients who died from causes other than ACC was established as the time of death. The variables that had prognostic potential were subjected to multivariate analyses with the Cox proportional hazards regression model. All analyses were performed on JMP 9 software (SAS Institute, Inc., Cary, North Carolina, USA) and confirmed by an independent statistician on an IBM SPSS Statistics package (IBM Corporation, Armonk, New York, USA). All *p* values were two-sided, and a *p* value of less than 0.05 was adopted as the threshold for significance. Variables used to stratify survival included age, gender, primary tumor site, tumor margin status, invasive features (i.e., invasion to adjacent structures or nerves) and treatment group (surgery alone versus surgery and radiation versus surgery and chemoradiation). The sixth edition of the tumor-node-metastasis staging system was used for tumor, nodal, and metastasis (TNM) staging.¹³ The meta-analysis was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁴

Results

Twenty-six relevant articles were reviewed, of which eight were excluded due to insufficient data or for not meeting the inclusion criteria (e.g., lack of essential data). Two publications that analyzed the same study population were excluded.^{3,15} One paper on ACC of the paranasal sinuses that focused on presenting an experimental treatment protocol (intra-arterial chemotherapy) was also excluded.¹⁶

The final study group consisted of 520 patients: 99 were enrolled in the international cohort and 421 were extracted from 15 published studies.^{6–8,17–28} The median age of the patients was 50 years (range, 38 to 55 years). The median follow-up period was 60 months (range, 32 to 100 months). The reason for a lower denominator being less than 520 is because details on an individual patient's demographics were not always available. Advanced stage (III–IV) disease at presentation was found in 288/369 (78%) patients. Perineural invasion was present in 214/392 (54.5%) patients, and positive tumor margins in 151/253 (59.6%). The maxillary sinus was the most commonly involved site (286/520, 54.7%), followed by the nasal cavity (57/520, 10.9%), nasopharynx (29/520, 5.5%), ethmoid sinus (22/520, 4.2%), and sphenoid sinus (16/520, 3%). The tumor epicenter was not specified in 110/520 (21%) cases.

To further characterize patterns of local and regional spread in patients with ACC of the paranasal sinuses and nasal cavity, we repeated the analysis in the 99 patients that were recruited from nine tertiary cancer centers that were enrolled in the ACC International Study Group. The database

Table 2 Demographics and Clinical Characteristics of Patients in the International Cohort

Variable		No. of patients	%
Median age, y	55 (20–91)	99	100
Gender	Male Female	44 55	44 55
Treatment	Surgery Surgery + RT/ChRT ChRT	28 47 24	28 47 24
Site	Maxillary sinus Nasal cavity Sphenoid/ ethmoid sinus Nasopharynx Unspecified	63 10 4 2 20	63 10 4 2 20
T classification	1–2 3–4	31 68	31 68
N classification	N0 N+	86 13	86 13
Perineural invasion	Present Absent	51 48	51 48
Surgical margins	Positive Negative	43 56	43 56
Follow-up (months)	Median (range)	41 (2–240)	100

Abbreviations: ChRT, chemoradiation therapy; RT, radiotherapy.

included detailed characteristics of the clinical, demographic, and pathological parameters of the patients, including 16 variables per patient. ▶Table 2 lists their clinical and pathological characteristics. Forty-one patients in this group (41%) underwent neck dissection and 13/99 (13%) had nodal metastases. In 26 patients, the radiological and clinical assessment suggested the existence of neck nodes metastases. Of these, 12 patients (46%) had pathological evidence of neck metastases. The accuracy of the clinical nodal staging procedure was 63%, similar to other studies on head and neck cancer.²⁹

Histopathological examination revealed that 81/99 patients (81%) had invasion to adjacent structures, including the orbit, dura, cavernous sinus, brain, muscles, or skin (▶Table 3). Perineural invasion was identified in 51/99 (51%) patients, and 43/99 (43%) had positive/close margins.

The 5-year OS and DSS of the entire 520-patient cohort were 62% (range, 25 to 81%) and 67% (range, 40 to 86%), respectively (▶Fig. 2). The OS and DSS of the international consortium subgroup (*n* = 99) was 64% and 69%, respectively. Local recurrence was found in 126/344 (36.6%) patients, whereas regional recurrence was infrequent (26/364, 7%). A total of 106 patients (29.1%) had distant metastasis, most commonly in the lung (82/106, 77%), liver (7%), and bone (6%). The 5-year DFS rate was 43% for the entire cohort and 53% for the international consortium (▶Fig. 2).

We next sought to identify predictors of outcome. As shown in ▶Fig. 3A, our meta-analysis revealed a significant

Table 3 Patterns of Invasion

Structure involved	n (%)
Nerve	51 (51)
Bone	28 (28)
Muscle	21 (21)
Orbital	3 (3)
Skin	2 (2)
Cavernous sinus	2 (2)
Brain	1 (1)
Dural	1 (1)

correlation between the origin of the tumor and the patient's OS and DSS ($p = 0.001$ and $p < 0.001$, respectively). The DSS rates for the nasal cavity and maxillary sinus ACC were 83% and 64%, respectively, whereas ethmoid or sphenoid sinus involvement resulted in a DSS of 25%, ($p < 0.001$, hazard ratio [HR] = 7.7, 95% confidence interval [CI] 1.7 to 23.5). The Kaplan-Meier analysis (►Fig. 3B) also revealed that perineural invasion was not associated with OS or DSS ($p = 0.3$ and $p = 0.37$, respectively). Patients with perineural invasion had a lower DFS rate than those without perineural invasion (35% versus 51%, respectively), but the difference did not reach a

level of significance ($p = 0.08$). In contrast, with an HR of 3.1 (95% CI 1.3 to 6.5), positive/close tumor margins were significantly more associated with a poor OS compared with negative tumor margins (69% versus 27%, respectively, $p = 0.04$, ►Fig. 3C). The results were similar for DSS (71% versus 30% for positive and negative tumor margins, respectively; $p = 0.03$). Local invasion was present in 160/520 (31%) patients, most commonly in the skull base (83/160, 51.8%) followed by bone (43/160, 26%), orbit (21/159, 13.7%), vasculature (8/160, 5%), and muscle (4/160, 2.5%). Our analysis revealed no association between outcome and skull base invasion ($p = 0.7$ for OS and $p = 0.32$ for DSS).

To determine whether there is any advantage for adjuvant therapy on outcome in this population, a Kaplan-Meier analysis was performed in three treatment groups ($n = 440$): surgery alone (74/440, 17%), surgery followed by radiotherapy, or chemoradiation (282/440, 64%) and primary chemoradiation therapy (84/440, 19%). The results demonstrated that there was no difference in 5-year OS between the three groups ($p = 0.58$, ►Fig. 3D).

Since multivariate analysis is not possible in a meta-analysis, we used the expanded data from the international consortium to validate the independent predictors of outcome in patients with ACC of the paranasal sinuses and nasal cavity. The results of the multivariate analysis are displayed in ►Table 4. Independent predictors of outcome were age and

Fig. 2 Survival rates in the included studies. (A) 5-year overall survival. (B) 5-year disease-specific survival. (C) 5-year disease-free survival. The dashed line indicates the mean survival rate for the whole group. *Only the sphenoid sinus is involved. †Only the maxillary sinus is involved. ‡Only the nasopharynx is involved.

Fig. 3 Kaplan-Meier 5-year disease-specific survival analysis. (A) Site of tumor. (B) Perineural invasion status. (C) Tumor margin status. (D) Treatment group. *Only the sphenoid sinus is involved. †Only the maxillary sinus is involved. ‡Only the nasopharynx is involved. ¶Data are not provided.

Table 4 Multivariate Analysis of Outcome

Variable		Overall survival (p value)	Disease-specific survival (p value)
Age (y)	<70 >70	0.03	0.02
T classification	1/2 3/4	0.78	0.56
N classification	1–4	0.05	0.06
Treatment	Surgery Surgery + RT ChRT	0.99	0.84
Margins status	Positive Negative	0.05	0.06
Perineural invasion	Yes No	0.13	0.24
Intraorbital invasion	Yes No	0.37	0.66
Dural invasion	Yes No	0.74	0.42
Cavernous sinus invasion	Yes No	0.67	0.78
Bone invasion	Yes No	0.36	0.65
Tumor site	Maxillary Nasal cavity Ethmoid/sphenoid	0.007	0.009

Abbreviations: ChRT, chemoradiation therapy; RT, radiotherapy.

tumor site for OS and DSS; tumor margin status was marginally significant ($p = 0.059$ and $p = 0.063$, respectively), probably due to the low number of patients.

Discussion

Previous studies on the prognostic factors that influence survival of patients with ACC of the paranasal sinuses and skull base have yielded contradictory results. For example, the impact of local invasion was evaluated in three studies and only one of them identified skull base infiltration as being a significant factor.^{6–8} Adjuvant treatment had a significant impact on survival in several studies,^{6,23} whereas others found an effect of adjuvant radiotherapy only in patients with negative surgical margins.²⁰ These discrepancies can be attributable to differences in the locations of tumors, the size of the cohort, the tumor stage, and the type of statistical analysis.

In our current work, we aimed to re-evaluate the significance of the above-cited variables in a more uniform population of patients—specifically, those with tumors isolated to the paranasal sinuses, as opposed to ACC tumors in a variety of locations. To improve the statistical strength of our study, we conducted a meta-analysis of previously published cohorts and a separate analysis of data retrieved from multiple tertiary cancer centers. Our analysis revealed that tumor margin status and tumor site were significant predictors of outcome. Both positive/close tumor margins and tumors of sphenoid/ethmoid origin were associated with dismal prognosis compared with negative tumor margins and tumors of maxillary/nasal cavity origin. Our data also indicate that positive lymph nodes are associated with decreased OS ($p = 0.05$).

We also evaluated the importance of perineural invasion, whose significance in ACC is controversial, with most of the previous studies having found no impact on survival.^{3,30,31} An early study from the M. D. Anderson Cancer Center evaluated 160 patients with malignant minor salivary gland tumors and 40 with tumors originating in the paranasal sinuses.³² Those authors found that perineural invasion in general, as well as perineural invasion in an identified nerve, were not associated with survival, and other studies showed that perineural invasion was associated with an increased treatment failure rate, but that it had no impact on outcome.³³ In contrast, a recent study by Mendenhall et al⁵ analyzed the importance of clinical evidence of perineural invasion on patients with ACC of all possible anatomical sites and found that it had a significant impact on survival. The collective results of our current meta-analysis, which represents the largest study performed to date on paranasal ACC, revealed that perineural invasion had no significant impact on survival. We speculate that, similar to cases of squamous cell carcinoma, it is possible that proximity of paranasal tumors to the skull base and other vital structures limits the impact of perineural invasion on survival.

An important finding of our study was that adjuvant treatment in the form of radiotherapy or chemoradiation was not associated with better outcome than surgery alone or primary chemoradiation. It is reasonable to consider that

some of the patients who were treated by primary chemoradiation were poor surgical candidates or had inoperable tumors. As such, the finding that surgery did not improve the survival rate (with or without radiotherapy) raises questions about the role of surgery in this population. Though on the one hand several studies on ACC of the head and neck showed that adjuvant radiotherapy generally leads to enhanced local control after surgery,⁵ a similar study from the Cleveland Clinic reported local control benefit of postoperative radiation therapy limited only to advanced tumors with/without positive margins.³⁴ It is reasonable to consider that some of the patients who were treated by primary chemoradiation were poor surgical candidates or had inoperable tumors. Furthermore, the small number of patients treated by primary chemoradiation with curative intent ($n = 84$), limits any meaningful analysis.

We realize that one of the limitations of this study is the lack of data regarding the histological classification of ACC (i.e., solid, cribriform, or tubular subtype). Although several authors showed that tumor grade does not have prognostic value, others have demonstrated correlation between high-grade solid tumors and poor prognosis.^{6,20,24,35}

Conclusions

The results of this meta-analysis revealed that margin status and tumor site were significant predictors of outcome in patients with paranasal and skull base ACC. In addition, tumors of the sphenoid and ethmoidal sinuses were associated with dismal prognosis, whereas perineural invasion was not associated with prognosis. Our findings showed no added benefit of adjuvant treatment and warrant prospective studies to verify the role of surgery and adjuvant treatment in the survival of patients with paranasal ACC.

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