Overall and disease-specific survival of sinonasal adenoid cystic carcinoma: a systematic review and meta-analysis*

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Abstract

This meta-analysis aims to investigate the outcome of sinonasal adenoid cystic carcinoma (snAdCC). We followed PRISMA guidelines and included studies reporting 5-year overall survival (OS) rates for snAdCC. Eligible studies were identified through a literature search and assessed using JBI critical appraisal checklist. A total of 17 studies were included comprising 2259 patients (mean age: 58.1 years, 52.7% female, 47.3% male). The meta-analysis demonstrated that the 5-year OS, 10-year OS, and 5-year disease-free survival (DFS) were 68%, 40%, and 47.2%, respectively. Descriptive statistics on study level showed high rates of locally advanced tumor stages at diagnosis: 23% cT3, 53% cT4, 3.4% N+, and 4.2% M+. 29.7% of the tumors were in the nasal cavity, 67.6% in the paranasal sinuses. The maxillary, ethmoid, sphenoid, and frontal sinus were affected in 50.9%, 7.2%, 4%, and 0.5%, of cases. A combination of surgery and radiotherapy was used in 45.4% of the patients and 19.3% of patients received surgery only. In conclusion, these findings emphasize the significance of thorough surveillance for individuals with snAdCC to identify any potential recurrence or progression of the disease.

Key words: adenoid cystic carcinoma, meta-analysis, paranasal sinuses, sinonasal, survival

Introduction

Adenoid cystic carcinoma (AdCC) is a rare malignancy, typically originating from the salivary glands [1]. Overall, manifestation in the sinonasal tract, where the entity is thought to origin from the minor salivary glands, is rare and scarcely reported [2, 3]. The maxillary sinus is the most affected tumor site, followed by the nasal cavity, the ethmoid, and sphenoid sinus [4, 5]. The disease slightly predominates in female patients and typically presents at around 60 years of age, although it can occur at any age with a broad range of onset [6, 7]. Sinonasal AdCC (snAdCC) features a slow, yet insidious growth, which frequently results in an advanced tumor stage at initial diagnosis [8, 9].

To date, surgical resection remains the gold standard treatment. Owing to the complex anatomy surrounding the operation field, with close proximity to vital health structures [10], as well as perineural spread [11], complete surgical resection of the tumor is challenging. Consequently, postoperative radiotherapy is frequently recommended [12, 13].

Due to the high incidence of late recurrences, which is among the highest rates observed in all head and neck malignancies, AdCC is commonly associated with a poor long-term prognosis [14-16]. Factors influencing survival are a matter of debate. However, the solid variant [17, 18], perineural invasion [19, 20], and high-grade transformation [21] seem to have a negative impact on the outcome. However, as snAdCC is an extremely rare entity, it is generally difficult to extract reliable and specific data on a single sinonasal subsite. Additionally, there is a tendency to conflate snAdCC with nasopharyngeal AdCC and AdCC primarily affecting the skull base, leading to inconsistencies and heterogeneity in the reported findings [22]. Therefore, there is a need for a systematic review and meta-analysis that focuses specifically on snAdCC. By synthesizing the available literature on this rare malignancy, we aim to provide a better understanding of the disease and its prognosis. To the best of our knowledge, this

study represents the first meta-analysis on AdCC of the nasal cavity and the paranasal sinuses exclusively, which does not include other anatomic sites such as the nasopharyngeal tract or primarily the skull base.

Materials and methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [23] and was registered on the International Prospective Register of Systematic Reviews (PROSPERO Publishing Number: CRD42023377576) [24, 25].

Eligibility criteria

Only studies with original data on snAdCC for which the 5-year overall survival (OS) rate (the main outcome) was reported were included in this meta-analysis. Studies reporting 5-year OS rates on tumor sites other than the paranasal sinuses and / or nasal cavity, or on any other histological subtype than AdCC were excluded from the analysis. Additionally, we excluded reviews, letters, or conference abstracts lacking primary data and studies that had a sample size of less than 5 patients. If data from two studies were from the same institution or database, the study with the larger sample size was included.

Searching methods

The literature search and deduplication process were conducted by an information specialist on March 18, 2022, in three databases: MEDLINE, EMBASE, and Cochrane. The search terms used were "sinonasal" and "adenoid cystic carcinoma," which were searched within the title, abstract, or keywords of the articles. The search was restricted to articles published in English, German, and French, with no limitations placed on the publication period. Unpublished studies were not sought. To ensure that no relevant literature was missed, we conducted manual searches of the bibliographies, citations, and related articles of the included studies. The search strategy used for each database is available in the appendix (Supplementary material 1).

Selection process and data extraction

The initial selection of studies was performed by one of the authors (TM), who screened the titles and abstracts of the search results. Full-text articles were then reviewed to determine their eligibility for inclusion. The decisions made were independently verified by another researcher (CMM). Any discrepancies were resolved through oral discussions. For each included study, essential data items such as sex, age at diagnosis, symptoms at presentation, tumor epicenter, staging according to the current UICC/AJCC manual at the time of study publication, therapeutic modality, and outcome data were sought. In addition, we recorded tumor's pathological characteristics, including its growth patterns and whether the specimen was pathologically reviewed. Information on the setting of the included studies, such as the institute, city, country, period of data collection, inclusion, and exclusion criteria, were documented. To ensure data accuracy, one person (TM) extracted the data while the other researcher (CMM) checked for any discrepancies. Disagreements between individual judgments were resolved through oral discussions or third-party arbitration (DH, MBS, SAM). The collected data were recorded in a structured format in an excel spreadsheet.

Risk of quality and bias assessment

A risk of quality and bias assessment was conducted using the JBI Critical Appraisal Checklist for Case Series (26). This appraisal covers both assessing the methodological quality of a study and addressing the possibility of bias [27]. The checklist consists of 10 domains, which were graded as either 'Yes' (criteria were met or the quality was good), 'No' (criteria were not met or quality was poor), or 'Unclear' (information was missing or insufficient). The evaluation was performed by one individual (TM) and cross-checked for discrepancies by another author (CMM).

Statistical methods

Descriptive statistics on study level were summarized with weighted means or percentages. When possible, results of the individual studies were meta-analyzed. We checked for normality and used a random effects meta-analysis model, accounting for the expected large between-study heterogeneity of the included single-arm studies, to allow for a more robust estimate of the overall effect. For the estimation of the heterogeneity variance parameter τ^2, the REML method was used. Proportions of patients in individual studies were addressed as the effect measure. To obtain a summary estimate of the proportions reported in each study, the proportions were transformed to logit scale, where they were meta-analysed and subsequently backtransformed to proportions scale. To display the results, we used forest plots, and summary estimates were presented with 95% confidence intervals. Heterogeneity among the included studies was analyzed by using the Q statistic, and I^2 statistic. We assessed publication bias by generating funnel plots and visually inspecting them. All statistical analyses were performed using R software (version 4.2.2.) [28].

Results

Study selection

Through literature research, 548 studies were identified, and 374 studies remained after deduplication. A comprehensive review of the titles and abstracts resulted in 202 full-text articles that reported on snAdCC, which were subjected to further analysis. Of these articles, 185 were excluded for failing to meet the inclusion criteria, which encompassed factors such as small sample size (<5), insufficient or unextractable data on the primary out-

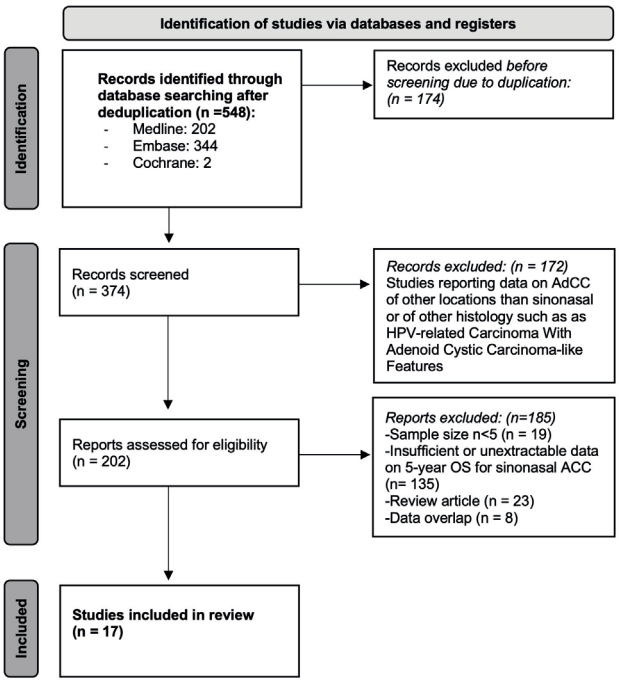


Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

come (5-year OS of snAdCC), review articles or articles without original data, and overlap of data, such as studies from the same institution. Leaving 17 articles that fully satisfied the eligibility criteria [4, 5, 9, 14, 16, 29-40]. A detailed account of the study selection process is shown in a flowchart in Figure 1.

Quality and risk of bias assessment

For the 5-year OS, the funnel plot analysis (Figure 2a) showed no relevant publication bias or effects of small studies. Four studies were identified as outliers [5, 7, 14, 40]. With respect to the 10-year OS, the funnel plot displayed some degrees of funnel plot asymmetry (Figure 2b). The funnel plot analysis for 5-year disease-free survival (DFS) showed no relevant publication bias or small-study effects (Figure 2c). We conducted a risk of bias and quality assessment according to the JBI Critical Appraisal Checklist for Case Series (Figure 3). The overall appraisal revealed that all 17 studies were rated as high quality and low risk of bias, rendering them suitable for inclusion in the meta-analysis.

Included studies

The included 17 articles were retrospective studies published between 2012 and 2021. Among these, data from 14 studies (82.4%) were derived from single-center series of nine different countries, whereas data for the remaining three studies (17.6%) were sourced from databases (National Cancer Data Base, SEER 18 Database, and Swedish National Cancer Registry). In total, the comprehensive patient population across all studies was 2259

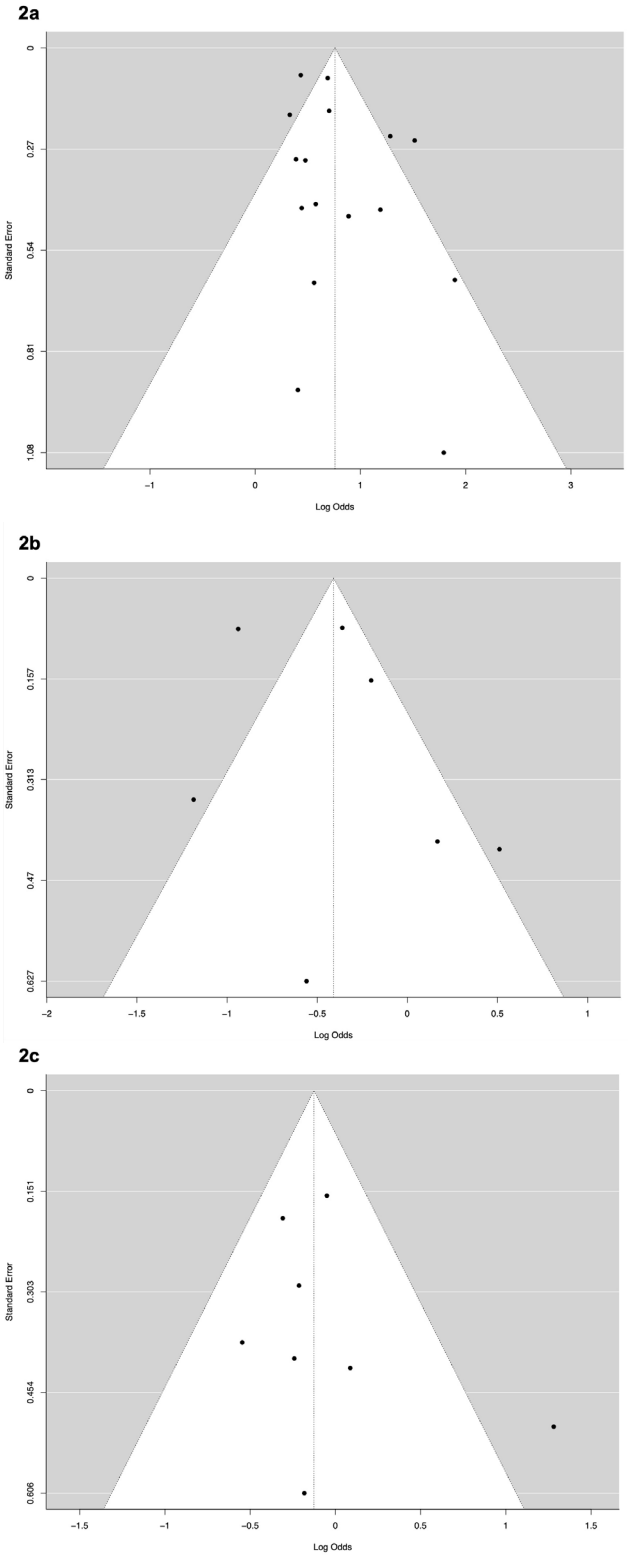


Figure 2. Funnel plots showing the results of studies assessing the 5-year OS (A), 10-year OS (B), and 5-year DFS (C), using a proportional meta-analysis with a random-effects model. The log odds ratios of each study are plotted on the x-axis, while the standard error of the log odds ratio is plotted on the y-axis. The vertical dashed line represents the pooled estimate of the meta-analysis, and the sloping lines represent the 95% CI. Studies that fall outside the funnel may indicate potential publication bias or other sources of heterogeneity.

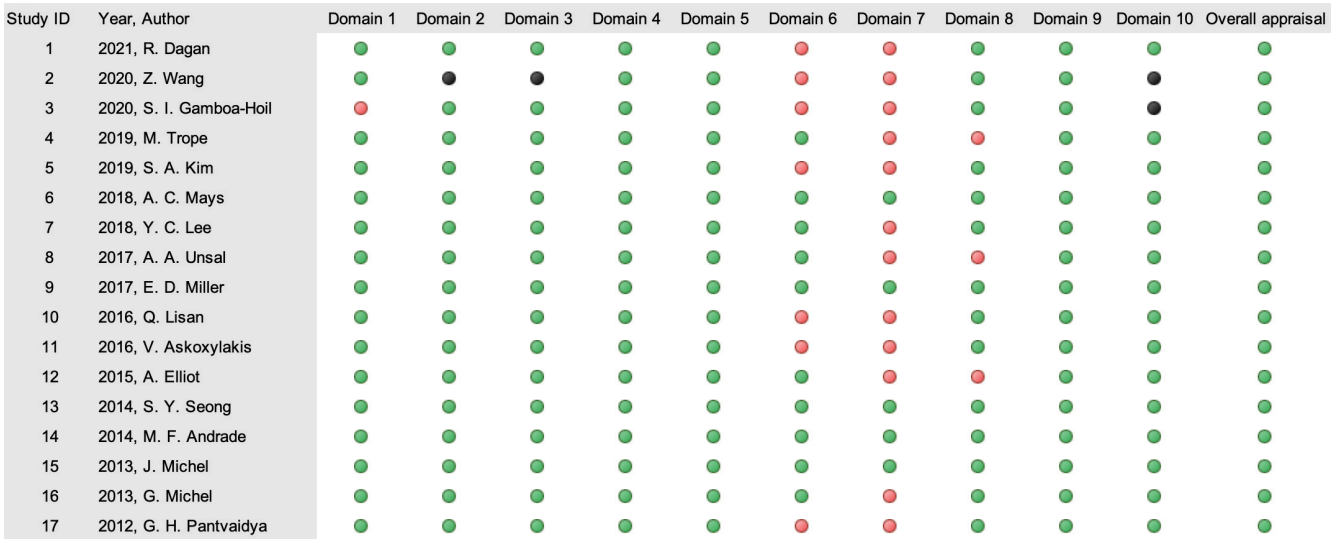


Figure 3. Risk of bias and quality assessment. This figure displays the results for all included studies using the JBI Critical Appraisal Checklist for Case Series. The criteria were graded as either 'Yes' (green), 'No' (red), or 'Unclear' (black). The assessment was performed across the following domains:
Domain 1: Were there clear criteria for inclusion in the case series?
Domain 2: Was the condition measured in a standard, reliable way for all participants included in the case series?
Domain 3: Were valid methods used for identification of the condition for all participants included in the case series?
Domain 4: Did the case series have consecutive inclusion of participants?
Domain 5: Did the case series have complete inclusion of participants?
Domain 6: Was there clear reporting of the demographics of the participants in the study? Domain 7: Was there clear reporting of clinical information of the participants?
Domain 8: Were the outcomes or follow-up results of cases clearly reported?
Domain 9: Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
Domain 10: Was statistical analysis appropriate?
For the overall appraisal the colour green is coded as 'inclusion'.

patients. Patient demographics were available in 10 studies comprising 1936 patients, in these 47.3% of patients were male and 52.7% were female, with a weighted mean age of 58.1 years (range: 51.1 - 62.5 years, standard deviation: 3.7). Characteristics of the included studies are summarized in Table 1.

Symptoms

Presenting symptoms were available for 248 (11%) patients. The most common symptoms were nasal obstruction (34%) and pain/headache (33%), followed by epistaxis, which was experienced by 26% of all patients. Additionally, 14% of all patients complained about eye symptoms (e.g., diplopia or exophthalmos) while 14% presented with other symptoms such as facial swelling, displacing mass, or conductive hearing loss.

Staging

Information on the T category was reported in 9 studies, including a total of 1801 (79.7%) patients. Of these patients, 86 (10%) were diagnosed with T1 tumors, while 122 (14%) had T2 tumors. T3 tumors were diagnosed in 198 (23%) patients, while 455 (53%) patients were diagnosed with T4a/b tumors. Of note, for 940 (41.5%) patients, information on T stage was not provided or could not be determined. Seven out of the nine studies also provided data on the N and M categories, comprising a total of 1617 patients (71.6%). Among these patients, 876 (96.6%) presented without lymph node metastasis, while 31 (3.4%) exhibited N1-3 stage at the time of diagnosis. Notably, the N stage remained indeterminate for 710 patients (43.9%). Similar rates were observed in the M stage, where 1014 patients (95.8%) demonstrated no evidence of distant metastasis upon diagnosis, while 45 patients (4.2%) presented with metastatic disease. Detailed information regarding the M stage was unavailable for 558 patients (34.5%) within the cohort of 1617 individuals.

Anatomic site

Tumor location was extractable from 12 studies, comprising a total of 1948 (86.2%) patients. Among these patients, 579 (29.7%) had tumors primarily originating in the nasal cavity, while 1317 (67.6%) had tumors arising in the paranasal sinuses. For 55 (2.7%) patients, the epicenter of the tumor was not

Table 1. Study characteristics of the included studies.

Year, Author	Country	Data collection	n patients	Women (%)	Men (%)	5-year OS	10-year OS	5-year DFS
2021, R. Dagan	USA	2007-2018	23	NA	NA	89	NA	77
2020, Z. Wang	China	1998-2016	106	NA	NA	78.2	NA	NA
2020, S.I. Gamboa-Hoil	Mexico	2008-2013	5	NA	NA	60	NA	NA
2019, M. Trope	USA	2004-2012	793	53.1	46.9	60.7	28.1	NA
2019, S. A. Kim	South Korea	1990-2011	24	NA	NA	72.2	55.6	NA
2018, A. C. Mays	USA	1980-2015	160	49.4	50.6	67	44.8	49
2018, Y. C. Lee	Taiwan	1984-2015	47	57.4	42.6	61.7	23.4	44.7
2017, A. A. Unsal	USA	1973-2013	694	53.2	46.8	66.5	41.1	NA
2017, E. D. Miller	USA	1998-2013	23	34.8	65.2	62	NA	52
2016, Q. Lisan	France	1997-2011	7	NA	NA	86	NA	NA
2016, V. Askoxylakis	Germany	1999-2009	47	NA	NA	60	NA	NA
2015, A. Elliot	Sweden	1960-2010	129	53.5	46.5	58	NA	NA
2014, S. Y. Seong	South Korea	1990-2010	30	63.3	36.7	75.3	NA	37.2
2014, M. F. Andrade	Brazil	1997-2006	24	50	50.0	72.6	62.1	NA
2013, J. Michel	France	1997-2006	11	45.5	54.5	64	35	41
2013, G. Michel	France	1998-2011	25	48	52	63	NA	43
2012, G. H. Pantvaidya	India	1991-2005	111	NA	NA	81.9	NA	42.6

NA = Not Available.

further classified.

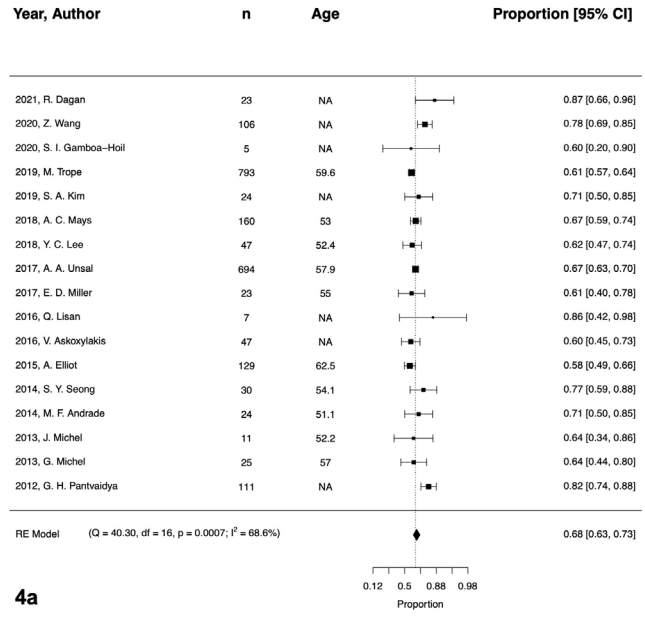
Of the tumors located in the paranasal sinuses, 992 (50.9%) were found in the maxillary sinus, 140 (7.2%) in the ethmoid sinus, 78 (4%) in the sphenoid sinus, and 10 (0.5%) in the frontal sinus. For 71 (3.5%) patients, the paranasal sinus was not otherwise classified, while for 26 (1.3%) patients, the epicenter of the tumor was found to overlap multiple sinus regions.

Treatment modality

Data on therapeutic modalities were available from eight studies for 1113 patients, with 220 patients (19.8%) receiving surgery only, 83 patients (7.5%) receiving radiotherapy only, and 11 patients (1%) receiving chemotherapy only. Surgery and radiotherapy were combined in 516 patients (46.4%), while 25 patients (2.2%) received both surgery and chemotherapy. Concurrent radiotherapy and chemotherapy were used in 75 patients (6.7%), while 82 patients (7.4%) received a combination of surgery, radiotherapy, and chemotherapy. 50 patients (4.5%) did not receive any therapy. In 46/50 cases (92%), the reasons for not receiving any therapy were not specified, while three patients (6%) declined treatment and one patient (2%) was deemed ineligible for any form of treatment and received supportive care instead.

Among the total cohort of patients who underwent surgery (n = 843, 100%), a subset of 220 individuals (26.1%) received exclusive surgical treatment, while most patients, 623 (73.9%), underwent surgery in combination with another treatment modality. A total of 100 cases (11.9%) underwent exclusive endoscopic endonasal tumor resection, while information on the surgical approach was unavailable for 201 (23.8%) patients. The remaining 542 (64.3%) patients underwent open or combined resection procedures. Data on surgical margins were available from 5 studies including 623 patients. Thereof, 343 patients (55%) revealed positive margins, while 280 patients (45%) exhibited negative margins.

Regarding radiotherapy, out of the entire group of patients who received this treatment (n = 725, 100%), 83 individuals (11.4%) were exclusively treated with radiotherapy, while the remaining 642 patients (88.6%) underwent radiotherapy alongside additional therapeutic approaches. In most cases (n= 559, 87%), radiotherapy was administered as an adjuvant treatment, with only a few exceptions. Specifically, six (0.9%) patients received neoadjuvant radiotherapy, one (0.2%) patient underwent intraoperative radiotherapy, and one (0.2%) patient received a combination of intraoperative and postoperative radiotherapy. Whenever radiotherapy was combined with chemotherapy (n= 75, 11.7%), it was administered concurrently. Due to the heterogeneity and limited reporting of the included studies, it is challenging to provide a comprehensive analysis of the specific types of radiation therapy utilized for snAdCC. Out of 17



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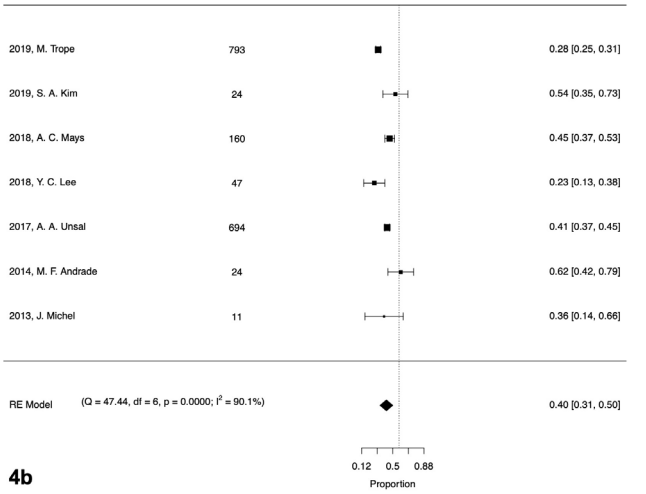

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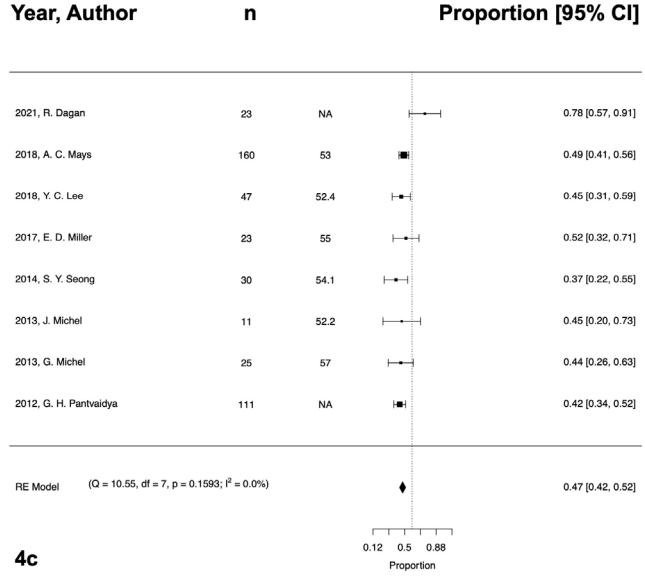

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studies, 13 did not further specify the type of radiation therapy employed. However, one study (n=23) exclusively utilized proton therapy as an inclusion criterion [29], while another study (n=47) exclusively employed intensity-modulated radiation therapy (IMRT) for all patients. In a study with 160 participants, both IMRT and intensity-modulated proton therapy (IMPT) were mentioned without specifying the distribution between the two [4]. Lastly, one study reported that 14 patients received external beam radiotherapy (EBRT), one patient received EBRT and intraoperative radiation therapy (IORT) together, one patient received IORT alone, and two patients received proton therapy [34]. The administered radiation doses reported by all included studies ranged from 45 Gy to 72 Gy.

Within the chemotherapy subgroup (n = 193, 100%), a small proportion of 11 patients (5.7%) received chemotherapy as the only treatment, whereas in most patients, 182 (94.3%), chemotherapy was administered in addition with other therapeutic modalities. As mentioned above, radiochemotherapy (n= 75, 41.2%) was consistently administered concurrently. Adjuvant chemotherapy was the standard approach in all other instances (n= 106, 58.2%) except for one case (0.5%), where chemotherapy was utilized in the neoadjuvant setting. The specific chemotherapeutic agents were not reported for most of the patients (68.9%). For the remaining cases (31.1%) Cisplatin was administered in 59 (98.3%) patients, while carboplatin/paclitaxel was used in one (1.7%%) case.

Pathological work-up

In five studies comprising of 343 patients (15.2%) the initial histopathological diagnosis was reviewed and reconfirmed. Eight studies provided additional information on histology. Among these, two studies used differentiation grading (well differentiated, n = 69/ 16.2%; moderately differentiated, n = 157/ 36.9%; poorly differentiated, n = 148/ 34.7%; undifferentiated n = 52/ 12.2%), while six studies (n = 273) used growth patterns as a classification method. Among the studies reporting growth patterns, the classification methods used were highly heterogeneous, implying that no conclusive statement can be made. None of the included studies reported conducting molecular analysis on the tumor samples except one study [32].

Figure 4. Forest plots showing the results of studies assessing the 5-year OS (A), 10-year OS (B), and 5-year DFS (C), using a proportional meta-analysis with a random-effects model. Each study is identified by the year of publication and the first author's name, along with the sample size (n). Each square represents the patient outcome proportion of each study. Square size reflects the study's weight. Vertical lines indicate 95% confidence intervals (CI). If the interval crosses a dashed line, the proportion is not significantly different from the pooled proportion.

Meta-analysis

In the meta-analysis of 5-year OS rate, of all 17 studies, the summary estimate was estimated to be 68%, (95% CI, 63.1% - 73%). Among the 7 studies that provided data on 10-year OS of the summary estimate was 40% (95% CI, 31% - 50.1%). Regarding DFS, data on the 5-year rate was available from 8 studies. The calculations revealed a summary estimate of 5-year DFS rate of 47.2% (95% CI, 42.4% - 51.9%). Insufficient availability and extractability of other survival rates precluded further analysis. Furthermore, meta-analyzing recurrence rates or conducting a subanalysis such as survival analysis stratified by approach was not feasible. Figures 4a-c show the forest plots illustrating the results.

For the 5-year OS, heterogeneity among studies was assessed using the Q statistic (Q = 40.3) and the I^2 statistic (I^2 = 68.6%), indicating large amounts of heterogeneity between studies. With respect to the 10-year OS, the assessment also detected heterogeneity between the studies (Q = 47.44, I^2 = 90.1%). For the 5-year DFS, there was no evidence of heterogeneity between the studies (Q = 10.55, I^2 = 0.0%).

Discussion

Main findings

To the best of our knowledge, this is the first meta-analysis to specifically examine the outcome of snAdCC, limiting the inclusion to the paranasal sinuses and the nasal cavity. In total, 17 retrospective studies comprising a total of 2259 patients were enclosed. The calculated 5-year OS, 10-year OS and 5-year-DFS of snAdCC were found to be 68%, 40%, and 47.2%, respectively.

Patients and disease characteristics

SnAdCC typically do not exhibit early symptoms, but rather manifest once they have grown to a certain size, progressed to an advanced tumor stage or infiltrated critical anatomical structures, which can have a significant impact on therapy and patient outcome [41]. In this study, the most common symptoms reported by patients with snAdCC were nasal obstruction, pain/headache, and epistaxis. The results also revealed that 76% of the patients had an advanced T-category of T3/T4 [42], which is notably higher compared to the rates of 42% T3/T4 reported in an international collaborative study on AdCC of the head and neck region in general [43]. These results suggest that AdCC in the sinonasal trakt present at more advanced local stage, likely due to the absence of early symptoms and the difficulty of early detection. However, only a small proportion of patients (3.4%) exhibited N1-3 stage at the time of diagnosis, and a minority (4.2%) presented with metastatic disease in this meta-analysis. This tendency of infiltrating surrounding tissues and exhibiting perineural spread rather than metastasizing to distant sites reflects the biological behavior of the tumor.

The standard diagnostic approach for AdCC includes cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging (MRI), which are regarded as complementary modalities. While CT addresses bony alterations and provides a roadmap for surgery, MRI delineates the tumor from surrounding tissue, may identify perineural spread [44] and guide target volume annotation for radiotherapy. Additionally, hybrid whole-body PET imaging is used, for detection and surveillance of distant metastases [45, 46]. Addressing the limitations of FDG PET/CT in detecting smaller salivary gland tumors, a systematic review on PSMA PET imaging conducted in 2022 concluded that PSMA scans have the potential to detect AdCC cases that may not be identified using standard radioimaging methods [47]. The unique advantages offered by each treatment modality often lead to their combined use.

For diagnosis a biopsy of the tumor under general anesthesia along with tumor exploration, followed by a thorough histopathological analysis is recommended [48]. Detailed information regarding the specific diagnostic or radiological modalities employed in the included studies was not provided. Although some studies mentioned the utilization of MRI or PET/CT in their methodology, no further specific information or percentages regarding their usage was provided.

According to our analysis, snAdCC have a higher incidence in the paranasal sinuses (67.6%) compared to the nasal cavity (29.7%), with most cases being observed in the maxillary sinus (50.9%). A retrospective study on sinonasal malignancies based on data from the National Cancer Data Base for the period between 2004 and 2012 indicated that tumors situated in the nasal cavity demonstrated a comparatively more favorable prognosis for OS than those located in the maxillary sinus [49]. The authors hypothesize that this might be due to better surgical accessibility. Therefore, it is essential to consider the anatomical site of the tumor when assessing the prognosis of patients with snAdCC.

Only five out of the 17 included studies reported that their samples were pathologically reviewed. This is worth mentioning, as firstly, the diagnosis of AdCC remains challenging due to its broad morphological spectrum and secondly, new, emerging tumor entities in the sinonasal tract further complicate the diagnostic process [50]. A recent study, albeit with limited sample size, has estimated a 10-15% misdiagnosis rate, suggesting that the rate of misdiagnosis of tumors mimicking AdCC is considerable [51]. For instance, the distinction between the cribriform or solid variant of AdCC and Human Papillomavirus-Related Multiphenotypic Sinonasal Carcinoma (HMSC), formerly known as Human Papillomavirus-Related Carcinoma with Adenoid Cystic-like Features is challenging [52]. HMSC has a more favorable prognosis than AdCC, and this may result in an improved OS estimate [53, 54].

Treatment

According to the latest guidelines of the American Society of Clinical Oncology (ASCO), surgery and postoperative radiotherapy are strongly recommended for all patients with AdCC, in order to improve local disease control [55]. Out of the patients that were included in the analysis, this bimodal approach was applied to 45.4%. Regarding the surgical strategy, state-of-the-art endoscopic techniques, most often allow a comprehensive tumor resection with at least equal ability to achieve negative margins, while minimizing associated morbidity [56-59]. Purely open or combined (open – endoscopic) approaches should be reserved for well-selected cases, such as maxillary sinus AdCCs, with infiltration of the bony lateral, inferior or anterior wall or extensive and lateral tumor manifestation in the frontal sinus. Postoperative radiotherapy is beneficial for several reasons. Firstly, there is a high rate of advanced tumor categories at initial diagnosis, which can be attributed to the lack of early symptoms. Secondly, perineural spread is frequently observed, necessitating additional treatment measures. Thirdly, achieving clear surgical margins can be can difficult in certain cases, as evidenced by our results, which revealed that 55% of all snAdCC patients had positive margins. While patients with tumors primarily originating from the nasopharynx, clivus, sphenoid sinus, or cavernous sinus are candidates for high-dose proton beam radiation therapy [60], IMRT is the standard of reference for snAdCC [61]. Notably, one study included in this meta-analysis specifically investigates long-term outcomes from proton therapy in sinonasal carcinomas, with all patients receiving primary or adjuvant proton therapy [29]. Additionally, 70% of these patients received concurrent chemotherapy as part of their treatment. Within the analyzed cohort of 143 patients, a subset of 23 individuals exhibited snAdCC. With a 5-year OS of 89% they had the most favorable outcome at five years from all the studies included in this meta-analysis. Based on these findings, the authors concluded that proton therapy after total tumor resection provides an excellent long-term local control for patients with locally advanced sinonasal cancer. This treatment modality may be particularly suitable for snAdCC, given their propensity to present with an advanced local stage at the time of diagnosis.

For long-term tumor control in the metastatic setting or in case of no remaining surgical and radiotherapeutic options for local tumor control, platinum-based single-agents and combination regimen are widely used, as this pattern is also evident in our meta-analysis. However, limited data on the efficacy of these treatments are available [62]. As PD-L1 is rarely expressed in AdCC, conventional immune checkpoint therapy does not play a noteworthy role [63]. On the other hand, translocated enhancer-driven overexpression of transcription factor MYB, which plays a pivotal role in AdCC pathogenesis, may lead to upregulation of receptor tyrosine kinases, including KIT, EGFR, FGFR, and VEGFR [64].

Data on the role of multi-target inhibitors, such as Lenvatinib, showed a moderate degree of disease stabilization to patients in the recurrent or metastatic stage, without strong evidence of significant clinical benefits so far [65]. However, a randomized controlled trial (RCT) has demonstrated that Axitinib could substantially enhance six-month progression-free survival (PFS) in patients with recurrent or metastatic AdCC [66].

Outcome

Our meta-analysis showed an overall estimate of 5-year OS of 68%. However, there were four studies that differ significantly from the pooled proportion in the meta-analysis. Among these studies, two had a better OS compared to the overall estimate. Pantvaidya et al. excluded patients with unresectable tumors who were treated with palliative intent or who refused further treatment [40]. Wang et al. excluded patients who had distant metastasis at diagnosis [5]. These exclusion criteria may have resulted in a more homogenous patient population with less advanced disease, potentially leading to better OS estimates. Two included studies reported a worse 5-year OS compared to the overall estimate. Interestingly, both studies were obtained from databases (National Cancer Data Base and Swedish National Cancer Registry). Elliot et al. had no exclusion criteria [7] and Trope et al. [14] only excluded patients with missing data or if they already had surgery at a distant site. Studies with less stringent exclusion criteria, including patients with advanced disease and/or medical comorbidities that hamper treatment, may have led to worse 5-year OS estimates.

A previous meta-analysis on snAdCC by Amit et al. in 2013, which reported a study population of 520 patients, also included AdCC of the nasopharynx with skull base involvement [67]. Our meta-analysis aimed to specifically focus on snAdCC without including any additional anatomical subsites and found slightly higher 5-year OS (68% vs. 62%) and 5-year DFS (47% vs. 43%) rates. Another meta-analysis on snAdCC from 2013, including 366 patients, reported a slightly lower weighted estimate of 5-year OS at 64.5% [12]. Notably, they also incorporated cases of the nasopharyngeal, orbit, and anterior skull base AdCC. Possible explanations for the lower survival rates in the former studies could be improved treatment options over time or the inclusion of nasopharyngeal and skull base AdCC, which have been associated with poorer outcomes [68]. A proximity to vital anatomical structures, a frequent involvement of cranial nerves and the cavernous sinus as well as limitations in achieving a complete tumor resection without extensive morbidity, may contribute to this fact.

The high recurrence rate of snAdCC translates into a low DFS rate, which was observed in our analysis. The overall recurrence rates in snAdCC have been reported in the range of 55-65%,

with approximately 30% of cases experiencing local recurrences and 40% experiencing distant metastases [4, 20]. Moreover, a significant percentage of patients experience combined treatment failures [69]. In a retrospective study on AdCC, it was observed that recurrence was predominantly local at two years but became predominantly distant after two years, suggesting a shift from local to distant metastasis after two years [30]. AdCC also has the highest recurrence rate beyond five years when compared to other sinonasal tumors [16]. The lack of sufficient data on recurrence patterns in the studies included in our meta-analysis prevented further analysis on this topic. However, the high incidence of late recurrences underscores the necessity of long-term follow-up in managing patients with this disease, which may be required for extended periods, even lifelong [70, 71].

Strengths and limitations

In lack of higher-level evidence, we exclusively included retrospective case series, a study type usually ranked as low quality and typically associated with different types of biases [72, 73]. Nevertheless, it is important to note that for rare tumors like snAdCC, case series provide the most pertinent source of data. Our meta-analysis showed significant heterogeneity among the studies in terms of OS, which may be attributed to differences in patient characteristics, treatment modalities, and follow-up periods. However, no evidence of heterogeneity was observed among the studies regarding the 5-year DFS. A limitation for conducting further subgroup analysis (such as survival analysis stratified by approach, by surgical margins, etc.) is the lack of specific data on snAdCC, which was due to many studies including mixed anatomical sites or different tumor entities and not reporting results exclusively for the sinonasal tract. Despite these limitations, our approach of exclusively focusing on snAdCC resulted in more homogenous results and provided valuable insight into the prognosis of this rare malignancy.

Conclusion

To our knowledge, this is the first systematic review and meta-analysis to focus exclusively on the outcome of snAdCC and incorporates the available evidence from the last decade. By pooling the available data from the literature, we estimated a 5-, and 10-year OS rate of 68% and 40%. The 5-year DFS rate was found to be 47.2%, indicating a poor long-term tumor control. These results showcase the challenges in the treatment of patients with snAdCC and highlight the importance of a multidisciplinary treatment approach and a long-term follow-up, ensuring rigorous surveillance throughout their lifetime.

Authorship contribution

TM was responsible for study selection, data extraction, risk of bias and quality assessment, statistical analysis, and writing the study. DH, MBS, and SAM were involved in the conception of the study, offering valuable input during discussions, and critically reviewing the study. PB gave expert advice for all inquiries related to the field of radiation oncology. UH supported the statistical analysis, including essential advice on appropriate methods and interpretation of the results. SNF and NJR provided consulting assistance for all questions regarding pathology. CMM gave crucial support throughout the project, cross-checking decisions, assisting with data extraction and manuscript preparation. All authors read, edited, and approved the final version of the manuscript.

Conflict of interest

All authors state no conflict of interest.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Supplementary material 1. Search strategy used for each database (Cochrane, EMBASE and MEDLINE).

Column1	Column2	Hits
Search Name:		
Date Run:	18/03/2022 22:27:02	
Comment:		
ID	Search	
#1	((adenoid OR adenocystic OR "pharyngeal tonsil") NEAR/3 (cancer or carcinoma*)):ti,ab,kw OR (spiegler NEAR/3 (tumor* OR tumour*)):ti,ab,kw OR cylindroma*:ti,ab,kw	100
#2	(sinonas* or sino-nas* or sinusnas* or sinus-nas* or nasal-sin* or nasalsin* or naso-sin* or nasosin*):ti,ab,kw	888
#3	#1 AND #2	2

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No.	Query	Results
#5	(#2 OR #3) AND ([english]/lim OR [french]/lim OR [german]/lim)	344
#4	#2 OR #3	364
#3	('sinonasal adenoid cystic carcinoma'/exp OR (('adenoid cystic carcinoma'/exp OR (((adenoid OR adenocystic OR 'pharyngeal tonsil') NEAR/3 (cancer OR carcinoma*)):ti,ab,kw) OR ((spiegler NEAR/3 (tumor* OR tumour*)):ti,ab,kw) OR cylindroma*:ti,ab,kw) AND (sinonas*:ti,ab,kw OR 'sino nas*':ti,ab,kw OR sinusnas*:ti,ab,kw OR 'sinus nas*':ti,ab,kw OR 'nasal sinus*':ti,ab,kw OR nasalsin*:ti,ab,kw OR 'naso sin*':ti,ab,kw OR nasosin*:ti,ab,kw))) AND [conference abstract]/lim AND [2019-2022]/py	39
#2	('sinonasal adenoid cystic carcinoma'/exp OR (('adenoid cystic carcinoma'/exp OR (((adenoid OR adenocystic OR 'pharyngeal tonsil') NEAR/3 (cancer OR carcinoma*)):ti,ab,kw) OR ((spiegler NEAR/3 (tumor* OR tumour*)):ti,ab,kw) OR cylindroma*:ti,ab,kw) AND (sinonas*:ti,ab,kw OR 'sino nas*':ti,ab,kw OR sinusnas*:ti,ab,kw OR 'sinus nas*':ti,ab,kw OR 'nasal sinus*':ti,ab,kw OR nasalsin*:ti,ab,kw OR 'naso sin*':ti,ab,kw OR nasosin*:ti,ab,kw))) NOT [conference abstract]/lim	325
#1	'sinonasal adenoid cystic carcinoma'/exp OR (('adenoid cystic carcinoma'/exp OR (((adenoid OR adenocystic OR 'pharyngeal tonsil') NEAR/3 (cancer OR carcinoma*)):ti,ab,kw) OR ((spiegler NEAR/3 (tumor* OR tumour*)):ti,ab,kw) OR cylindroma*:ti,ab,kw) AND (sinonas*:ti,ab,kw OR 'sino nas*':ti,ab,kw OR sinusnas*:ti,ab,kw OR 'sinus nas*':ti,ab,kw OR 'nasal sinus*':ti,ab,kw OR nasalsin*:ti,ab,kw OR 'naso sin*':ti,ab,kw OR nasosin*:ti,ab,kw))	445

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Search Strategy:

#	Searches	Results
1	exp Carcinoma, Adenoid Cystic/ or ((adenoid or adenocystic or "pharyngeal tonsil") adj3 (cancer or carcinoma*)).ti,ab,kw. or (spiegler adj3 (tumor* or tumour*)).ti,ab,kw. or cylindroma*.ti,ab,kw.	9057
2	(sinonas* or sino-nas* or sinusnas* or sinus-nas* or nasal-sin* or nasalsin* or naso-sin* or nasosin*).ti,ab,kw.	10475
3	1 and 2	215
4	limit 3 to (english or french or german)	202

1. Corticosteroid Use in Otolaryngology: Current Considerations During the COVID-19 Era.

   Chang CWD, McCoul ED, Briggs SE, Guardiani EA, Durand ML, Hadlock TA, Hillel AT, Kattar N, Openshaw PJM, Osazuwa-Peters N, Poetker DM, Shin JJ, Chandrasekhar SS, Bradford CR, Brenner MJ

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