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Advanced adenoid cystic carcinoma of the skull base – The role of surgery

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ABSTRACT

Background: Adenoid cystic carcinoma (ACC) is a salivary gland malignancy with a propensity for perineural spread and diffuse soft tissue infiltration. In the head and neck this unique biological behaviour can result in skull base involvement. A lack of consensus regarding management of ACC involving the skull base in conjunction with the technical and reconstructive challenges of oncological resection in this region has led to variation in practice between institutions.

Method: Retrospective multicentre review of patients with advanced ACC infiltrating the skull base, treated surgically by the Queensland Skull Base Unit between 2005 and 2017, with a minimum follow up time of 24 months.

Results: 32 patients were treated for ACC with skull base involvement with oncological resection and post-operative radiation in the study period with a median follow up of 82.18 months (33.11–159.53 months). 5 and 10 year locoregional control were both 88.2% (95% CI 67.5–96.1) despite a high rate of microscopically positive margins (81.3%). Metastatic disease rates were high, resulting in low rates of disease free survival (DFS) (53.0% at 5 years (95% CI 33.7–69.0) and 23.0% at 10 years (9.5–39.8)).

Overall survival (OS) was high (5 year 91.8% (95% CI 71.1–97.9), 10 year 63.7% (95% 37.5–81.2)), despite the advanced nature of disease.

Conclusion: High rates of locoregional control can be achieved in skull base ACC with oncological resection of disease and post-operative radiation. Whilst disease recurrence rates are high, a majority of recurrence is metastatic and does not confer poor intermediate term overall survival.

Introduction

Adenoid cystic carcinoma (ACC) is a primary salivary gland neoplasm with a unique biological behaviour. The propensity for perineural spread (PNS) and diffuse local tissue infiltration often results in skull base involvement in advanced head and neck disease [1–3]. The treatment consensus in ACC is surgical resection to negative clinical margins followed by post-operative radiation [4–8]. However, oncological resection of the skull base is technically challenging requiring multi-speciality ablative teams and complex reconstructive demands [9–11]. Additionally, the surgery is physiologically demanding for the patient and the extent of surgical resection must be carefully considered to avoid unacceptable patient morbidity. This had lead some centres to abandon oncological resection and treat these cases with definitive or palliative radiotherapy. The aim of this study was to analyse the associations between clinical features, surgical treatment, and the survival outcomes in patients affected by ACC involving the skull base treated with surgery.

Materials and methods

Patient population

A retrospective review of patients diagnosed with ACC involving the skull base, treated by the Queensland Skull Base Unit at the Princess Alexandra and Mater Hospitals between 2005 and 2017, was

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performed. Institutional ethics approval was obtained. Inclusion criteria for this study required a histological diagnosis of ACC with direct involvement of either the anterior, central or posterior skull base or perineural spread of disease within a cranial nerve up to or past the skull base foramen. Patients must have been treated with surgery with a minimum follow up time of 24 months. Epidemiological and clinical data, surgical and histopathology reports, radiology, complications, adjuvant therapies and follow up consultations were reviewed. All patients were assessed preoperatively at our institutions tumour board and received preoperative imaging. Patients included in the study were staged retrospectively according to the TNM staging system (8th edition).

Treatment

Patients were evaluated at a multi-disciplinary team meeting which included head and neck surgeons with a sub-speciality skull base interest, reconstructive surgeons, medical oncologists, radiation oncologists and allied health professionals. Patients underwent pretreatment radiographic imaging including contrasted magnetic resonance imaging (MRI) of the skull base and neck and/or computed tomography (CT) of the skull base and neck, and either positron emission tomography (PET) and/or CT scan of the chest to evaluate for distant metastases. Imaging and clinical evaluation was used to assess candidacy for surgical resection and ultimate treatment was determined by a multidisciplinary tumour board. Surgery involved open, endoscopic alone, or combined open and endoscopic approaches - as deemed appropriate by the tumour board and the operating surgeon.

Patient characteristics and epidemiological data was collected retrospectively from the patient notes. Treatment characteristics including operative details, operative time, perioperative and postoperative course were examined. Histopathology reports were reviewed and surgical margins, perineural spread, tumour size and the infiltration of adjacent structures (such as bone, dura, orbit and brain) were recorded. Histopathological specimens were classified according to the Perzin grading system: Grade 1- tubular pattern without solid component, 2- cribriform pattern with a maximum 30% solid pattern, or 3- more than 30% solid pattern.

Outcome measures

The primary clinical end points examined were overall survival (OS), disease free survival (DFS) and locoregional control (LC) rates at both 5 and 10 years. Secondary end points included multivariable analysis for known prognostic factors including T stage, presence of perineural spread , surgical margin status and tumour subsite.

Statistical analysis

Statistical analysis was performed with R version 3.5.0 with the survival package (v2.43–3). Kaplan- Meier curves were calculated for the outcomes of interest- OS, DFS and (LC). Survival probabilities with 95% confidence intervals (CI) were estimated at 5 and 10 years. Separate Kaplain-Meier curves were calculated for major known prognostic factors. The log-rank test was used to compare these curves.

Results

Patients

Out of a total of 112 patients presenting within the study period, 32 patients fulfilled the inclusion criteria. The clinical and epidemiological data are summarised in Table 1. The patients consisted of 18 females and 14 males with ages ranging from 26 to 85 years (mean 50.75 years) The majority of skull base ACC (SB ACC) originated in the sinonasal region (n = 17, 53.1%) followed by the parotid gland (n = 13, 40.6%), with smaller numbers from the sublingual, submandibular and lacrimal glands. Tumours were all advanced T stage (T3 = 3, T4a = 18, T4b = 11). In keeping with the biological behaviour of ACC, only one patient had nodal disease at time of treatment. The most common presenting symptoms were nasal obstruction, facial dysaesthesia or weakness, epistaxis and headache. Four patients (12.5%) had previous surgery and were presenting with recurrent disease.

Table 1
Clinical and epidemiological data.

Variable	*N = 32*
Sex	
Female	18 (56.3%)
Male	14 (43.8%)
Age (in yrs)	50.75 years (range 26-85yrs)
Tumour epicenter	
Sinonasal tract	17 (53.1%)
Parotid Gland	13 (40.6%)
Submandibular Gland	1 (3.1%)
Sublingual Gland	1 (3.1%)
T Classification	
T3	3 (9.4%)
T4	29 (90.6%)
N Stage	
N0	31 (96.9%)
N+	1 (3.1%)

Treatment characteristics

All patients were treated with surgery, as per the inclusion criteria, followed by adjuvant radiotherapy. The surgical procedure performed depended on the tumour epicentre and the extent of disease. Sinonasal tumours were treated with endoscopic resection in 7 patients (41.1%), open resection in 6 patients (35.3%) and a combined endoscopic/open resection in 4 patients (23.5%). All tumours treated with endoscopic endonasal resection alone originated in the nasal cavity or ethmoids. Direct anterior skull base or cribriform infiltration were addressed with an endoscopic transnasal craniectomy. Maxillary nerve (V2) and vidian nerve involvement were resected to dura via an endoscopic transpterygoid approach. Tumours originating in the maxilla, required maxillectomy, and were treated with open surgical resection. However, endoscopic techniques were used in combination with open resection in four patients - either to address additional nasal/paranasal sinus disease, or to assist in V2 nerve dissection. All patients with major salivary gland disease (parotid, submandibular, sublingual) required open resection. Parotid disease with facial nerve palsies were treated with a radical parotidectomy with some form of temporal bone dissection and facial nerve resection in all patients. 4 patients required the addition of open infratemporal fossa dissection for Mandibular nerve (V3) disease via the auriculotemporal nerve.

Craniotomy was performed in nine patients. The most common indication for craniotomy was intracranial trigeminal nerve infiltration, allowing peripheral nerve resection in conjunction with part of the trigeminal ganglion. The skull base was reconstructed with local tissue in 7 patients. Smaller anterior skull base defects were reconstructed with a nasoseptal flap in 5 patients, and 2 patients had larger skull base defects requiring pericranial flap reconstruction. Free flap reconstruction was performed in 15 patients which, in addition to restoring facial contour, provided reconstruction of the skull base. In keeping with the biological behaviour of ACC, only one patient presented with cervical nodal disease requiring oncological neck dissection. However, a further 15 patients had selective neck dissections performed to provide vessels for free flap reconstruction.

Post-operative radiotherapy (PORT)

All patients were treated with PORT. All patients underwent pre-treatment dental assessment and CT planning using a thermoplastic immbolisation mask. Prior to 2008 patients were treated using 3-Dimensional conformal RT and from 2008 were treated with Intensity Modulated RT or Volumetric Modulated Arc Therapy (VMAT). Prescribed volumes to the primary were typically dependent on histo-pathological margin status. In the presence of microscopic positive margins 66 Gy in 33 fractions was prescribed for non-IMRT/VMAT techniques and 63 Gy in 30 fractions using a simultaneous integrated boost for IMRT/VMAT techniques while respecting the critical organs at risk (OAR). The disrupted surgical bed that did not harbor disease received 54 Gy in 27 fractions for non-IMRT/VMAT techniques and 56 Gy in 30 fractions for IMRT/VMAT techniques. The dose to the OAR of brainstem, optic chiasm and optic nerves were limited to 54 Gy. However, in some cases the ipsilateral optic nerve, following discussion with the patient, was treated up to 60 Gy if there was concern that there was residual disease at the orbital apex. The spinal cord was limited to 45 Gy. Volumes to large nerve PNS were dependent on the zonal extent of disease on imaging and pathology: zone 1,2,3 were treated to the ganglion, prepontine aspect of the nerve and brainstem respectively. Regional lymph nodes were only addressed if pathological involved and thus one patient received nodal irradiation. Complications after PORT included wound breakdown (n = 3) and osteoradionecrosis (n = 1).

Perioperative outcomes and complications

Postoperative hospital stay varied from 5 to 32 days (mean 14.2 days, median 10.7 days). Patients treated with endoscopic dissection alone had a significantly shorter postoperative stay (mean 5.8 days). Complications were reported in 46.8% (n = 15 patients) during surgical admission. The most frequent post-surgical complication was free flap reconstruction related (n = 4), followed by cerebrospinal fluid (CSF) leak (n = 3) and pulmonary embolism (PE) (n = 3) (see Table 2) [12]. Free flap reconstruction related complications included 2 minor flap dehiscence treated with simple wound dressings. 2 patients returned to theatre due to flap ischemia for pedicle revision, 1 patient on Day 0, 8 h post-operatively and 1 patient on Day 1, 28 h post-operatively. Post-operative CSF leak occurred in 2 patients post endoscopic transnasal craniectomy, both were treated with a combination of conservative measures (bed rest, stool softners) and lumbar drain placement. 1 patient had CSF noted in the surgical drain at Day 3 post radical parotidectomy, temporal bone dissection, infratemporal fossa dissection and craniectomy, and was treated with conservative measures with drain output resolving at Day 10. PE occurred in 3 patients post-operatively, despite all patients received thromboprophylaxis including thromboembolism deterrent (TEDS) stockings and sequential compression devices (SCDs) commencing at Day 0 and subcutaneous heparin commencing Day 1. 2 patients had uncomplicated recovery with therapeutic anticoagulation. 1 patient developed significant respiratory embarrassment on Day 4 post-operatively requiring intensive care (ICU) support and ventilation. This patient required mechanical ventilation for 72 h, treated with appropriate anticoagulation, and was ultimately discharged at Day 17 postoperatively with no respiratory compromise. Overall, 3 patients required a return to theatre - two patients for free flap reconstruction revision, and one for postoperative hematoma. There was no mortality associated with the immediate post-operative period (see Table 2).

Pathological outcomes

Perzin histological tumour grade [13] was available in 29 patients. Grade 3 was the most frequently reported (13 cases 44.8%), followed by grade 2 (11 cases, 37.9%) and grade 1 (5 patients, 17.2%). Reflecting the advanced disease and the infiltrative nature of the disease - microscopic histological margins were reported as positive in 81.3% of patients (n = 26). Microscopic pernineural invasion (PNI) was reported histologically in 96.9% of patients (n = 31). Large nerve perineural spread (PNS) was seen in 62.5% of patients (n = 20). The extent of PNS was most commonly Zone 2 (n = 11, 55%) followed by Zone 1 (n = 9, 45%) [14].

Table 2
Treatment data.

Variable	***N = 32***
Treatment	
Endoscopic	7 (21.9%)
Open	21 (65.6%)
Combined	4 (12.5%)
Craniotomy	9 (28.1%)
Reconstruction	
Regional	7 (21.9%)
Free Flap	15 (46.9%)
Combined	3 (9.4%)
Complications (according to Clavien-Dindo classification)	
Any	15 (46.9%)
Grade 1- Minor deviation from normal postoperative course. (n = 4)	Wound Dressings (n = 3) - Free flap dehiscence (n = 2) - Simple wound dehiscence (n = 1) Prolonged surgical drain - CSF leak- conservatively managed (n = 1)
Grade 2- Complication requiring pharmacological intervention. (n = 5)	Anticoagulation (n = 2) - Pulmonary embolism (n = 2) Antibiotics (n = 3) - Pulmonary infection (n = 2) - Urinary tract infection (n = 1)
Grade 3- Complication requiring surgical or radiological intervention (n = 5).	Return to OT (n = 3) - Free flap reconstruction revision (n = 2) - Postoperative hematoma (n = 1) Procedure under local anaesthetic (n = 2) - Insertion of Lumbar Drain for CSF leak (n = 2)
Grade 4- Life threatening complications requiring intensive care (ICU) support. (n = 1)	Respiratory Support + Anticoagulation (n = 1) - Pulmonary embolism (n = 1)
Grade 5- Death of patient.	n = 0

Oncological outcomes

Of the 32 patients included in this study, 25 were alive at time of analysis. 10 patients were free of disease (NED). 23 patients were currently being followed up at our institution, with a median follow up of 82.18 months (33.11–159.53 months).

Survival

The 5 and 10 year overall survival (OS) was 91.8% (95% CI 71.1–97.9) and 63.7% (95% 37.5–81.2) respectively (See Table 3 and Fig. 1). Disease free survival (DFS) was 53.0% at 5 years (95% CI 33.7–69.0) and 23.0% at 10 years (9.5–39.8) (See Table 3 and Fig. 2). Analysis of the Kaplan-Meier curves of OS and DFS showed no significant difference between the prognostic factor values (Table 4).

Table 3
Five and ten year survival estimates for outcomes of interest.

Outcome	5 year survival (95% CI)	10 year survival (95% CI)
Overall survival	91.8% (71.1–97.9)	63.7% (37.5–81.2)
Locoregional control	88.2% (67.5–96.1)	88.2% (67.5–96.1)
Disease free survival	53.0% (33.7–69.0)	23.0% (9.5–39.8)

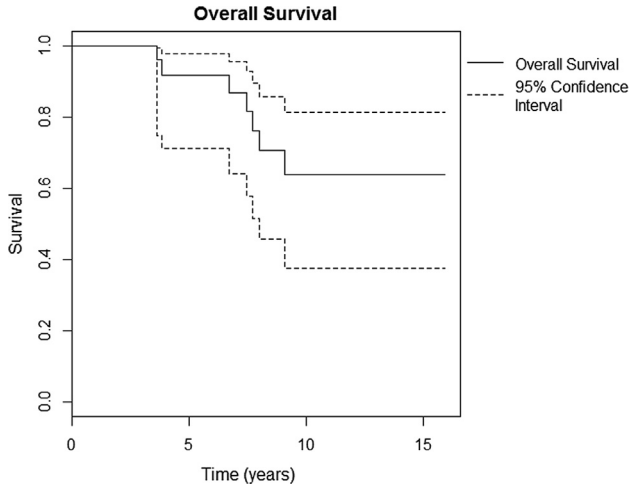

Fig. 1. Kaplan-Meier curve for overall survival.

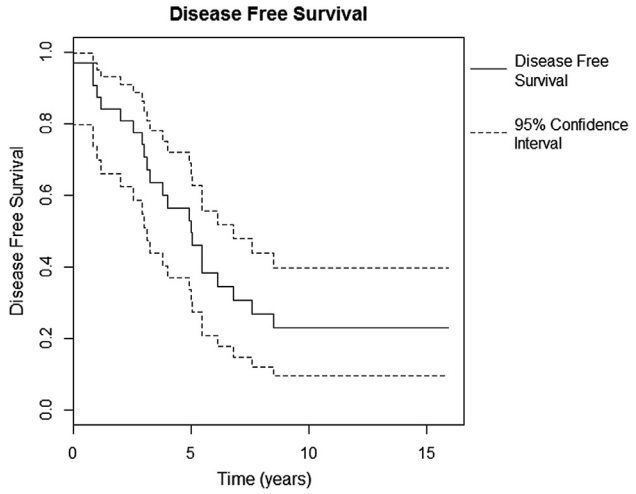

Fig. 2. Kaplan-Meier curve for disease free survival (survival from disease recurrence).

Locoregional control

Three patients developed locoregional recurrence (Fig. 3). Both 5 and 10 year locoregional control rates were 88.2% (95% CI 67.5–96.1), as all patients recurred locally prior to 5 years. Time to locoregional recurrence varied considerably from 24 to 52 months, with an average of 39.2 months. Small patient numbers precluded any meaningful attempt at multivariable analysis for known prognostic factors.

Distant metastasis

Nineteen patients developed metastatic disease. 5 and 10 year metastatic disease free control rates were 62.3% (95% CI 42.1–77.2) and 27.3% (95% CI 11.5–45.7) respectively (Fig. 4). The average time to metastatic disease was 46.7 months (range 0–104 months, median 42). All metastatic disease was either pulmonary or osseous. OS with metastatic disease was a 92.9% (95% CI 59.1–99.0) at 5 years and 45.1% (95% CI 13.8–72.7) at 10 yrs (see Fig. 5).

Discussion

ACC is usually a slowly progressive tumour with a propensity for local infiltration and large nerve perineural spread (PNS) [15–17]. Despite its slowly progressive biological behaviour, it has a high local

Table 4
Five and ten year survival estimates split by patient characteristics.

	Outcome											
	Overall survival (n = 7 deaths)				Disease free control (n = 22 recurrence)				Metastatic disease free control (n = 19)			
Stratification	n deaths	5 year (95% CI)	10 year (95% CI)	p	n deaths	5 year (95% CI)	10 year (95% CI)	p	n deaths	5 year (95% CI)	10 year (95% CI)	p
Overall		91.8% (71.1–97.9)	63.7% (37.5–81.2)			53.0% (33.7–69.0)	23.0% (9.5–39.8)			62.3% (42.1–77.2)	27.3% (11.5–45.7)	
T stage												
T3 (n = 3)	1	66.7% (5.4–94.5)	66.7% (5.4–94.5)	1.0	2	66.7% (5.4–94.5)	33.3% (0.9–77.4)	0.7	2	66.7% (5.4–94.5)	33.3% (0.9–77.4)	0.9
T4 (n = 29)	6	95.5% (71.9–99.3)	61.8% (32.7–81.3)		20	51.6% (31.4–68.5)	21.6% (8.1–39.4)		17	61.8% (40.4–77.5)	26.1% (9.9–45.9)	
PNS												
Present (n = 20)	6	95.0% (69.5–99.3)	60.0% (30.8–80.2)	0.7	19	47.3% (26.9–65.3)	21.5% (7.9–39.5)	0.4	16	58.4% (36.1–75.3)	26.8% (10.1–46.8)	0.7
Not present (n = 12)	1	80.0% (20.4–96.9)	80.0% (20.4–96.9)		3	80.0% (20.4–96.9)	30.0% (1.2–71.9)		3	80.0% (20.4–96.9)	30.0% (1.2–71.9)	
Surgical margin status												
Involved (n = 26)	6	95.0% (69.5–99.3)	61.5% (32.4–81.1)	0.9	18	53.7% (31.9–71.2)	22.4% (8.2–40.8)	0.8	15	65.2% (41.9–81.0)	27.3% (10.2–47.8)	0.5
Not involved (n = 6)	1	80.0% (20.4–96.9)	80.0% (20.4–96.9)		4	50.0% (11.1–80.4)	33.3% (4.6–67.6)		4	50.0% (11.1–80.4)	33.3% (4.6–67.6)	
Subsite/location [+]												
Parotid (n = 13)	5	88.9% (43.3–98.4)	38.1% (8.9–68.0)	0.1	10	26.4% (6.5–52.2)	17.6% (2.8–42.8)	0.2	9	32.5% (8.9–59.2)	21.6% (3.7–49.1)	0.1
Sinonasal (n = 17)	2	92.3% (56.6–98.9)	83.1% (47.2–95.5)		11	67.6% (38.6–85.1)	27.0% (8.4–50.1)		9	80.4% (50.6–93.2)	32.5% (10.2–57.4)	

[+] Lacrimal (n = 1), submandibular gland (n = 1) excluded from the analysis.

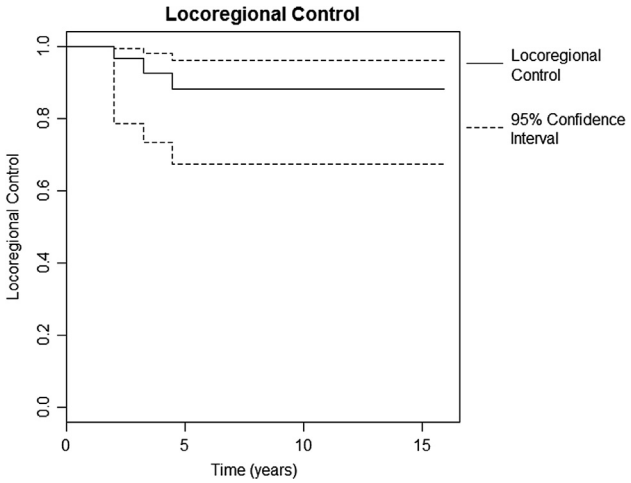

Fig. 3. Kaplan-Meier curve for locoregional control.

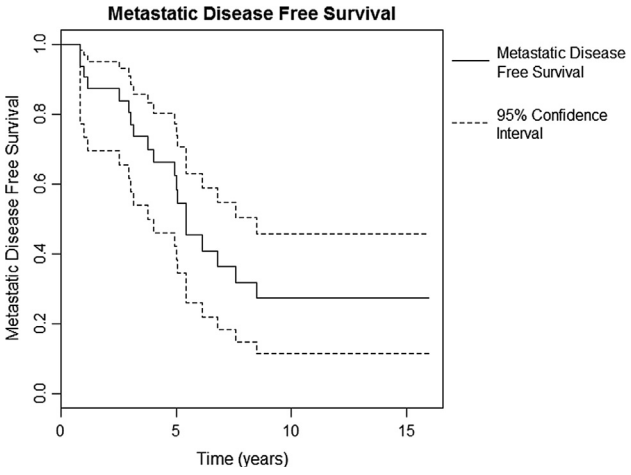

Fig. 4. Kaplan-Meier curve for survival from metastatic disease.

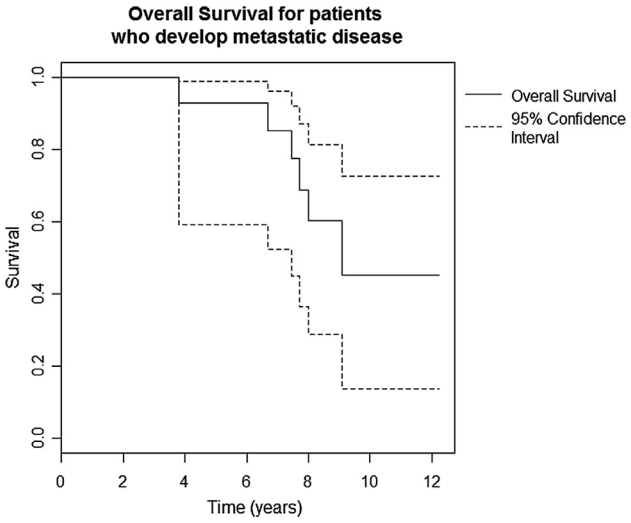

Fig. 5. Overall survival Kaplan-Meier for patients who develop metastatic disease.

recurrence rate and high metastatic potential to both lungs and bone [18–21]. Five year survival rates are generally high, but long term survival reduces dramatically, with the majority of patients dying of local recurrence [1,2,15,22]. The general treatment consensus in ACC is surgical resection to negative clinical margins followed by post-operative radiation to control locoregional disease [4–8]. However, when disease infiltrates the skull base, resection becomes more technically challenging. A microscopic tumour free surgical margin is difficult to attain at the skull base, given the proximity to intracranial structures and perineural nerve disease extension. This has led many centres to define this disease as “unresectable”.

ACC can arise in any salivary gland tissue [21]; and within the head and neck - the major salivary glands represent the most common subsite, followed by tumours originating in the sinonasal tract [23,24]. Sinonasal tumours represented a majority of cases (n = 17, 53.1%) included in this study. It is thought that this is due to the proximity of the sinonasal tract to the anterior and central skull base. The reduced diameter and perforation by olfactory filaments, render the cribriform plate particularly vulnerable to direct skull base infiltration and intracranial disease extension [3,15]. Additionally, multiple cranial and named nerves enter the central skull base through the sinonasal cavity - such as the maxillary nerve and the vidian nerve- via which disease can traverse the skull base foramina and extend centrally [25]. Disease encroaching on the skull base via the sinonasal tract can be addressed transnasal endoscopically or via open craniofacial resection. Transnasal craniectomy can allow resection of large amounts of involved anterior skull base and cribriform plate without the risk profile of conventional craniotomy [25]. Maxillary and vidian perineural spread can be addressed endoscopically to attempt clear margins, often without the need for a formal craniotomy (see Fig. 6).

Major salivary gland disease was the second most frequent tumour subsite represented in this series, predominately from the parotid (n = 13, 40.6%). Local infiltration from the parotid gland into the facial and auriculotemporal nerve, allows retrograde extension to the skull base via the intratemporal facial nerve and maxillary nerve within the infratemporal fossa [25]. Open resection via a radical parotidectomy and some form of temporal bone resection is our institution’s practice to address intratemporal bone facial nerve disease. A preauricular infratemporal fossa approach allows enbloc resection of disease either directly infiltrating in the infratemporal fossa, or extending centrally via the mandibular nerve.

Limited intracranial ACC extension can be addressed in the anterior skull base and middle fossa via transnasal and transtemporal craniectomy respectively. However, if access or disease clearance is suboptimal via these approaches, a formal craniotomy is required. 9 patients in this study required craniotomy. The most common indication for craniotomy was Zone 2 trigeminal perineural spread to allow resection back to - and including part of - the trigeminal ganglion. Craniotomy was associated with a significant increase in perioperative morbidity, length of post-operative hospital stay ($p = 0.032$) and increased operative time ($p = 0.047$). Literature on perineural spread in squamous cell carcinoma (SCC) suggests that disease spreads in a continuous manner and that patients with clear or close margins have a significantly improved overall survival compared to those with involved margins [26,27]. The assumption is that the same is true for ACC, and that the morbidity associated with craniotomy is outweighed by the presumed improved locoregional control and overall survival.

In contrast to other malignancies encountered in the head and neck, such as SCC, cervical locoregional metastasis in ACC are uncommon [28,29]. Our study again demonstrated this with one patient presenting with cervical nodal metastasis and one patient presenting with neck metastasis on follow up. Therefore, from an oncological perspective, the role for neck dissection in the absence of clinical disease is limited. However, the neck dissection may need to be performed for vascular control during the tumour resection or for access to vessels for free flap reconstruction. In our study, the most common indication for the selective neck dissection was to provide vascular access during reconstruction.

Ensuring the oncological results warrant the potential patient morbidity is of paramount concern in skull base surgery. It is generally

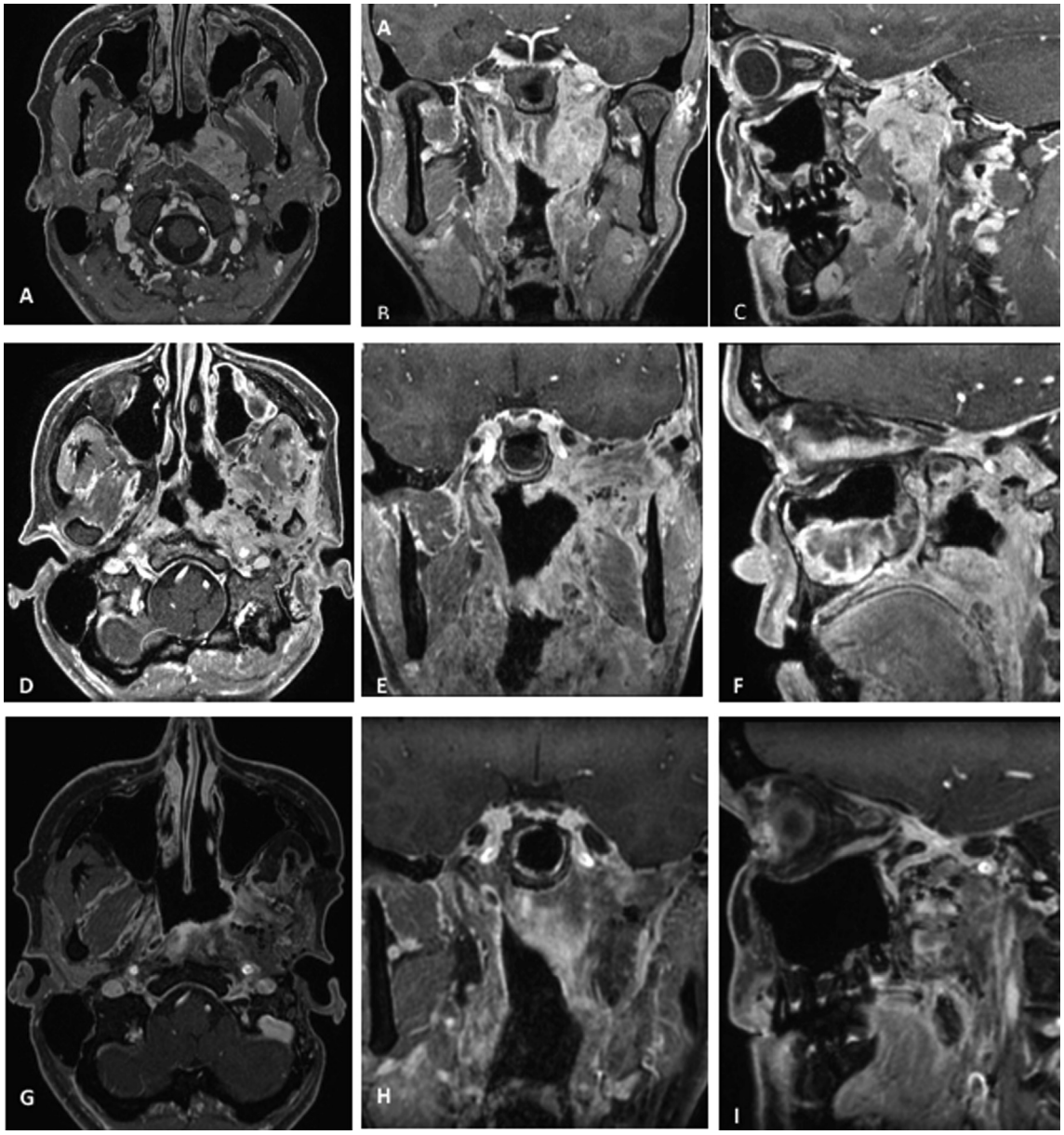

Fig. 6. Patient with advanced sinonasal ACC treated via an endoscopic transnasal/transoral and oral lateral approach. A–C - Pre-treatment, D–F - Post treatment. G-I- 4.5 years post completion of post-operative radiation.

accepted that the optimal treatment of ACC is surgery to negative histological margins, followed by postoperative radiation [30]. However, when treating advanced skull base disease, central extension often precludes resection to negative histological margins due to unacceptable patient morbidity [31]. This has led to wide variations in oncological practice in advanced skull base ACC. Some centres similar to ours advocate complete macroscopic resection with an expected high rate of histologically positive margins followed by post-operative radiation [3,15,21,32]. Others have adopted a non-surgical paradigm, treating this patient cohort with definitive radiation [30,33]. There is a paucity of literature available comparing the efficacy of definitive radiation alone with that of surgery and post-operative RT – and this is further confounded by selection bias. Literature specifically comparing treatment modalities in skull base ACC - to the authors' knowledge - does not exist. However, the published literature on ACC generally supports the notion that surgery combined with postoperative radiation offers superior locoregional control compared to radiation alone. However, improvements in overall survival are less consistent given biological behaviour of the disease [9,30].

Balamucki et al reported on 120 patients treated at the University of Florida between 1996 and 2008; 74 patients (62%) were treated with surgery and adjuvant RT, and 46 patients (38%) were treated with RT alone. Patients treated with RT alone were most commonly defined as unresectable due to PNS to the skull base similar to our cohort. Median follow up was 8.6 yrs with 10 year outcomes for the advanced disease showing a locoregional control of 36%, compared to our 88.2% at 10 years. Less substantial improvements were seen in OS, with 10 year OS in the advanced tumour group being 47% compared to our groups 63.7%. This demonstrates the slowly progressive indolent nature of the disease [30].

In a different analysis of the same patient group, Mendenhall et al published their experience with 101 patients with head and neck ACC, not specifically involving the skull base. 61 patients were treated surgically with post-operative RT, and 40 patients were treated with RT alone. In the group treated surgically 70.5% (n = 43) had positive microscopic margins. Local control at 5 and 10 years were vastly

improved in the surgery and post-operative RT (94% and 91%) group compared to radiation alone (56% and 43%). Whilst selection biases would again influence these findings, it reinforces the superior locoregional control provided by surgery compared to RT alone [9].

This study supports the literature that good locoregional control can be achieved with surgical resection and post-operative RT, despite a high proportion of microscopically positive surgical margins. Additionally, this study demonstrates that this treatment philosophy can be extrapolated to skull base disease. Although all study patient's disease was resected completely macroscopically, microscopically positive margins were present in 81.3% of patients (n = 26). This is likely due to a combination of the high incidence of ACC tumour interphase with critical structures at the skull base, and the innate biological behaviour of the disease. Given the high locoregional control rate seen in this study and in the published literature, it appears that microscopic disease is responsive to post-operative RT. Moreover, this study demonstrates that in centres with an experienced multidisciplinary skull base team, that oncological skull base resection does not represent unacceptable patient morbidity. Whilst a significant proportion of patients suffered post-operative complications (46.8%, n = 15), the complication profile was similar to that seen in other oncological head and neck resections, with the exception of CSF leak. There was no mortality associated with the immediate post-operative period. However, this study also reinforces ACC's innate biology of relentless recurrence. Whilst this study demonstrated good locoregional control, metastatic disease recurrence occurred in a majority of patients. Despite positive OS figures, disease free survival was much lower. This suggests that although a majority of patients develop recurrent metastatic disease, that long term survival with metastatic disease is common.

Limitations of this study include that it is single institution and retrospective in nature. Moreover, selection bias is present with all patients being treated with surgery and radiotherapy, and the absence of a comparative treatment group. Although, this study represents one of the largest ACC skull base cohorts in the literature, the study population remains relatively small presenting difficulties performing meaningful multivariable analysis. Although traditional markers of oncological success such as OS, DFS and LCS were examined, quality-of-life measures were not performed. Quality-of-life (QOL) measures are vital in those undergoing aggressive surgical dissection - particularly in the head and neck region where vital functions such as breathing, speech and swallow can be disrupted; as well as the potential for significant craniofacial cosmetic deformity. Conversely, ACC cranial nerve disease infiltration can result in significant morbidity due to neuralgia. Our institution's experience is that surgical resection often provides palliation of symptoms. This could also be reflected in a prospective QOL data.

Conclusion

ACC is a unique malignancy given its typical slow relentless progression. Disease involving the skull base, in some centres, is defined as unresectable and treated with definitive radiation or palliative therapies. However, this study demonstrates that despite the advanced nature of the disease, surgical resection of ACC involving the skull base provides high rates of locoregional control, with survival outcomes similar to that quoted in the literature. Whilst the rate of microscopically positive margins is high, provided macroscopic disease is resected and patients are treated postoperatively with radiation, long term locoregional control is achievable. Given the lack of alternative curative treatments, surgical resection should be considered in patients who present with skull base disease.

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Declaration of Competing Interest

None declared.

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