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Long-Term Outcomes Following Definitive or Adjuvant Proton Radiotherapy for Adenoid Cystic Carcinoma

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ABSTRACT

Purpose: Adenoid cystic carcinoma (ACC) is a rare malignancy accounting for 1% of all head and neck cancers. Treatment for ACC has its challenges and risks, yet few outcomes studies exist. We present long-term outcomes of patients with ACC of the head and neck treated with proton therapy (PT).

Materials and Methods: Under an institutional review board-approved, single-institutional prospective outcomes registry, we reviewed the records of 56 patients with de novo, nonmetastatic ACC of the head and neck treated with PT with definitive (n = 9) or adjuvant PT (n = 47) from June 2007 to December 2021. The median dose to the primary site was 72.6 gray relative biological equivalent (range, 64-74.4) delivered as either once (n = 19) or twice (n = 37) daily treatments. Thirty patients received concurrent chemotherapy. Thirty-one patients received nodal radiation, 30 electively and 1 for nodal involvement.

Results: With a median follow-up of 6.2 years (range, 0.9-14.7), the 5-year local-regional control (LRC), disease-free survival, cause-specific survival, and overall survival rates were 88%, 85%, 89%, and 89%, respectively. Intracranial extension (P = .003) and gross residual tumor (P = .0388) were factors associated with LRC rates. While the LRC rate for those with a gross total resection was 96%, those with subtotal resection or biopsy alone were 81% and 76%, respectively. The 5-year cumulative incidence of clinically significant grade ≥3 toxicity was 15%, and the crude incidence at the most recent follow-up was 23% (n = 13).

Conclusion: This is the largest sample size with the longest median follow-up to date of patients with ACC treated with PT. PT can provide excellent disease control for ACC of the head and neck with acceptable toxicity. T4 disease, intracranial involvement, and gross residual disease at the time of PT following either biopsy or subtotal resection were significant prognostic features for worse outcomes.

Introduction

Adenoid cystic carcinoma (ACC) is a rare malignancy arising from secretory epithelial cells, predominantly of the major and minor salivary glands. It accounts for 5% to 15% of tumors arising from the paranasal sinuses and, overall, 1% of all head and neck cancers. It is indolent but locally aggressive, with a high risk of local and distant recurrence, including late treatment failures. Primary management for most cases involves gross total resection (GTR) followed by radiotherapy (RT) generally without chemotherapy.[1–4]

While ACC rarely involves regional nodes, there is a high incidence of incidental and clinical perineural invasion, with the potential for intracranial, orbital, and cranial nerve involvement.[1,3] Because of the sensitive neurovascular and functional organs in the head and neck, highly conformal RT, such as intensity-modulated radiotherapy (IMRT), proton therapy (PT), or carbon-ion radiotherapy (CIRT) are the

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prevailing techniques for delivering sufficient radiation dose to the tumor without exceeding dosimetric constraints to organs at risk.[5] Additionally, these tumors have been generally considered radioresistant, requiring both high therapeutic doses. Considering this, the use of particle therapy, notably fast neutron radiotherapy (NRT), PT, and CIRT has been increasingly utilized when available, yet few long-term outcomes studies exist.[4]

Herein, we report the long-term outcomes following PT for ACC of the head and neck.

Materials and methods

Under an institutional review board-approved prospective outcomes registry (IRB202001258; NCT00797498), we conducted a single-institution analysis of all patients with adenoid cystic carcinoma of the head and neck who were treated with PT at the University of Florida Health Proton Therapy Institution between June 2007 and December 2021. This is a prospective registry with data retrospectively reviewed. Of an initial 64 eligible patients, 8 were excluded for the following reasons: 4 had prior RT, 2 had less than 1 year of potential follow-up, 1 was lost to follow-up, and 1 patient chose to stop curative intent therapy during PT.

Patient characteristics

Patient, tumor, and treatment characteristics are summarized in Table 1. The median patient age was 52 years (range, 10-81). Twenty-nine percent (n = 16) had an intracranial extension with bone involvement and tumor invading within the skull but no direct involvement of brain tissue; 23% (n = 13) had an orbital extension with mass effects on the eye apparatus such as nerves, extraocular muscles, lacrimal ducts, and blood vessels; and 55% (n = 31) had clinical nerve involvement. Most tumors involved the sinonasal region, with the nasal cavity (n = 19) being the most common subsite, followed by the ethmoid (n = 5), maxillary (n = 5), and sphenoid sinuses (n = 1). Those patients included in the other (n = 5) category of the primary sites included the nasopharynx (n = 2), the ocular including the lacrimal gland (n = 2), and the external auditory canal (n = 2). The tumor staging was based on the eighth edition American Joint Committee on Cancer manual.[6]

Treatment characteristics

All patients had a histologic diagnosis of ACC who underwent either biopsy (n = 9), subtotal resection (STR) (n = 10), or GTR (n = 30), followed by RT. Treatment characteristics, including surgical and RT details, are listed in Table 1. While 30 patients underwent GTR, 26 (46%) had gross disease at the time of treatment, undergoing STR (n = 17) or biopsy alone (n = 9). All patients received PT at the primary site, either as double scattered (n = 45, 80%) or pencil beam scanning (PBS) (n = 11, 20%). Two patients received a single fraction IMRT to the primary site due to proton cyclotron downtime. The median dose to the primary site was 72.6 gray relative biological equivalent (GyRBE) (range, 64-74.4) delivered as either once (n = 19) or twice (n = 37) daily treatments. For those who received accelerated hyperfractionated PT, treatments were delivered at 1.2 GyRBE per fraction twice daily with a minimum 8-hour interval. Hyperfractionated RT was typically delivered to patients with either gross residual or locally advanced disease in treatment regions that abut the optic pathways. Treatment volumes were defined as per International Commission on Radiation Units & Measurements (ICRU) and National Comprehensive Cancer Network (NCCN) guidelines and supported by previously published data by Pelak et al.[7] The dose to the initial field was 45 to 50.4 GyRBE defined as a standard risk planning target volume (PTV), and the high-risk PTV was delivered as a boost to the primary site to the total prescription dose. Gross tumor volume (GTV) was

Table 1
Patient, tumor, and treatment characteristics (N = 56).

Characteristic	Number of patients (%) or other value
Age, median (range)	52 years (10-81)
Sex	
Female	30 (54)
Male	26 (46)
Race/Ethnicity	
White	45 (80)
Black	6 (11)
Asian	4 (7)
Hispanic	1 (2)
Primary site	
Sinonasal	30 (54)
Major salivary gland	12 (21)
Oral cavity/Oropharynx	9 (16)
Other	5 (9)
Smoking status	
Smoker	20 (36)
Nonsmoker	36 (64)
Grade	
1 (tubular and cribriform without solid pattern)	10 (18)
2 (pure cribriform or less than 30% solid)	22 (39)
3 (predominantly solid pattern)	8 (14)
N/A	16 (29)
T Stage	
T1	6 (10.7)
T2	6 (10.7)
T3	9 (16.1)
T4	35 (62.5)
Orbital extension	
Yes	13 (23)
No	43 (77)
Intracranial extension	
Yes	16 (29)
No	40 (71)
Cranial nerve involvement	
Yes	31 (55)
No	25 (45)
Extent of resection	
Biopsy only	9 (16)
Subtotal resection	17 (30)
Gross tumor resection	30 (54)
Neck dissection	
Unilateral	7 (12)
None	49 (88)
Margin (n = 47)	
Positive/close	35 (75)
Indeterminant	11 (23)
Negative	1 (2)
Gross disease at the time of RT	
Yes	26 (46)
No	30 (54)
Number of surgeries prior to RT	
1	35 (62.5)
2 or more	21 (37.5)
Total RT dose, GyRBE (range)	72.6 GyRBE (64-74.4)
RT modality	
DS	45 (80)
PBS	11 (20)
Fractionation	
QD	19 (34)
BID	37 (66)
Elective nodal irradiation	
None	25 (45)
Unilateral	16 (29)
Bilateral	15 (27)
Elective neck RT modality (n = 31)	
3DCRT	21 (38)
Protons	9 (16)
IMRT	1 (2)

Abbreviations: BID, twice a day; DS, double scatter; 3DCRT, three-dimensional conformal radiation therapy; GyRBE, gray relative biological equivalent; IMRT, intensity-modulated radiation therapy; N/A, not applicable; QD, once a day; PBS, pencil beam scanning; RT, radiation therapy.

defined as a macroscopic tumor identified on imaging. Generally, the standard risk PTV included the involved and adjacent sinus cavities, clinical pathways to tumor spread, and relevant nodal areas based on the extent of disease and location of the primary site. In all cases, the standard-risk clinical tumor volume (CTV) included the known pathways of perineural tumor spread back to the skull base and cavernous sinus. The high-risk CTV was a 5 to 10 mm expansion from the gross disease or postoperative bed edited for boundaries to tumor spread. One patient who received daily treatments received a weekly concomitant boost in weeks 2 to 6, completing 70 GyRBE in 35 treatments over 6 weeks. PTV was defined as a 3mm isotropic expansion from respective CTV SR or CTV HR.

Thirty patients received elective nodal irradiation (ENI) and 1 patient received therapeutic nodal irradiation. Nodal irradiation was delivered in combination with PT at the primary site (n = 9, 16%), with IMRT (n = 1, 2%), or with a 3-dimensional conformal low-anterior neck field (n = 21, 38%). The decision to irradiate the elective neck was provider-dependent and generally was included for high-grade subtypes, locally advanced or residual disease. The median dose was 50 GyRBE (range, 46-52.8). Thirty patients received concurrent chemotherapy, which was delivered as weekly platinum. Treatment planning techniques, including simulation, patient immobilization, target delineation, dose coverage goals and constraints, daily image guidance, and adaptive replanning criteria, have been described in prior publications.[8,9] Figure 1 depicts an example of color wash dose distribution of a woman with subtotally resected lacrimal gland adenoid cystic carcinoma with the gross residual disease along V1 and V2 tracking to the cavernous sinus. She was treated with a sequential 6 field (3 initial, 3 boosts) PBS technique to 73.8 GyRBE with concurrent weekly cisplatin using a hyperfractionated treatment schedule.

Statistical criteria

Outcomes data, including disease control and toxicity, were prospectively collected every 3 to 6 months for the first year, biannually for up to 5 years, then annually after that. Follow-up included a physician assessment of toxicities, physical examination, magnetic resonance imaging and/or computed tomography imaging of the primary site, and distant metastasis surveillance. Endoscopic, ophthalmologic, audiologic, and/or endocrine testing was performed when indicated based on the location of the primary site and the patient-specific dose to organs at risk. Documentation of clinical outcomes was obtained through physician-reported assessments.

SAS version 9.4 and JMP Pro version 16.1.0 were used for statistical analysis (SAS Institute, Cary, North Carolina). The following endpoints were analyzed: local control (LC), local-regional control survival (LRC), disease-free survival (DFS), cause-specific survival (CSS), and overall survival (OS) rates. The cumulative incidence method provided estimates for the LC, LRC, DFS, CSS, and OS rates. The Fine-Gray test statistic provided estimates of statistical significance between the strata of selected prognostic factors.

Univariate analyses of prognostic factors included the following for local, LRC, DFS, metastasis-free survival, DFS, CSS, and OS rates: grade (1 vs 2 vs 3), T stage (T1-3 vs T4), the extent of surgery (GTR vs STR vs biopsy), margin (positive/close vs indeterminant/negative), chemotherapy, gross residual tumor, elective nodal irradiation, and the presence of orbital, intracranial or cranial nerve involvement. Chi-square analysis was also used to analyze the association between surgical resection versus intracranial extension.

We assessed serious, late grade 3+ toxicity using toxicity as defined by version 5.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events, reporting the date of the single worst toxicity per patient. To calculate the 5-year cumulative incidence, expected grade 3 events such as hearing loss and cataracts were not included.

Results

With a median follow-up of 6.2 years (range, 0.9-14.7), the 5-year LRC, freedom from distant metastasis, DFS, and CSS rates were 88% (95% confidence interval [CI], 77%-95%), 85% (95% CI, 74%-94%), 78% (95% CI, 65%-88%), and 89% (95% CI, 77%-96%), respectively. Rates for LC and overall survival were equivalent to LRC and CSS, accordingly. There were no nodal failures. Cumulative incidence curves are illustrated in Figure 2.

As illustrated in Table 2, univariate analyses of prognostic factors showed that intracranial extension (P = .01) and gross residual tumor (P = .04) were associated with decreased local and LRC rates. While the LRC rate for those with a GTR was 96%, those with STR or biopsy alone saw LRC rates of 81% and 76%, respectively. No factors were associated with an increased risk of metastasis. T stage (P = .02), intracranial extension ($P \leq .01$), extent of resection (P = .04), and gross residual tumor ($P \leq .01$) were associated with decreased DFS rates. T4 disease ($P \leq .01$), extent of surgery (P = .03), and gross tumor ($P \leq .01$) were significant for CSS rates. Only T4 disease was associated with inferior overall survival rates ($P \leq .01$). There was no LRC rate benefit with ENI (P = .94). Chi-squared analysis demonstrated that the presence of intracranial extension was associated with the presence of gross residual disease at the time of RT ($P \leq .01$).

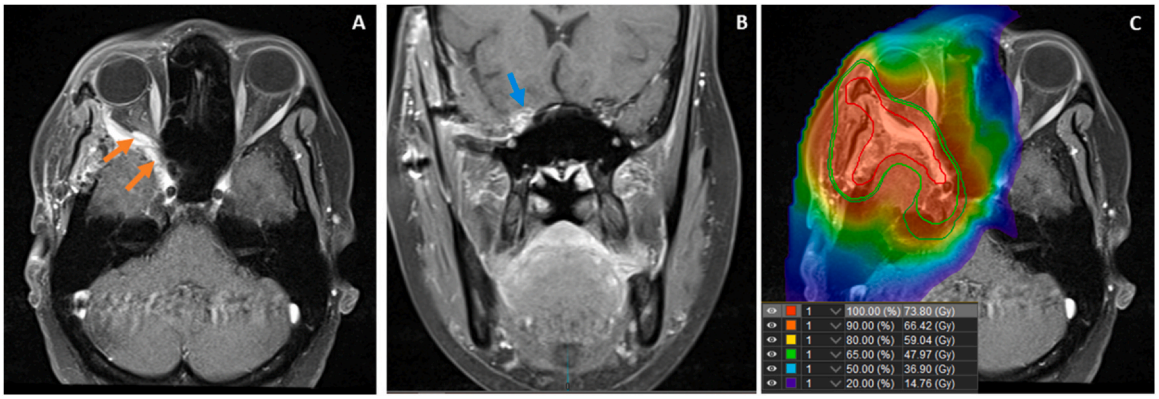

Figure 1. Colorwash Dose Distribution with PNI. T1 axial (**A**) and coronal (**B**) fat-suppressed MRI sequences of a woman with adenoid cystic carcinoma of the lacrimal gland. She underwent a subtotal resection with retrobulbar perineural disease tracking along the orbital apex through the foramen rotundum (orange arrow) to the cavernous sinus (blue arrow). Colorwash dose distribution (**C**) shows the total dose to 73.8 GyRBE at 1.2 GyRBE twice daily with concurrent chemotherapy. The gross tumor is outlined in red, and the green delineations depict the initial and boost volumes of the treatment plan. Abbreviations: GyRBE, gray relative biological effectiveness; MRI, magnetic resonance imaging; PNI, perineural invasion.

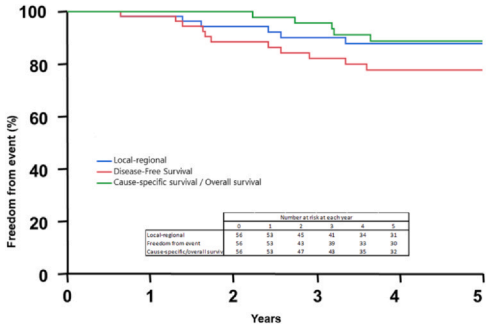

Figure 2. Survival Curves. Cumulative incidence curves depicting local-regional control rate, disease-free survival rate, and cause-specific survival/overall survival rates with the respective number at risk by year. Abbreviations: CSS/OS, cause-specific survival/overall survival rates; DFS, disease-free survival rate; LRC, local-regional control rate.

Dose

The majority of patients within the present series received accelerated hyperfractionation (n = 37) in twice-daily treatments. This was predominately in those who had tumors located in optic pathways with primary sites involving the sinuses, nasopharynx or orbit (n = 31). Nearly all of the patients receiving twice-daily radiation had locally advanced disease T3 (n = 7) or T4 disease (n = 28), and the majority had gross residual disease (n = 20). The median dose for the definitive and adjuvant settings were 73 GyRBE (range, 68.4-74.4) and 70 GyRBE (range, 64-74.4), respectively. The median dose for those with early-stage tumors (T1/2) was 66 GyRBE (range, 64-74.4). These treatment protocols and total dose were similar to Pelak, Holliday, Lesueur, and Linton[7,10–12] for patients receiving definitive or adjuvant RT.

Toxicity

The same toxicity grading was used for all patients included in this analysis. No patients had acute grade 3 toxicity or higher. The 5-year cumulative incidence of clinically significant late grade 3+ toxicity was 15%, and the crude incidence at the most recent follow-up was 23% (n = 13/56). Grade 3 or greater events included symptomatic brain necrosis (n = 3), osteonecrosis (n = 2; maxillary, frontal), soft tissue necrosis and fistula (n = 3), in-field second malignancy (n = 2; melanoma, osteosarcoma), radiation-induced optic neuropathy (n = 1), retinopathy (n = 1), and dysphagia requiring a gastrostomy tube (n = 1). Expected grade 3 events not included in the cumulative incidence and crude totals are cataracts (n = 5) and epiphora (n = 1) because of the globe and lacrimal gland being in the treatment field. An additional 6 patients had grade 1 or 2 brain necrosis, that was either asymptomatic (n = 3) or conservatively managed (n = 3) with pentoxyfylline, vitamin E, or corticosteroids.

Discussion

In the present series of nonmetastatic, de novo ACC of the head and neck, primary or adjuvant PT provided excellent oncologic control with acceptable toxicity. Early interest in particle therapy treatments centered on NRT, and during this period, a randomized cooperative group trial showed a local-regional control benefit with NRT over photon-based therapy for unresectable salivary gland tumors. However, because of shielding requirements, reports of higher toxicity, and depth

Table 2
Univariate analysis of clinical factors (N = 56).

Variable	Patients	LRC		DFS		OS	
		%	P value	%	P value	%	P value
T Stage			.05		.02		< .01
All		88		78		89	
T1-T3	22	100		95		100	
T4	34	80		67		82	
Orbital extension			.31		.14		.06
No	43	87		79		99	
Yes	13	89		72		91	
Intracranial extension			< .01		< .01		.09
No	40	97		85		97	
Yes	16	67		61		77	
Cranial nerve involvement			.19		.12		.14
No	25	95		86		95	
Yes	31	82		71		84	
Surgery extent			.12		.04		.03
Bx only	9	76		76		86	
GTR	30	96		88		95	
STR	17	81		61		78	
Margin[a]			.77		.62		.86
Indeterminate/negative	12	90		79		100	
Positive/close	35	90		77		85	
Gross tumor at the time of RT			.04		< .01		< .01
No	30	96		88		95	
Yes	26	79		66		81	
Chemotherapy			.02		.30		.74
No	26	95		78		90	
Yes	30	81		78		97	
ENI in No patients[b]			.94		.96		.36
No	30	85		77		94	
Yes	25	89		82		85	

Abbreviations: Bx, biopsy; DFS, disease-free survival rate; ENI, elective nodal irradiation; GTR, gross total resection; LRC, local-regional control rate; OS, overall survival rate; RT, radiation therapy; STR, subtotal resection.

[a] Nine had a biopsy alone (no margin status).

[b] One not included due to clinical N1.

Table 3
Literature review.

Reference (pub yr)	Total pts	Location	Median FU (months)	Dose[a] (range)	Modality	LRC	DFS	OS	Toxicity
Augustin et al (current series)	56	Head and neck	74.4	72.6 GyRBE (64-74.4)	48 DS 8 PBS	88%	78%	89%	15% Grade 3+ (late)
Mavrikios et al[20] (2023)	18	Sinonasal	52	73.8 Gy	7 PBS 4 Photon 5 Combined proton and photon	50%	33%	47%	12% Grade 3+ (acute)50% Grade 3 + (late); 3 visual, 7 hearing impairment, 2 nasal congestion
Pelak et al[7] (2020)	35	Head and neck	30	Post-op 70 GyRBE (66-76) Primary RT 75.6 GyRBE	PBS	92.2%	74.3%	88.8%	14.3% Grade 3+ (acute) 6.1% Grade 3+ (late)
Lesueur et al[11] (2020)	15	Lacrimal gland	67.4	73.8 GyRBE	12 DS 3 PBS	70%	58%	78%	27% Grade 3+ (late)
Holliday et al[12] (2016)	16	Head and neck	24.9	60 GyRBE (60-70)	PT	94%	NR	94%	33% Grade 3+ (late)
Linton et al[10] (2015)	26	Skull base	25	72 GyRBE	PT	95%	NR	93%	15% Grade 3+ (late)
Takagi et al[21] (2014)	80	Head and neck	53	67.7 $GyE_{10/2}$ (67.7–74.3 $GyE_{10/2}$)	40 Proton 40 Carbon	75.8%	30.4%	63.3%	21 patients with grade 3 (acute)36 patients with grade 3+ (late)No difference between proton or carbon
Pommier et al[22] (2006)	23	Nasopharynx and skull base	64	75.9 GyRBE(70-79.1)	Combined proton and photon	93%	56%	77%	13% Grade 3+ (visual toxicity) 22% neurological toxicity

Abbreviations: CGE, cobalt gray equivalent; DS, double scatter; DFS, disease-free survival rate; FU, follow-up; GyRBE, gray relative biological effectiveness; $EQD_{10/2}$, equivalent dose as 2-Gy fractions for a/b = 10; LRC, local-regional control rate; OS, overall survival rate; PBS, pencil beam scanning; Pub yr, publication year; post-op, postoperative; pts, patients; PT, proton therapy, RT, radiation therapy; NR, not reported.

[a] If included reRT.

dose characteristics, NRT largely fell out of favor compared to modern photon-based techniques except for niche situations.

Comparisons among modern IMRT and PT series

More recently, Patel et al performed a meta-analysis and systematic review of 41 observational studies comparing PT to photon-based cohorts for those with sinonasal malignancies.[13] Subgroup analysis showed that those who underwent PT had significantly higher DFS rates at 5 years and LRC rates at the longest follow-up compared with IMRT. Because of the promising results with PT, more patients are being considered for particles when adjuvant radiation is indicated for sinonasal primaries, which is demonstrated by the fact they are represented in over 50% of the present series. Therefore, the results regarding disease control, outcomes, toxicity may not be directly comparable to other historic photon-based series and contemporary series that primarily include photon-based IMRT for sinonasal ACC both few in number and small or combined with other histologies and/or primary sites.[3,14–19]

A representative literature review and summary of representative proton outcomes to date is included in Table 3. Researchers at the Paul Scherer Institute reviewed 35 patients treated with PBS.[7] With a median follow-up of 30 months, the 2-year LC, progression-free survival (PFS), and OS rates were 92.2%, 74.3%, and 88.8%, respectively. They found that while age influenced LC rates, T stage was a significant factor for PFS rates while the tumor prognostic group was significant for OS. Nine patients were included with inoperable disease, and no survival advantage was identified for operable versus inoperable disease, which differs from the present series (although the operable group included R2 resection, which differs from the stratification of the present series). Acute and late toxicities profiles differed, although more acute toxicities were seen in the Paul Scherer Institute series (14%), only 2 patients (6%) developed late grade 3 complications, and none had grade 4 or 5. Additionally, this includes a unilateral cataract, which, although we list as expected toxicity, we censored from the cumulative incidence, which was 15% at 5 years and as high as 23% at the most recent follow-up.

Linton et al reviewed 26 patients at the Indiana University Health Proton Therapy Center in 2014.[10] Most patients (77%) had base-of-skull involvement and were treated for initial disease (73%). With a median follow-up of over 2 years, the overall survival rate was 95% for those treated with de novo disease. Four patients experienced late grade 3 or greater toxicity. While this affirms the present series that those treated with PT have excellent local control with acceptable toxicity, it does raise the question regarding modern practices that now incorporate PBS into treatment planning. PBS allows for more conformal dose distribution compared to what was achievable with double scattered techniques. This is of particular importance given suggestions of higher distal range gray relative biological equivalent (RBE).[23] Therefore, it is possible that with further advances in proton treatment delivery such as rotational arc proton therapy, linear energy transfer (LET) optimization, and evaluation the therapeutic index may be improved.[5]

Surgery

Given the disease extent and location of ACC, often en bloc, margin negative resections are not technically feasible. Several series as with the present cohort have shown that positive margins are associated with worse local control rates.[24,25] In the present series, however, similar to other cohorts with a higher percentage of sinonasal malignancies, those with indeterminant piecemeal resections do not compromise disease control.[26] Having gross residual disease at the time of treatment, however, significantly influenced LRC ($P = .04$), DFS ($P = .01$), and CSS ($P = .01$) rates. Intracranial extension ($P < .01$) at the time of treatment was highly associated with the presence of residual disease at the time of PT.

Not only do we show that microscopically positive margins had little impact on outcomes, but there does not appear to be a convincing benefit that a debulking surgery provides measurable objective benefits. This questions the value of highly morbid operations or procedures that do not require symptomatic decompression or relief of mass effects or symptoms.

Conversely, while all patients received adjuvant RT, the LRC rate was 100% for those with pT1-3 tumors. The complete omission of RT in any population with ACC is controversial, even for those with early-stage (T1/2) and nonsolid, low-grade histology.[27–29] In highly select, favorable subsets of patients who undergo a GTR in locations for which RT may be highly morbid, the local control benefit of high-dose adjuvant RT may be uncertain, although more research is needed to de-escalate safely identify this cohort.

Elective nodal irradiation

Within the present series, the 5-year LRC rate for those who received ENI was 89% compared to 85% for those who did not ($P = .94$). There were no isolated nodal failures seen. This confirms prior series demonstrating low regional recurrence rates for head and neck ACC, particularly in clinical N0 sinonasal primaries, which questions the need for routine elective coverage.[28,30] At UF our practice has been to elective cover the neck for high-grade, locally advanced tumors and in situations where the primary site overlaps with the neck in such that elective nodal irradiation would not change the treatment toxicity profile.

Chemotherapy

The role of chemotherapy in treating ACC is controversial.[31–33] While the 5-year LRC rate was significantly worse in those who did receive concurrent chemotherapy, 95% versus 81% ($P = .0205$), there was no difference in either the DFS rate ($P = .31$) or CSS rate ($P = .74$). Our current practice is to give concurrent chemotherapy for those with gross residual disease, which is supported in other modern series.[19,20] This finding was supportive for chemotherapy for advanced-stage ACC and highlights that this population tends to have a poor prognosis even with the addition of concurrent systemic therapy compared to those in which a gross total resection is achieved.

Hyperfractionation

Accelerated hyperfractionation in head and neck cancer has been a topic of interest as both cooperative group studies and large database reviews demonstrate improved survival in those treated for squamous cell carcinoma.[34,35] The benefit of accelerated hyperfractionation in ACC is unknown. There is additional evidence that fraction sizes greater than 1.8 may increase the risk of late complications to the optic pathways.[36,37] Conversely, the downside to accelerated hyperfraction schedules are the increased costs associated with therapy, the logistical burden on the facility, staff and patient, and the inability to prescribe a simultaneous integrated boost among others. As noted in the present series, altered fractionation was typically given for those with locally advanced or gross residual disease at the time of treatment, particularly with treatment sites that overlap with the visual pathway.

Heavy ions

In addition to the use of NRT and PT, CIRT is an emerging therapy for treating salivary gland tumors, including head and neck ACC. In 2020, a systematic review and meta-analysis showed that among 44 cohorts and nearly 2200 patients, LC and OS rates were significantly higher with CIRT compared to PT or IMRT.[38] While this cohort reviewed those with sinonasal malignancies and was not specific to ACC, it may suggest that CIRT can be an option for those with gross residual disease and radioresistant tumors. Multiple series have evaluated the use of CIRT in ACC.[21,39–47] One is a subanalysis from a multicenter study from Japan (J-CROSS study 1402HN), which retrospectively reviewed 289 patients who underwent CIRT. Similar to the present series, most patients had tumors involving the nasal cavity and paranasal sinuses. The median total dose was 64 GyRBE in 16 fractions. With a median follow-up of 2.5 years, the 5-year OS, PFS, and LC rates were inferior to the present series at 74%, 44%, and 68%, respectively, although they had a higher percentage of unresectable disease at the time of CIRT (81% vs 46% in the present cohort). Similar to our series, 15% experienced grade 3 or higher late complications, of which osteonecrosis of the jaw bone was the most common.[46] although that series only included R2 or unresectable patients. Similar to NRT, given the lack of availability of CIRT, the role of heavy ions is limited and likely best for those undergoing reirradiation, residual gross tumor, or other radioresistant features.

Limitations

Limitations include that while all patients were prospectively enrolled, the oncologic and toxicity assessments were retrospectively analyzed. Notably, we have the longest duration of follow-up of any reported proton series with a very low rate of patients lost to follow-up, with 80% ($n = 32$) of those patients alive, having known outcomes, and having toxicity updated within the preceding 12 months of data analysis, with all deceased patient outcomes documented. This series is also primarily sinonasal treated with double scattered, it is not known if PBS would potentially reduce the risk of grade 3+ central nervous system necrosis. An additional limitation is that unless there was an incongruence or discrepancy, a central review of outside pathology for grading might have led to inconsistency in documenting histologic patterns and further analysis of grade. Lastly, given the indolent and insidious nature of ACC, with a median follow-up of 6 years and continued surveillance, we expect there exists the potential for further treatment failures and quality-of-life issues from treatment morbidity.

Conclusions

PT provides excellent disease control for head and neck ACC with acceptable toxicity. Gross residual disease at the time of treatment and intracranial involvement were significant prognostic features for worse outcomes. STR did not confer benefit over biopsy only at 5 years and may question the role of extensive and morbid operations if GTR is not technically feasible, particularly in those with intracranial extension and a high incidence of postoperative residual disease.

Ethics statement

The study protocol was approved by the University of Florida Institutional Review Board (IRB202001258). All participants provided informed consent to participate in this study.

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Author Contributions

Etzer Augustin: Data curation, Formal analysis, Resources, Investigation, Writing – original draft, Writing – review & editing. **Adam Holtzman:** Conceptualization, Methodology, Funding acquisition, Project administration, Supervision, Writing – review & editing. **Roi Dagan:** Resources, Project administration, Validation, Writing – review & editing. **Curtis Bryant:** Validation, Writing – review & editing. **Daniel Indelicato:** Validation, Writing – review & editing. **Christopher Morris:** Formal analysis, Software, Data curation,

Validation, Writing – original draft. **Rohan Deraniyagala:** Validation, Writing – review & editing. **Rui Fernandes:** Validation, Writing – review & editing. **Anthony Bunnell:** Validation, Writing – review & editing. **Stacey Nedrud:** Validation, Writing – review & editing. **William Mendenhall:** Validation, Writing – review & editing.

Declaration of Conflicts of Interest

WMM is the Advisory Editor for IJPT. All authors report no conflict of interests.

Data Availability Statement

The authors agree to share anonymized data upon reasonable request by researchers.

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