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Sinonasal Adenoid Cystic Carcinoma: Systematic Review of Survival and Treatment Strategies

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Abstract

Objective. This study reviews the published outcomes related to sinonasal adenoid cystic carcinoma (SNACC). Clinical presentation, radiographic diagnosis, pathology, treatment, and management outcomes of this uncommon disease are reported.

Data Sources. PubMed database.

Methods. A systematic review of studies for SNACC from 1960 to 2012 was conducted. A PubMed search for articles related to SNACC, along with bibliographies of those articles, was performed. Articles were examined for both individual patient data (IPD) and aggregate patient data (APD) that reported survivability. Demographics, disease site and spread, treatment strategies, follow-up, outcome, and survival were described for IPD, and a meta-analysis for survival rates was performed for APD.

Results. A total of 55 journal articles were included. Individual patient data were reported in 39 journal articles, comprising a total of 88 cases of SNACC. Sixteen articles, totaling 366 patients that reported aggregate 5-year survivorship pertaining to SNACC, were also included. Average follow-up in the IPD was 51.2 months (range, 1-198 months), and 5-year survivorship was 63.5%. In the studies reviewed, surgery followed by postoperative radiotherapy was the most common therapy used and resulted in the highest percentage of survivors. Aggregate patient data meta-analysis revealed a 5-year survival rate of 62.5%.

Conclusion. This study contains the largest pool of SNACC patients to date. The data suggest that SNACC has a poor overall prognosis. It also suggests that surgery with postoperative radiotherapy is the most commonly used and may possibly be the most effective therapy.

Keywords

adenoid cystic carcinoma, sinonasal carcinoma, malignant nasal cavity tumors, malignant nasal tumor, malignant sinus tumor, malignant skull base tumors, anterior skull base resection

Adenoid cystic carcinoma (ACC), first described as a ''cylindroma'' by Billroth in the 1800s, is a rare tumor (**Figure 1**).[1,2] Adenoid cystic carcinomas are malignant epithelial tumors of the exocrine glands originating from minor salivary glands of the upper respiratory tract.[3,4] Although ACCs have a predilection for the head and neck, they account for less than 2% of head and neck malignancies and 5% to 15% of malignant paranasal sinus tumors.[4-7] Unspecific symptomatology leads to misdiagnosis of paranasal sinus tumors as infectious or inflammatory reactions, thus delaying the diagnosis.[8,9] Adenoid cystic carcinomas are known for their prolonged history, insidious growth, and late diagnosis, with indolent recurrence and metastasis through the bloodstream.[3,6,10,11] This tumor has been considered incurable, due to its tendency to recur and metastasize by spreading submucosally and throughout major and minor nerves.[12-15] Sinonasal ACC (SNACC) has an especially poor prognosis and has remained relatively understudied. This report is a systematic review of the published literature on SNACC with focus on its clinical presentation, diagnosis, pathology, therapeutic approaches, and treatment outcome.

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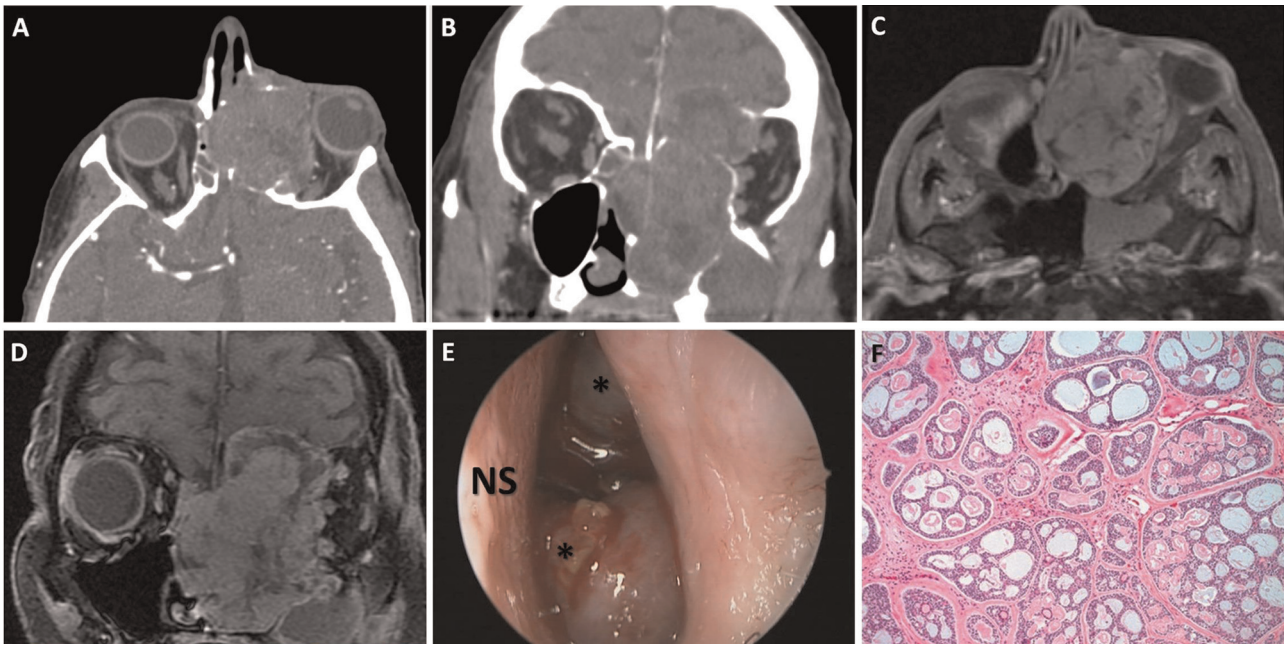

Figure 1. Axial (A) and coronal (B) contrast-enhanced computed tomography (CT) scans of a patient with a left sinonasal adenoid cystic carcinoma with intraorbital and intracranial extension. Axial (C) and coronal (D) T1-weighted gadolinium-enhanced magnetic resonance imaging of the same patient demonstrating a heterogeneous lesion with intraorbital and intracranial extension. (E) Thirty-degree endoscopic view of the left sinonasal adenoid cystic carcinoma (asterisks depict lesion; NS, nasal septum). (F) Histologic view of the adenoid cystic carcinoma demonstrating the Swiss cheese appearance.

Materials and Methods

Search Strategy

A systematic review of published literature on cases of SNACC was performed. The PubMed database was searched from 1960 to 2012 for ''nasal AND adenoid cystic carcinoma,'' ''nasal adenoid cystic carcinoma,'' ''sinonasal AND adenoid cystic carcinoma,'' and ''sinonasal adenoid cystic carcinoma.'' First, titles were reviewed to identify studies that appeared to involve SNACC. Next, abstracts were examined, followed by review of acquired full-text articles. Last, the references in the retrieved articles were manually searched for associated studies. Institutional review board approval was not required since this study qualified as ''nonhuman subject research.''

Selection Criteria

All English studies that reported SNACC were included. Articles with individual patient data (IPD) were included if they reported diagnosis, treatment, follow-up, and outcome. Articles with aggregate patient data (APD) were only included if they reported diagnosis, number of patients, treatment, and outcome (as 5-year overall survival rate). Nonhuman, radiologic, cadaveric, anatomic, histologic, and molecular studies were excluded, as were sources with insufficient or unextractable data. Articles with unobtainable full text were excluded.

Data Extraction

Two independent observers extracted data, and all discrepancies were agreed upon after discussion. Outcome measures extracted included demographic data, tumor location, symptoms, spread, radiographic imaging, primary treatment modality, adjuvant treatment, complications, recurrence, metastasis, follow-up, and overall survival. Using the IPD and APD, assessment of study quality was performed despite the predominance of case reports and case series in the data set. This type of data is typically on the lower end of quality scales that have been developed for cohort and case-control studies[16] and randomized control trials,[7,18] resulting in a global rating of ''weak'' according to the Quality Assessment Tool for Quantitative Studies (Effective Public Health Practice Project 2007).[19-21] However, given the rarity of SNACC, the studies presented represent the only type of data available in the literature for this entity.

Data Analysis

This study used Microsoft Excel (Microsoft Corp, Redmond, Washington) for data aggregation and analysis, MedCalc Software (MariaKerke, Belgium) for Kaplan-Meier analysis charts, and StatsDirect (StatsDirect Ltd, Altrincham, UK) for meta-analysis, sensitivity/subgroup analysis, forest plots, and funnel plots.

DerSimonian and Laird's random-effects model was used to pool the 5-year survival rate from aggregated observational studies to form a weighted parameter estimate. The random-effects

model takes into consideration that the studies are a sample of all potential studies, allowing it to estimate between-study variability.[22,23] Proportions from the 5-year survival data set were converted into a quantity using the Freeman-Tukey transformation to compensate for overdispersion and subsequently combined with the above meta-analytical techniques.[24] Heterogeneity among studies was assessed using the I^2 statistic for inconsistency. Publication bias was assessed using Egger's test in tandem with visual inspection of the funnel plot, which plotted calculated effect size and confidence interval for each study. Sensitivity analysis was performed, omitting individual studies and subgroups to assess for deviations in the overall estimate.

Results

Searching the PubMed database using the keywords and manual bibliography search identified 406 studies (**Figure 2**). Exclusion criteria included foreign language (107), unextractable data (49), insufficient data (39), irrelevant articles (36), different diagnosis (28), nonhuman (22), surgical without outcome (14), cannot locate (13), radiologic studies (12), different tumor site (10), histologic studies (8), molecular studies (5), anatomic/cadaveric studies (3), radiologic without outcome (3), and veterinarian studies (2). After applying the aforementioned criteria, 55 articles were included in the systematic review.

These 55 studies were composed of 39 studies with IPD and 16 studies with APD (**Tables 1** and **2**). The studies with IPD spanned 1964 to 2010, totaling 88 patients. Information on age, sex, location of tumor, associated symptoms, tumor spread, radiographic imaging, recurrence, and metastasis was recorded if available. The aggregate studies spanned from 1969 to 2008, totaled 366 patients, and at minimum included the diagnosis and the 5-year survival rate of the study.

Demography and Tumor Specifics

In the IPD, average age was 56.4 years (range, 22-78 years). The male to female ratio was 1.3:1. All but 4 of the individualized studies reported age (81/88), and all but 7 reported sex (72/88). Tumor site is listed in **Table 3**. Information about the size of the primary tumor was seldom reported and therefore not included. Recurrence rates, metastasis rates, and other tumor characteristics are included in **Table 3**. Areas of local tumor spread and metastatic sites are listed in **Tables 4** and **5**.

Radiographic Imaging

The most common imaging technique was X-ray studies used either alone or in combination with other modalities in 19 cases. The next most common techniques were computed tomography (CT) (18 cases), followed by magnetic resonance imaging (MRI) (9 cases). Cerebral angiograms (2 cases) were used less frequently.

Treatment Modalities

Various treatment modalities were used in these studies, including single-modality treatment via radiation, surgery, or chemotherapy as well as combinations of these therapeutic

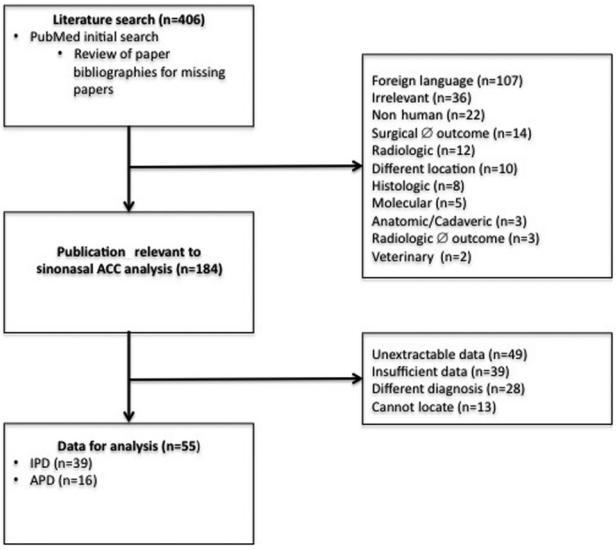

Figure 2. Flow diagram of identified, excluded, and included studies. ACC, adenoid cystic carcinoma; APD, aggregate patient data; IPD, individual patient data.

interventions (**Table 6**). Treatment information was reported in all patients; however, in 1 case, the patient declined treatment. The most common treatment used was a combination of surgery and radiation seen in 38 of the 88 cases (43.2%). Both surgery and radiotherapy were reported in 19 cases (21.6%). Chemotherapy was less common, seen in 2 cases (2.3%), in combination with surgery in 4 cases (4.5%) and with radiotherapy in 3 cases (3.4%). Finally, use of all 3 modalities was only seen in 2 cases (2.3%).

Overall Survival

A Kaplan-Meier curve was created using available IPD, all of which included clear indications of follow-up time. The plotted curve (**Figure 3**) shows a 1-year survival probability with treatment of 95.1%, a 5-year survival probability of 63.2%, and a 10-year survival probability of 32.4%.

Survival Based on Treatment

Survival in the surgery, radiation, and the combination groups was described. For those who received surgery for primary treatment, 12 of 19 patients (63.2%) survived at reported follow-up (average 50.1 months; range, 1-146 months). With regard to radiation therapy as a primary treatment, 8 of 19 patients (42.1%) survived at reported follow-up (average 48.4 months; range, 10-162 months). In the most common treatment used, surgery and radiation combined, 26 of 38 patients (68.4%) were alive at the time of reported follow-up (average 61.5 months; range, 5-198 months).

Aggregate Patient Data Meta-Analysis

To further explore SNACC survival, we performed an APD meta-analysis on 16 articles and 366 cases that reported the 5-year survival rate. The weighted estimate of 5-year survival was 64.5% (95% confidence interval [CI],

Table 1. Studies with Individual Patient Data Meeting Criteria for Systematic Review

Lead Author	Year	No. of Patients
Adelglass[39]	1980	1
Benazzou[3]	2006	1
Cantor[68]	1981	1
Caruso[92]	1973	2
Cheng[93]	1982	1
Choi[94]	1991	2
Cleveland[37]	1990	3
Close[95]	1985	1
Close[96]	1992	2
Dal Maso[12]	1985	8
Delbouk[31]	2009	1
Dickoff[97]	1993	1
Fuchihata[98]	1973	7
Furue[99]	2001	1
Goldwyn[100]	1979	1
Gormley[101]	1996	2
Hair[102]	1967	2
Johnson[27]	1964	1
Kim[73]	1999	22
Kimmich[103]	1971	1
Kraus[104]	1992	1
Kwon[105]	2010	1
LoRusso[106]	1988	1
McCaffrey[107]	1994	1
Nakao[108]	2007	1
Parsons[109]	1988	1
Poetker[70]	2005	1
Rapidis[110]	2005	7
Ruo Redda[60]	2005	1
Sato[111]	1990	1
Schneiderman[112]	2002	1
Sessions[113]	1982	1
Spiers[54]	1996	1
Tai[114]	2007	1
Veillon[115]	1996	1
Wakisaka[57]	1990	1
Wolfowitz[116]	1971	3
Wolfowitz[117]	1975	1
Woo[118]	2004	1
Total		88

Table 2. Studies with Aggregate Data Meeting Criteria for Systematic Review

Lead Author	Year	No. of Patients
Albu[119]	2011	8
Budihna[8]	1992	4
Carinci[120]	1996	17
Chummun[121]	2001	10
Goepfert[15]	1983	33
Grau[122]	2001	21
Harbo[123]	1997	16
Hawkins[124]	1988	6
Korzeniowski[125]	1985	6
Leafstedt[126]	1971	16
Lupinetti[33]	2007	105
Resto[127]	2008	20
Rhee[34]	2006	35
Sisson[128]	1989	10
Tran[81]	1989	24
Wiseman[72]	2002	35
Total		366

0.604-0.709) using the fixed-effect model and 62.5% (95% CI, 0.540-0.706) using the random-effects model (**Figure 4**). Sensitivity analysis did not show any significant difference when meta-analysis was repeated after each individual study was omitted or after excluding studies conducted prior to 1990 and studies with 10 or fewer patients. Egger's test was not significant, and the funnel plot for 5-year survival showed only slight asymmetry, which reduces the likelihood of significant publication bias (**Figure 5**). The analysis demonstrated a moderate to high amount of heterogeneity among the studies, I^2 = 59% (CI, 17.5%-75.1%), and therefore the random-effects model for meta-analysis[25] and the Freeman-Tukey transformation were used to partially compensate for this heterogeneity. Our calculated 5-year survival probability for the IPD was 63.2%, similar to the combined APD rate (62.5%).

Discussion

General Information

Sinonasal tumors are rare, accounting for approximately 5% of head and neck carcinomas, with ACC the second most common after squamous cell carcinoma.[26] These tumors possess characteristics making them difficult to detect and treat, including (1) slow progression, (2) frequent local recurrence, (3) frequent metastases, and (4) low radiocurability.[27] The indolence of SNACCs leads to late detection and treatment, increasing morbidity and mortality.[3,6,10]

Prospective randomized double-blind analysis is a difficult task in medicine and is especially difficult when evaluating a rare entity like SNACC. Therefore, a systematic review and meta-analysis of the existing literature can provide valuable insight into the past, present, and future management of this condition.

Clinical Information

Historically, a female predilection by ACC has been reported, but this review shows that SNACCs occurred more commonly in men compared with women (1.3:1).[28-30] The average age of SNACC onset in this analysis was 56.4 years, within the previously reported range of 40 to 60 years.[2,31,32] Nasal obstruction and difficulty breathing were the most frequently reported presenting symptoms, in line with prior reports.[32,33] Pain (head,

Table 3. Summary of Cases for Individuals

Characteristic	Totals
Number of subjects	88
Demographics	
Age, y, mean (range)	56.4 (22-78)
Sex, male/female, %	56/44
Follow-up, mo, mean (range)	51.2 (1-198)
Symptoms, No. (%)	n = 81
Obstruction	20 (24.5)
Pain	11 (13.6)
Eye symptoms (diplopia/ocular complaints/exophthalmos)	10 (12.3)
Mass/swelling	10 (12.3)
Epistaxis/bleeding	8 (9.9)
Headaches	7 (8.6)
Paralysis	5 (6.2)
Recurrence	2 (2.5)
Anesthesia/hypesthesia	2 (2.5)
Otitis media/conductive hearing loss	2 (2.5)
Tears/epiphora	2 (2.5)
Rhinorrhea	1 (1.2)
Dental complaints	1 (1.2)
Anatomic site, No. (%)	n = 88
Maxillary sinus (antrum)	54 (61.3)
Nasal cavity (+ septum)	11 (12.5)
Ethmoid sinus	5 (5.7)
Nasopharynx	4 (4.5)
Multiple sites	3 (3.4)
Paranasal sinus	3 (3.4)
Sphenoid sinus	3 (3.4)
Frontal sinus	2 (2.3)
Anterior skull base (ethmoid)[a]	2 (2.3)
Orbit[b]	1 (1.1)
Outcome, No. (%)	n = 88
NED	34 (38.6)
DOD	33 (37.5)
AWD	17 (19.3)
DOC	4 (4.5)
Follow-up measures, No. (%)	n = 88
Local recurrence	30 (34.1)
Metastasis	27 (30.7)
Local recurrence and metastasis	7 (7.9)

Abbreviations: AWD, alive with disease; DOC, dead of other cause; DOD, dead of disease; NED, no evidence of disease.
[a]Skull base, referenced ethmoid sinus.
[b]Orbit was first diagnosis, but it was later found to be sinonasal.

Table 4. Areas of Local Tumor Spread

Site	Number	Percentage
Orbit	14	27.4
Perineural	13	25.5
Skull base, cranial fossa	11	21.6
Brain	4	7.8
Ethmoid	3	5.9
Sphenoid	2	3.9
Cavernous sinus	2	3.9
Pterygopalatine	2	3.9
Total	51	100

Table 5. List of Metastasis Sites

Site	Number	Percentage
Lung	11	39.2
Liver	5	17.9
Bone	4	14.3
Distant (nonspecific)	3	10.7
Spine	3	10.7
Brain	2	7.1
Total	28	100

Table 6. Frequency of Using Various Treatment Modalities in Adenoid Cystic Carcinoma of the Sinonasal Tract

Treatment	No. of Cases	Percentage of Total Cases
Radiation and surgery	38	43.2
Surgery alone	19	21.6
Radiation alone	19	21.6
Surgery and chemotherapy	4	4.5
Radiation and chemotherapy	3	3.4
Chemotherapy alone	2	2.3
Radiation, surgery, and chemotherapy	2	2.3
Treatment declined	1	1.1
Total	88	100

sinonasal, ocular, otologic, dental), enlarging mass/swelling, epistaxis, bone destruction, rhinorrhea/nasal discharge, facial anesthesia, blurred vision, exophthalmos, facial paralysis, and cognitive deficits were also reported.[34]

Consistent with earlier reports, the maxillary sinus was most frequently involved.[26,33,35,36] Tumor size and staging were not adequately reported, but tumors spread to the orbit most commonly. Adenoid cystic carcinoma invades locally by destruction of adjacent bone and/or through perineural/perivascular spread along the second and third divisions of the trigeminal nerve.[31,37] Because of the late presentation and diagnosis of ACCs, 22% to 40% of tumors invade the orbit and 4% to 22% exhibit intracranial expansion.[2,31,38] Environmental exposure as an etiology for ACC was singularly reported following thorotrast exposure.[39]

Radiography and Diagnostic Studies

X-ray, CT, and MRI were the most commonly used imaging modalities for diagnosis of SNACC, although this

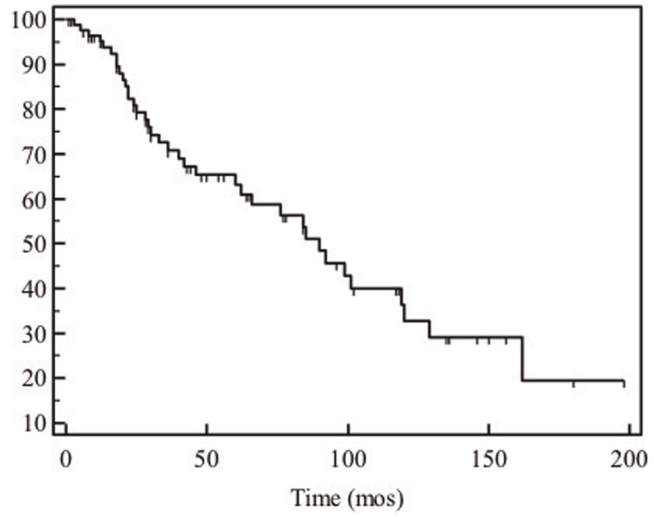

Figure 3. Kaplan-Meier curve for overall survival in adenoid cystic carcinoma of the sinonasal tract.

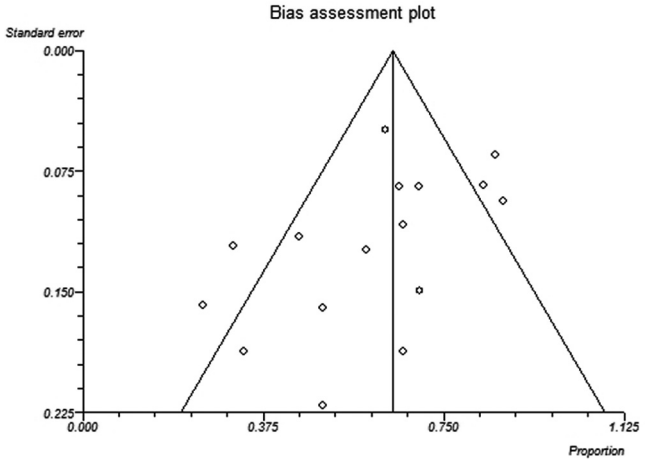

Figure 5. Funnel plot with minimal asymmetry indicating reduced likelihood of publication bias.

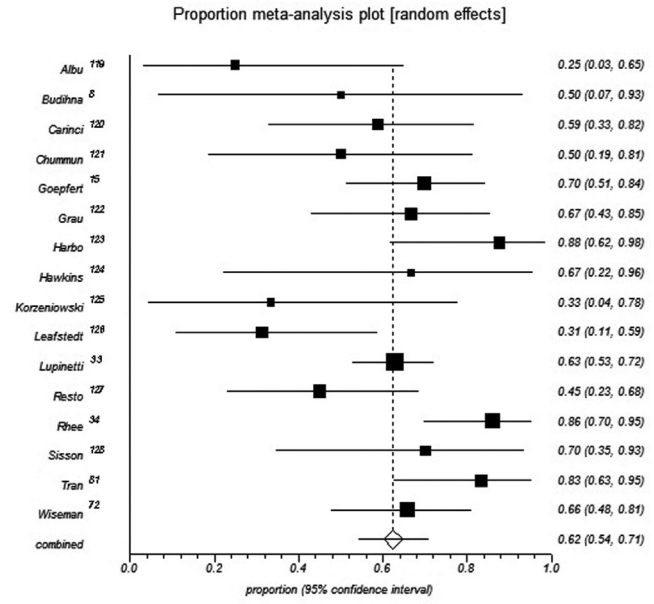

Figure 4. Forest plot showing the probability of 5-year survival in aggregate patient data (APD) studies with confidence intervals.

information was reported in less than 50% of cases. There were no reported MRI signal tendencies attributed to ACC. This is likely from variation in signal intensity among the multiple histological types due to differences in cell density and cystic composition.[40] In addition, its propensity for perineural spread necessitates careful imaging of the trigeminal nerve branches, especially in the pterygopalatine fossa, to evaluate for intracranial extension.[40]

Pathology

In the past, the histomorphology of ACC was considered "Swiss cheese or sieve-like" (**Figure 1**), although it can show a variety of other morphologies and growth patterns.[37] Histologically, ACC is divided into the more differentiated cribriform type (oval islands of small, darkly staining cells with minimal cytoplasm) and the less differentiated solid form (hyperchromatic cells with indistinct cell borders and high mitotic activity).[31] The cribriform type is further subdivided into the tubular type (cords of small dark epithelial cells).[31,41] These histologic patterns are graded as follows: grade I, tubular; grade II, cribriform; and grade III, solid.[42] Other characteristics of ACCs include extensive nuclear pleomorphisms, stromal hyalinization, and necrosis.[37,43,44] The histopathology confers prognostic significance, as the tubular and cribriform ACCs have a more favorable prognosis compared with the solid form, albeit not statistically significant.[7,41,45-50] Survival analysis with respect to tumor histology, grade, and staging was not performed secondary to nonhomogeneous reporting of data.

Treatment

In the past, the treatment of choice for ACC has been radical surgery.[51,52] As radiotherapy for ACC progressed, it was noted that 96% of tumors responded to radiation; however, the recurrence rate after radiotherapy was 94%.[53,54] This shows that ACC is radiosensitive but not radiocurable, making radiotherapy an ineffective singular treatment modality.[2,53,55] However, others have reported a 5-year overall survival and local control rate of 81% and 76%, respectively, in those undergoing primary radiotherapy.[56] In light of these findings, pure radiotherapy has been indicated to treat unresectable T4 tumors, reduce tumor burden prior to surgical resection, improve probability of achieving local control, and provide palliative therapy.[53,56-59] Others have described the effective use of gamma knife radiosurgery for unresectable ACC, which may provide local control.[50,60] In tumors of the sinonasal tract, anatomic accessibility may factor into a greater use of radiotherapy.

Occasionally, chemotherapy is used preoperatively to reduce tumor burden, postoperatively for residual tumor,

and for palliation. Chemotherapeutic agents such as cisplatin, adriamycin, 5-flucouracil, doxorubicin, and methane sulfonamide have been proposed mostly for palliation, when tumor resection is difficult or when faced with rapidly progressing disease.[26,31,32,49,61-66]

When comparing all treatment modalities in isolation, those who underwent surgery appear to have highest survival.[67] Traditional surgical techniques for SNACC involved open procedures, including maxillectomy, lateral rhinotomy, and transfacial craniofacial resection.[32,55,68] In recent years, endoscopy has been applied to treat SNACC. Some have reported that ACC's tendency for perineural spread makes endoscopic resection less suitable than the traditional open approaches.[31,69,70] Nevertheless, others have reported endoscopic resection of SNACC with comparable success, with some studies reporting up to 100% five-year survivorship.[71]

Many have advocated that the optimal treatment in the management of SNACC should be surgical resection followed by postoperative radiotherapy.[34,47,50,52,72] This review shows this combination was the most frequently reported treatment modality, occurring in 38 of 88 cases of IPD (Suppl. Table S1, available at otojournal.org). This also echoes the results of the largest reported study of IPD conducted by Kim et al.[73]

Despite the ability for postoperative radiation to increase survival in SNACC, there has been no statistical difference reported between the surgery cohort and surgery with postoperative radiation cohort.[52,74] In this analysis, we found a similar survival percentage in the combination (surgery and radiotherapy) treatment group compared with surgery alone, 68.4% vs 63.2%. Two case series reported that the combination therapy cohort had greater survival than the radiotherapy-only cohort, although this was not found to be statistically significant possibly due to small sample size.[56,74] We report that 68.4% of patients in the combination treatment group survived compared with just 42.1% undergoing radiotherapy alone. These results suggest that a more rigorous study of the advantages of combination therapy may prove useful in validating this clinical approach vs single-approach modalities.

Outcome and Prognosis

Adenoid cystic carcinoma has a high incidence of local recurrence and metastasis irrespective of the treatment modality.[72,75,76] The site of origin has prognostic implications; tumors in the minor salivary glands have been associated with more favorable prognosis than those in the major salivary glands or paranasal sinuses.[13] Even postoperative radiotherapy was considered most difficult in the paranasal sinuses in terms of local control.[77] Of head and neck cancers, tumors of the paranasal sinuses have the highest local recurrence rate of 61%.[13,49,74] It is believed that the vague symptoms associated with tumors located in the paranasal sinuses lead to misdiagnosis and late detection of advanced disease.[8,9,32,78,79] Our analysis of IPD yields an overall 5-year survival rate of 63.2%. Although this figure may be unreliable because of the lack of a formal meta-analysis (which was precluded by the presence of numerous single-patient case reports), it is notably similar to the combined survival, 62.5%, from the APD meta-analysis. Both these rates are lower than the 5-year survival of ACC involving the mouth, the most frequently involved anatomic site, which was reported as 81%.[33,48]

The most common sites of local spread of SNACC in this study were to the orbit and skull base. Skull base involvement is a common presentation of recurrence because SNACC destroys adjacent bone and spreads perineurally, although some postulate that this occurs from tumor microembolisms.[80,81] Interestingly, metastasis does not appear to correlate with local control and has a higher determining factor for survival. In addition, bony metastases have shown to be more aggressive than pulmonary metastases.[81,82] The local recurrence rate and metastasis rate of SNACC in this study were 34.1% and 30.7%, respectively, for the IPD, similar to prior reports.[33] Local recurrence with metastasis occurred 7.9% of the time, which may increase these numbers comparatively.

Because of the poor long-term history for patients with ACC, there have been many attempts to find prognostic indicators to predict outcome. Negative prognostic indicators include histology, tumor site, perineural invasion, positive surgical margins, and tumor markers.[10,79] The prognostic effects of solid histopathology are controversial; some say it offers lower rates of survival when compared with the tubular or cribriform types, whereas others have shown that there is no correlation.[6,47,83] Positive margins are the best prognostic indicator of local recurrence, and some studies have shown clear improvement in survivability with negative margins.[75,84] Last, the tumor markers c-KIT and Ki-67 have been investigated as a potential drug target and negative outcome indicator, respectively.[85,86] Because ACCs are slow growing with such high rates of recurrence, follow-up is necessary for life, despite clear surgical margins and prolonged disease-free intervals.[74]

Limitations

Assessing studies that span a significant time frame introduces biases with respect to the advancements in diagnosis and treatment. In addition, the greatest weakness of any pooled data analysis includes allocation bias and selection bias. Given the relatively large proportion of case reports in the IPD, a meta-analysis was not conducted, but a Kaplan-Meier survival analysis was performed using these data. We recognize the limitations that this presents, particularly concerns about independence of combined data and higher risk of bias inherent to case reports and case series. Geographical or temporal biases may have been introduced with this process. Finally, meta-analyses for proportion outcomes (like survival) can be problematic, but this is partially compensated for using the Freeman-Tukey transform, a technique that has been used in prior literature.[24,87-91]

Improvements to this study could be an analysis into tumor grade and its effect on survival probability, which was not possible given the lack of standardized reporting for staging. We hope that with the publication of this

review, future authors may pursue studies that allow for a more rigorous analysis of treatment approaches.

Conclusion

Sinonasal adenoid cystic carcinoma is a rare tumor and, with its slow growth, tendency for recurrence, local regional spread, and distant metastasis, is particularly difficult to diagnose and treat. In the studies reviewed, surgery with postoperative radiotherapy was the most commonly used treatment modality and resulted in the highest survival at follow-up.

Author Contributions

Qasim Husain, data acquisition, analysis and interpretation, drafting, final approval; **Vivek V. Kanumuri**, data acquisition, analysis, revision, final approval; **Peter F. Svider**, analysis, revision, final approval; **Brian M. Radvansky**, data acquisition, analysis, revision, final approval; **Zain Boghani**, analysis, revision, final approval; **James K. Liu**, interpretation, revision, final approval; **Jean Anderson Eloy**, conception, design, data acquisition, analysis and interpretation, revision, final approval.

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Supplemental Material

Additional supporting information may be found at http://oto.sagepub.com/content/by/supplemental-data

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