Abstract. Background/Aim: To systematically review the patient characteristics and management approaches of adenoid cystic carcinoma (ACC) infiltrating the skull base. Materials and Methods: According to PRISMA guidelines, PubMed, Scopus, and Cochrane were searched to retrieve studies reporting management protocols and survival outcomes of patients with skull base ACCs. Patient characteristics, management strategies, and outcomes were investigated. Results: The review encompassed 17 studies involving 171 patients, with a female predominance (57.9%) and a mean age of 49±7.12 years. ACCs mostly infiltrated the paranasal sinus (22.2%), cavernous sinus (8.8%), and nasopharynx (7.1%). Perineural invasion was reported in 6.4% of cases. Facial pain, nasal obstruction, and facial paresthesia were the most common symptoms. Surgical resection (45.6%) was favored over biopsy (12.2%). Employing the free flap technique (4.7%), surgical reconstruction of the bony defect after resection was performed using abdominal and anterior thigh muscle grafts in 1.8% of patients each. As adjuvant management, 22.8% of cases had radiotherapy and 14.6% received chemotherapy. Recurrence of skull base ACCs occurred in 26.9% of cases during a mean follow-up time of 30.8±1.8 months. Conclusion: Skull base ACCs pose a surgical challenge mainly due to their proximity to critical neurovascular structures and aggressive behavior. Surgical resection and radiotherapy are shown to be safe and effective treatment modalities. The dismal prognosis and limited data on non-surgical strategies highlight the need for further evaluation of the current management paradigm and upraising innovative therapies to improve patient mortality and quality of life.

Key Words: Adenoid cystic carcinoma, skull base, review.

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cells, with minor to moderate cytoplasm, and far fewer luminal, short cuboidal, eosinophilic cells (3). Although ACCs tend to proliferate slowly, they eventually lead to bone destruction and diffuse skull base infiltration at primary sites, leading to a locoregional recurrence and seeding the leptomeninges via the cerebrospinal fluid (CSF) (4, 5). Therefore, developing a therapeutic strategy of maximal resection with minimal morbidity is a substantial challenge (2).

Because of SBACCs dearth in the literature, a consensus standard of care has not been established, resulting in a wide
<table>
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<tr>
<th>Author</th>
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<th>Age median (range)</th>
<th>Sex females No. (%)</th>
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<th>Biopsy only No. (%)</th>
<th>Extent of surgery No. (%)</th>
<th>Reconstruction technique No. (%)</th>
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<th>Chemotherapy No. (%)</th>
<th>Radiotherapy No. (%)</th>
<th>Recurrence No. (%)</th>
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<th>Alive status at last follow-up No. (%)</th>
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<td>Liu et al. 2021 (13)</td>
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<td>55 (49-63)</td>
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<td>Abdominis Flap, 1 (25); Anterolateral thigh Flap, 3 (75)</td>
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PR: Partial resection; GTR: gross total resection.
array of diagnostic protocols and management approaches (6). Currently, the conventional diagnostic workup consists of imaging modalities, primarily MRI, for preliminary diagnosis and determining tumor characteristics often followed by biopsy and histological examination for definitive diagnosis (7, 8). Additionally, available evidence also recommends surgical management in combination with postoperative radiation, which offers higher tumor control rates compared to radiation alone (6, 9). However, investigations into other therapeutic modalities such as chemotherapy and targeted therapy are limited (4, 10).

In addition to clinical characteristics and therapeutic strategies, the survival outcomes of skull base infiltrating ACCs are sparsely reported in the literature, leaving many questions still unanswered. This study therefore aims to review and summarize the current literature regarding the clinical management of adult SBACCs, with particular focus on patient characteristics, management strategies, and survival outcomes.

Materials and Methods

Literature search. A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, as previously described (11, 12). PubMed, Scopus, and Cochrane databases were searched from inception to June 2021. A medical subject headings (MeSH) term and keyword search of each database was conducted using the Boolean operators OR and AND. Terms used were as follows: “adenoid cystic carcinoma” AND “skull AND base”.

Study selection. We included studies meeting the following criteria: 1) prospective or retrospective studies reporting more than one patient with adenoid cystic carcinoma infiltrating the skull base, 2) patients with histologically confirmed adenoid cystic carcinoma, 3) patients aged 18 years or older, and 4) sufficient data report on patient characteristics and management outcomes. Studies were excluded if they: 1) were meta-analyses, reviews, editorials, letters, or books, 2) contained insufficient clinical data (lacking both patient demographics or management details), and 3) were not written in English.

Data extraction. One author (A.C.) extracted data from the target articles, which were confirmed independently by another author (O.B.A.) to ensure accuracy. Variables extracted included: 1) author’s name, 2) date of publication, 3) sample size, 4) sex, 5) presenting symptoms, 6) management strategy and treatment modalities used (radiotherapy, chemotherapy, surgical resection), 7) recurrence, and 8) survival. Missing data are either not reported by the authors or reported indistinctively from other data that could not be differentiated.

Results

Study selection. The literature search of PubMed, Scopus, and Cochrane databases yielded 680 citations. The selection process (Figure 1) yielded a total of 17 articles, categorized as level IV, that met the pre-specified inclusion criteria (Table I) (10, 13-28) The risk of bias assessment categorized the included studies as “good” quality (i.e. low risk of bias).

Patient demographics and clinical features. Our demographic results showed a mean age of 49±7.1 with a female predominance (57.9%) in our patient cohort (Table II). Facial pain was the most common symptom (11.6%), followed by...
facial paresthesia (5.2%), and nasal obstruction (2.9%). In our cohort, 13.4% reported cranial nerve deficits; trigeminal, optic, and glossopharyngeal nerves were the most frequently affected in 8.1%, 1.1%, and 1.1% of cases. The most commonly invaded structures were the paranasal sinus (22.2%), the cavernous sinus (8.8%), nasopharynx (7.1%), and Meckel’s cave (5.2%). Perineural invasion was recorded in only 6.4%.

Management approaches and survival outcomes. At the last follow-up, 46 patients (26.9%) had recurrent tumors, and 47% of reported data (n=62) died due to tumor progression. Mean follow up time was 30.8±1.8 months with a 5-year survival rate of 18% (Figure 2). Surgical intervention was the primary treatment strategy, with 45.6% undergoing surgical resection; however, 12.2% had biopsy only. Of the surgical cases, only a few reported reconstruction details (n=8). A free flap was used in all cases, and the rectus abdominis and anterior lateral thigh were the most frequently used flap material. A total of 39 patients (22.8%) received radiotherapy, with a mean dose of 64.1±9.2 Gy. External beam radiotherapy was the most common radiotherapeutic modality employed (8.8% of patients). Chemotherapy was used in a small fraction of patients (n=25; 14.6%), and Cisplatin was the most frequently used agent (5.8%). No survival benefit was detected in surgical resection, radiotherapy, or chemotherapy (Figure 3).

Discussion

ACCs invading the skull base represent challenging tumors, given their anatomical proximity to critical neurovascular structures and unique perineural metastatic potential. Microsurgical resection in conjunction with radiotherapy has been the primary treatment strategy. However, large series on SBACCs are limited in the literature. The present review described the clinical characteristics and management outcomes of SBACC. We found that surgical resection, radiotherapy, or chemotherapy confer no survival benefits. Part of these data has been previously published (29).

Patients and clinical characteristics. In our review, the mean age at presentation was 49±7.1, similar to laryngeal ACCs, which were reported to generally affect patients in their fifth decade (30). Although most agree that there is no difference in prevalence between males and females in ACCs, our results found a slight female predominance in SBACC (57.9%).

Skull base tumors usually present with CSF obstruction-related symptoms or direct brainstem compression (31, 32). Likewise, nasal obstruction, facial pain, and facial paresthesia were the main symptoms in our data set. The trigeminal nerve was the most affected, followed by the optic and glossopharyngeal nerves. The high rate of cranial

Figure 2. Kaplan-Meier survival curves for the overall survival (OS) of the cohort.
nervous deficit is attributed to either the tumor mass effect or the tumors’ perineural invasion ability, although perineural invasion was reported in only 6.4% of the cases analyzed. In contrast, in a separate systematic review investigating perineural invasion on head and neck ACC (HNACC) prognosis, the perineural invasion was detected in 43% of the cohort (33). This rate difference in perineural invasion is likely ascribed to the heterogeneous reporting and the study scope of our systematic review, as most SBACC articles focus on surgical techniques and reconstruction.

Other studies on HNACC document the palate as the most common invaded structure (34). However, we found that the paranasal sinuses were the most invaded structure. This is reasonable as ACCs represent a primary salivary neoplasm putting paranasal sinuses and craniofacial structures at risk of invasion due to their proximal anatomical location.
Treatment and outcomes. From the available data, 47% of patients died because of tumor progression, with a 5-year survival rate of 18%, while 26.9% had tumor recurrence. Our results agree with the HNACC recurrence rates (13.3% - 55%) but represent a more devastating survival rate (35-37).

Although surgical resection remains the cornerstone management for ACC, the extent of resection and the role of radiotherapy remain controversial (38-40). In the present study, surgical intervention was the most employed strategy, with biopsy alone being used in only 12.2% of cases. This is likely due to patients presenting with disfiguring tumors requiring surgical decompression. Historically, indications for radical surgery were limited for advanced skull base tumors as adequate reconstruction was often difficult to perform. However, advancements in reconstructive techniques have significantly improved the management of skull base tumors (14). We found that all articles that reported reconstruction performed free flap techniques, using either abdominal flap, anterior thigh flap, or fibula osteomyocutaneous flap. Our findings were consistent with the general recommendations on cranial base reconstruction materials and techniques for skull base tumor resections involving the anterior and middle cranial bases (41, 42).

ACC has been historically believed to be radioresistant (43). However, recent data have reported higher survival and lower recurrence rates following radiotherapy, supporting the radiosensitivity of ACC (44). We found that 22.8% of patients received radiotherapy, with external beam radiotherapy being the most frequently used modality, while only 14.6% received chemotherapy. A similar observation of the low rate of chemotherapy administration was also reported in the HNACC literature (33). Lastly, although surgical resection, radiotherapy, and chemotherapy showed better survival benefits, statistical significance was not reached in any modality.

Study limitations. This study had several limitations. Firstly, the reported data was heterogeneous with inconsistent definitions of variables. Similarly, the included articles suffered from selection bias in patient inclusion and the management protocols, including, but not limited to, surgical approach, radiation parameters and technique, and chemotherapy. Several variables such as histopathological type, invaded structures, tumor volume and treatment type were incompletely reported. Most articles reported SBACCs as part of craniofacial ACC, and others reported ACCs as part of other skull base tumors, limiting data extraction.

Conclusion

ACC involving the skull base is a challenging pathology, typically with indolent, relentless progression. Included articles reported various symptoms related to the invaded neurovascular structures consistent with the invasive nature of the pathology. Due to the absence of superior alternative treatments, surgical management in conjunction with radiotherapy has remained the primary treatment strategy. Free flap techniques and skull base reconstruction represent an essential element of the management after salvage resection of advanced SBACCs.
Conflicts of Interest

The Authors report no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

Authors’ Contributions


References
