frontiers in Oncology

TYPE Original Research
PUBLISHED 04 November 2026
DOI 10.3389/fonc.2026.1968350

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OPEN ACCESS

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RECEIVED 14 August 2026
REVISED 21 September 2026
ACCEPTED 20 October 2026
PUBLISHED 04 November 2026

CITATION
Rohit A, Voss M, Gunn H, Ma D, Patel S, Lester S, Rwigema J-C, Neben-Wittich M, Foote R, Routman DM, Garces Y, Wison J, Price D, Janus J, Hinni M, Chintakuntlawar AV, Price K, McGarrah P, Holtzman A, Mohammadi H and McGee L (2026) Proton beam therapy in the treatment of adenoid cystic carcinoma of the head and neck: a single enterprise retrospective cohort study. *Front. Oncol.* 16:1968350. doi: 10.3389/fonc.2026.1968350

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Proton beam therapy in the treatment of adenoid cystic carcinoma of the head and neck: a single enterprise retrospective cohort study

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Background and aims: Adenoid cystic carcinoma (ACC) is a rare salivary gland malignancy with high propensity for perineural invasion (PNI) and relative radioresistance. Proton beam therapy (PBT) may improve tumor control through improved target coverage, as well as higher physical and biologic dose while limiting dose to surrounding critical structures. This single-enterprise two-site study reports outcomes and toxicity in patients with ACC of the head and neck (HN) region treated with curative-intent PBT.

Methods: From 2015–2025, 89 patients with HN ACC were treated with curative-intent PBT. Patients with distant metastases or prior radiotherapy (RT) were excluded. Clinical outcomes were assessed retrospectively. Toxicities were recorded prospectively using CTCAE v5.0. The Kaplan–Meier method was used to estimate local tumor control (LC), distant metastasis-free survival (DMFS) and overall survival (OS). Hazard ratios, 95% confidence intervals (CIs), and test of association between tumor and treatment variables and outcomes were estimated using Cox proportional hazards regression analysis.

Results: Median follow-up was 3.1 years. Sixty-nine patients underwent surgery followed by postoperative PBT, while 20 received definitive PBT for unresectable disease. The 3-year LC rate was 98.3% following postoperative PBT and 82.6% following definitive PBT. Treatment approach was not significantly associated with LC. Three-year DMFS was 86.2% and 64.9%, respectively, while 3-year OS was 94.4% in both cohorts. Twenty-one patients developed distant metastases, most commonly involving the lungs. Six patients experienced acute grade 3 toxicities, including dysphagia, mucositis, and dermatitis; seven experienced late

grade 3 toxicities, most commonly osteoradionecrosis (n=4). One patient had both acute and late toxicity. No grade 4 or 5 toxicities occurred.

Conclusions: Curative-intent PBT was associated with favorable LC and acceptable toxicity. Outcomes according to definitive versus postoperative treatment should be interpreted descriptively due to substantial baseline differences between groups and confounding by indication. Longer follow-up and larger studies are needed.

KEYWORDS

adenoid cystic carcinoma (ACC), particle therapy, patient outcome, proton beam therapy (PBT), salivary gland cancer (SGC)

Introduction

Adenoid cystic carcinoma (ACC) is a rare, often indolent malignancy that most commonly arises from the salivary glands, encompassing approximately 1% of all head and neck (HN) cancers (1–11). ACC is characterized by a marked propensity for neurotropic spread and perineural invasion (PNI), resulting in locally aggressive disease that frequently extends to the skull base (2, 4, 9–12). These unique growth characteristics can complicate surgical resection and radiotherapy treatment planning, particularly for those patients with locally advanced disease. In addition, ACC has a low risk of lymph node involvement and a well-recognized tendency for late hematogenous dissemination, particularly to the lungs, necessitating long-term surveillance (1, 2, 4, 10, 13, 14).

The rarity of ACC, coupled with its heterogeneous clinical presentation within major and minor salivary glands and prolonged natural history, has limited the availability of prospective studies and randomized clinical trials to guide evidence-based management. Consequently, treatment recommendations are largely derived from retrospective series and institutional experience (9, 11, 13, 15). Surgical resection followed by adjuvant radiotherapy (RT) when indicated remains the standard of care for resectable disease, whereas definitive RT is generally first-line for unresectable tumors or patients who decline surgery or are not surgical candidates (16). Although improved outcomes have consistently been reported following complete surgical resection and adjuvant RT, comparisons between treatment approaches are inherently limited by selection bias, as unresectable tumors often represent more advanced disease (6, 17, 18). Because ACC frequently arises in anatomically complex regions and often demonstrates extensive perineural spread, treatment requires balancing aggressive local therapy with preservation of normal tissue function and minimization of long-term treatment-related morbidity. These challenges are particularly pronounced when high-dose RT of the skull base is required (7, 19, 20).

Historically, photon-based RT has demonstrated modest rates of long-term local tumor control (LC), with reported 5-year LC ranging from approximately 26% to 61%, contributing to the perception that ACC is relatively radioresistant (5, 6, 8, 17, 18, 21–26). Interest in particle therapy arose in part from the hypothesis that higher linear energy transfer (LET) RT may overcome some of the biologic mechanisms underlying treatment resistance (27–30). As theorized, early studies of fast neutron therapy (FNT), a high-LET modality, demonstrated improved LC compared with conventional photon RT. In a randomized trial of patients with unresectable salivary gland malignancies, 10-year LC was 56% with FNT compared with 17% with photon RT (25). Similarly, retrospective studies of ACC reported improved 5-year LC with FNT: 75% versus 32% (5). However, these gains were achieved at the expense of substantially higher rates of severe toxicity, likely reflecting both the high relative biological effectiveness (RBE) and LET of neutrons, the limitations of historical treatment planning and delivery techniques, and the absence of the Bragg peak physical advantage. Consequently, FNT has largely fallen out of routine clinical practice (6).

The increasing availability of proton beam therapy (PBT) has renewed interest in charged particle therapy for ACC (31). Unlike FNT, protons have an RBE comparable to conventional photon RT while providing superior dose conformality through the Bragg peak, allowing for substantial reduction in radiation dose to normal tissues (6, 28, 29, 32). These dosimetric advantages are particularly attractive for ACC, in which treatment volumes frequently encompass the skull base, cranial nerves, orbit, brainstem, brain, cochlea, and other critical organs at risk. Emerging institutional series have reported encouraging LC with acceptable toxicity profiles following PBT; however, published data remain limited, particularly with contemporary treatment techniques (15).

In this retrospective, single-enterprise two-site study, we describe clinical characteristics, treatment patterns, oncologic outcomes and treatment-related toxicities in patients with HN ACC treated with curative-intent PBT. We hypothesized that PBT will provide favorable local control (LC) and acceptable toxicity in this patient population.

Materials and methods

A retrospective review was conducted of all patients with HN ACC treated with curative-intent intensity modulated proton therapy (IMPT) using pencil beam scanning (PBS) at a single-enterprise two-site institution between 2015 and 2025 following Institutional Review Board (IRB) approval. Eligible patients received either definitive or adjuvant IMPT using PBS. Patients with distant metastases at initial presentation, a history of prior HN RT or lacrimal gland ACC were excluded.

All patients underwent multidisciplinary evaluation by head and neck surgery and radiation oncology with medical oncology consultation obtained for locally advanced high-risk cases to assess the role of concurrent systemic therapy. Clinical staging was assigned according to the American Joint Committee on Cancer (AJCC) 8th edition staging system. Baseline evaluation included physical examination, contrast-enhanced HN computed tomography (CT) including the skull base, and positron emission tomography/computed tomography (PET/CT). Magnetic resonance imaging (MRI) was obtained when PNI was suspected.

Patients were treated in accordance with the National Comprehensive Cancer Network (NCCN) guidelines, with patients undergoing upfront surgical management if feasible or definitive radiotherapy if patients were deemed not to be a surgical candidate. For postoperative PBT treatment, clinical target volumes (CTVs) included the postoperative tumor bed and the course of the named cranial nerve corresponding to the primary anatomic site to the skull base. For definitive treatment, the CTV included gross disease and the corresponding cranial nerve pathway to the skull base. Elective nodal irradiation was generally omitted in patients with an N0 neck but could be considered on a case-by-case basis for tumors arising in lymphatic-rich sites, such as minor salivary gland tumors of the base of tongue. Postoperative patients were treated to 60–66 Gray Equivalent (GyE) and definitive patients to 70 GyE using conventional fractionation. Treatment was delivered with pencil beam scanning intensity-modulated proton therapy (PBS-IMPT) on a Hitachi ProBeat system with daily kV image guidance. Robustness was evaluated using 3-mm setup and 3% proton range uncertainty, with plans evaluated to ensure 95% target coverage by 95% of the prescription dose under the evaluated uncertainty scenarios. Although treatment planning and delivery practices underwent incremental refinements during the study period as skillset evolved with PBT planning, the fundamental treatment approach, including target-volume principles, dose and fractionation, robustness evaluation, and daily image guidance, remained consistent.

Follow-up was performed cording to NCCN recommendations with history and physical examination performed every three months during the first two years after treatment, every six months through year five, and yearly or every other year after 5 years. Surveillance imaging included PET-CT approximately three months after completion of PBT with subsequent imaging obtained at the treating physician's discretion.

LC, distant metastasis-free survival (DMFS) and overall survival (OS) were measured from the completion of PBT and estimated using the Kaplan Meier method. Local disease progression was defined as radiographic or pathologic evidence of recurrent or progressive disease at the primary tumor site. Patients without an event or patients who were lost to follow up were censored at last follow-up. Associations between clinicopathologic and treatment variables and outcomes were evaluated using exploratory Cox proportional hazards regression univariable analysis. High risk variables that were assessed for association with LC, DMFS and OS included the following: patient age, race, tumor grade, T stage, lymph node positivity, PNI, surgical management, margin status, and PBT dose. Treatment-related toxicities were prospectively recorded using the Common Terminology Criteria for Adverse Effects utilizing CTCAE version 5.0). Acute toxicities were defined as events occurring during treatment or within 180 days of treatment initiation while late toxicities were defined as events more than 180 days after treatment initiation. Two-sided α=0.05 defined statistical significance for all analyses with no adjustment for multiplicity. Statistical analyses were performed using R version 4.4.1.

Results

89 patients received PBT at a single-enterprise two-site institution from 2015–2025 with a median observed follow-up of 3.1 years (range, 0.05–8.5 years). Patient characteristics are listed in Table 1. Tumors arose from minor salivary glands in 56 (62.9%) patients and major salivary glands in 33 (37.1%) patients. Patients in the definitive PBT cohort were more likely to have advanced T-stage (T3-T4) 95% vs 52.1% in the postoperative PBT cohort. PNI was identified clinically or radiographically in 15 (75.0%) patients treated with definitive PBT, and in 33 (37.1%) patients treated with postoperative PBT. 69 patients underwent surgery (R0: N = 43; R1: N = 19; R2: N = 7) followed by postoperative PBT, while 20 patients had unresectable disease and received definitive PBT. Median PBT dose was 70.0 GyE (68–70 GyE) in the definitive setting and 63 GyE (60–66 GyE) in the postoperative setting. 11 (55.0%) patients in the definitive PBT cohort received concurrent platinum-based chemotherapy; 18 (26.1%) patients received concurrent platinum-based chemotherapy in the postoperative PBT cohort. Locally advanced disease (T3–T4) was present in 19 (95.0%) patients who received definitive PBT and 36 (52.2%) who received postoperative PBT. Nodal metastases were present in one patient who received definitive PBT and seven patients who received postoperative PBT. Four patients were treated for recurrent disease without prior RT, all in the postoperative PBT cohort.

The 3-year LC rate was 82.6% (95% CI 62.2-100%) in the definitive PBT cohort and 98.3% (95% CI 95-100%) in the postoperative PBT cohort (Figure 1). Treatment approach, advanced T stage, lymph node involvement, high tumor grade, unresectability, or positive margins were not significantly associated with inferior LC. However, analyses were limited by the small number of events. DMFS at 3-years was 64.9% (95% CI 43.0-98.0%) in the definitive PBT cohort and 86.2% (95% CI 77.7-95.6%) in the postoperative PBT cohort. PBT treatment approach was not significantly associated with DMFS(HR 2.12, 95% CI 0.80-5.60 (p=0.129)) (Figure 2). In total 21 patients developed distant metastatic disease, most commonly to the lung (N = 14). The 3-year OS rate was 94.4% (95% CI 88.4-100%) in both the definitive and postoperative PBT cohorts, with no significant associations observed between OS and advanced T stage, tumor grade, nodal involvement, or definitive PBT technique (or approach) (Figure 3).

Three patients developed progressive disease in regional lymph nodes, two in the postoperative PBT cohort and one in the definitive PBT cohort. All three nodal recurrences occurred in patients who were initially staged as N0 and did not receive elective nodal

TABLE 1 Patient characteristics.

Patient and treatment characteristics	Definitive PBT (N=20)	Postoperative PBT (N=69)
Gender		
Male	11 (55.0%)	25 (36.2%)
Female	9 (45.0%)	44 (63.8%)
Age at RT in years	65 (52.5–72.75)	59 (43.0–68.0)
Histologic grade		
Grade 1	2 (10.0%)	14 (20.3%)
Grade 2	8 (40.0%)	40 (58.0%)
Grade 3	7 (35.0%)	13 (18.8%)
Not Reported	3 (15.0%)	2 (2.9%)
Primary site		
Major Salivary Gland	2 (10.0%)	31 (44.9%)
Parotid	1 (5.0%)	20 (64.5%)
Submandibular Gland	1 (5.0%)	10 (32.3%)
Sublingual Gland	0 (0.0%)	1 (3.2%)
Minor Salivary Gland	18 (90.0%)	38 (55.1%)
Perineural invasion		
None	4 (20.0%)	16 (23.2%)
Clinical or Radiographic	15 (75.0%)	18 (26.1%)
Pathological	1 (5.0%)	35 (50.7%)
T stage		
T1	0 (0.0%)	15 (21.7%)
T2	1 (5.0%)	18 (26.1%)
T3	1 (5.0%)	9 (13.0%)
T4	18 (90.0%)	27 (39.1%)
N stage		
N0	19 (95.0%)	62 (89.9%)
N+	1 (5.0%)	7 (10.1%)
Overall stage		
I	0 (0.0%)	14 (20.3%)
II	1 (5.0%)	17 (24.6%)
III	0 (0.0%)	8 (11.6%)
IV	19 (95.0%)	30 (43.5%)
Surgical margin status		
Negative Margins	Not Applicable	43 (62.3%)
Positive Margins	Not Applicable	19 (27.5%)
Gross Residual Disease	Not Applicable	7 (10.1%)
PBT Dose, median (IQR)	70 GyE (70–70)	63 GyE (60–66)
Concurrent Chemotherapy	11 (55.0%)	18 (26.1%)

coverage with PBT. One patient had T4 N0 intermediate grade ACC of the hard palate with pathologic PNI and was treated with surgical excision to negative margins followed by postoperative PBT to 66 GyE. The second patient had a T2 N0 high grade ACC of the submandibular gland with pathologic PNI, treated with surgical excision to positive margins and postoperative PBT to 66 GyE. The third patient had a T4 N0 high grade ACC of the nasal cavity with radiographic PNI treated with definitive PBT to 70 GyE.

In total, 12 patients experienced 13 grade 3 toxicities (Table 2). Acute grade 3 toxicities occurred in six patients, most commonly dysphagia (n=4), for which three required temporary feeding tube placement, mucositis (n=1), and dermatitis (n=1). Late grade 3 toxicities occurred in seven patients, including osteoradionecrosis (n=4), osteomyelitis (n=1, secondary to surgery), vision loss (n=1), and lacrimal gland stenosis (n=1, secondary to PBT and surgery). One patient experienced both an acute and a late grade 3 toxicity. No grade ≥4 toxicities were observed.

Discussion

ACC is an often-indolent rare salivary gland malignancy characterized by frequent PNI, low rates of nodal involvement and a high propensity for late hematogenous dissemination primarily to the lung (1–10, 14, 19, 27). In general, current consensus recommendations favor up-front surgical resection when feasible. followed by adjuvant RT when clinically indicated; definitive RT is generally used for unresectable tumors or for patients who are not surgical candidates, often requiring high dose to the skull base in proximity to critical normal organs due to the tumor's propensity for PNI (7, 16, 19, 20). Historically, outcomes following conventional photon RT have been modest, particularly in the definitive setting, with reported 5-year LC rates ranging from 26% to 61% which has led to the belief that ACC is a relatively radioresistant malignancy (5, 6, 8, 17, 18, 21–26). These limitations prompted investigation of particle-based treatment approaches. While FNT demonstrated improved LC, its clinical adoption was limited by substantial treatment-related toxicity (19, 21, 27, 33, 34). More recently, both PBT and carbon ion radiotherapy have emerged as attractive alternatives. PBT has the ability to safely deliver full prescription dose due to highly conformal dose distribution as well as due to the physical dose escalation from improved LET and RBE while reducing dose to adjacent organs at risk (6, 28, 29, 32). Although carbon ions possess higher LET and RBE than protons, existing retrospective studies have demonstrated excellent outcomes with both modalities, and no definitive evidence currently supports the superiority of one charged particle therapy over the other (15). This retrospective, single-enterprise series describes clinical outcomes and toxicity among patients with HN ACC treated with curative-intent IMPT with PBS PBT. The favorable LC and toxicity outcomes observed in this cohort are encouraging, particularly given the frequency of anatomically complex, locally advanced, unresectable, margin-positive, and gross residual disease. Because this study did not include a comparison cohort treated with modern photon-based RT, including IMRT, it cannot directly establish that PBT provides superior LC, OS and lower toxicity, relative to photon RT and should thus be considered hypothesis-generating. This study adds to the growing body of literature supporting the use of PBT in the treatment of HN ACC as it provides contemporary

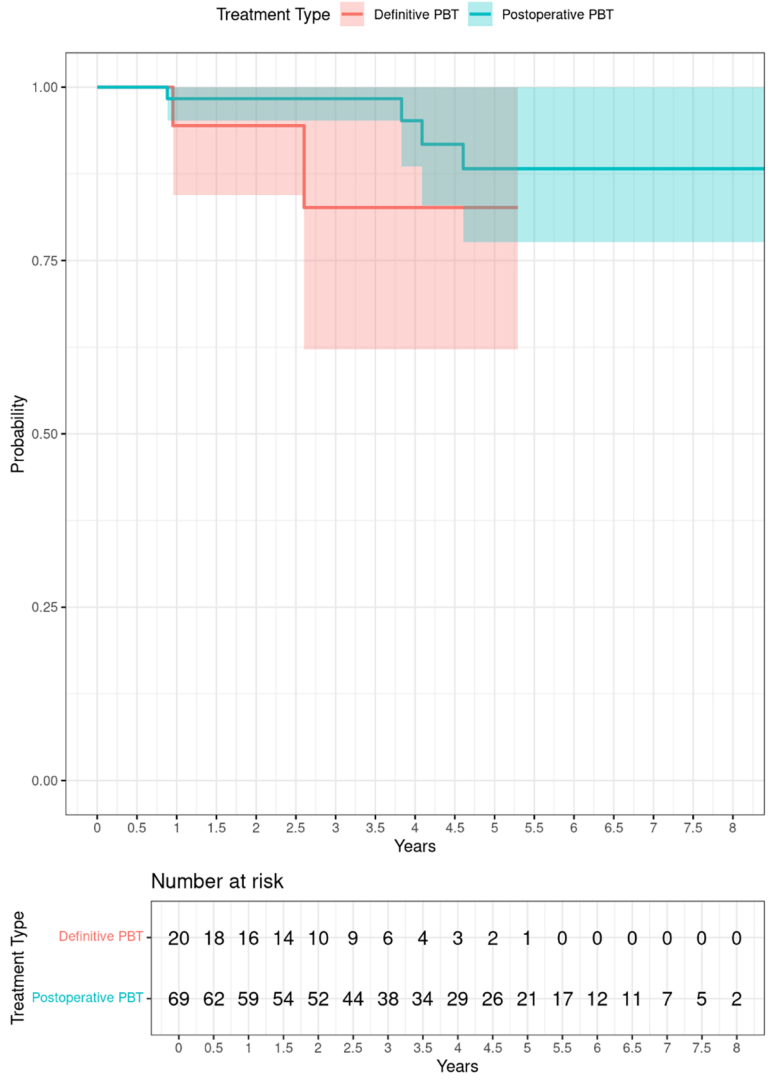


FIGURE 1
Local Control was not significantly different between the cohort of patients treated with definitive intent PBT versus posoperative PBT.

descriptive real-world data on the feasibility, observed outcomes, and toxicity of curative-intent PBT in a relatively large cohort of patients with a rare disease.

The principal advantage of IMPT using PBS PBT lies in its dosimetric properties. Through the Bragg peak effect, PBT reduces unnecessary radiation exposure to surrounding normal tissues while maintaining excellent target coverage. This is particularly advantageous in ACC, where treatment volumes frequently encompass the skull base, cranial nerves, brainstem, optic apparatus, cochlea, temporal lobes, and other critical structures. The ability to safely deliver curative RT doses to these anatomically challenging regions is especially important in patients with unresectable disease, extensive perineural spread, positive surgical margins, or R2 resection (gross residual disease) (6, 15, 22, 29, 32, 35, 37–46).

In this contemporary series, the overall 3-year LC was excellent following both postoperative and definitive PBT; however, these estimates should not be interpreted as a direct comparison of treatment approaches. Patients receiving definitive PBT represented a substantially higher-risk population, with more advanced T-stage disease, greater clinical/radiographic PNI, and unresectable disease, and they also received higher PBT doses and more frequent concurrent chemotherapy. These systematic differences reflect treatment selection based on disease severity and may introduce confounding by indication. Furthermore, the small definitive cohort and limited number of local failures resulted in low statistical power. Therefore, the absence of statistically significant associations between treatment approach or other clinicopathologic factors and LC does not establish equivalence or absence of clinically meaningful differences. OS was likewise favorable, with a 3-year OS rate of 94.4%, despite the advanced disease characteristics of many patients. Similar to previous reports, clinicopathologic factors including advanced T stage, tumor grade, nodal involvement, and treatment intent were not significantly associated with OS. However, the relatively short follow-up inherent to this series should be considered when interpreting survival outcomes in ACC, a disease characterized by prolonged survival and late disease progression.

Despite excellent LC, distant metastasis remained the predominant pattern of disease progression, most commonly involving the

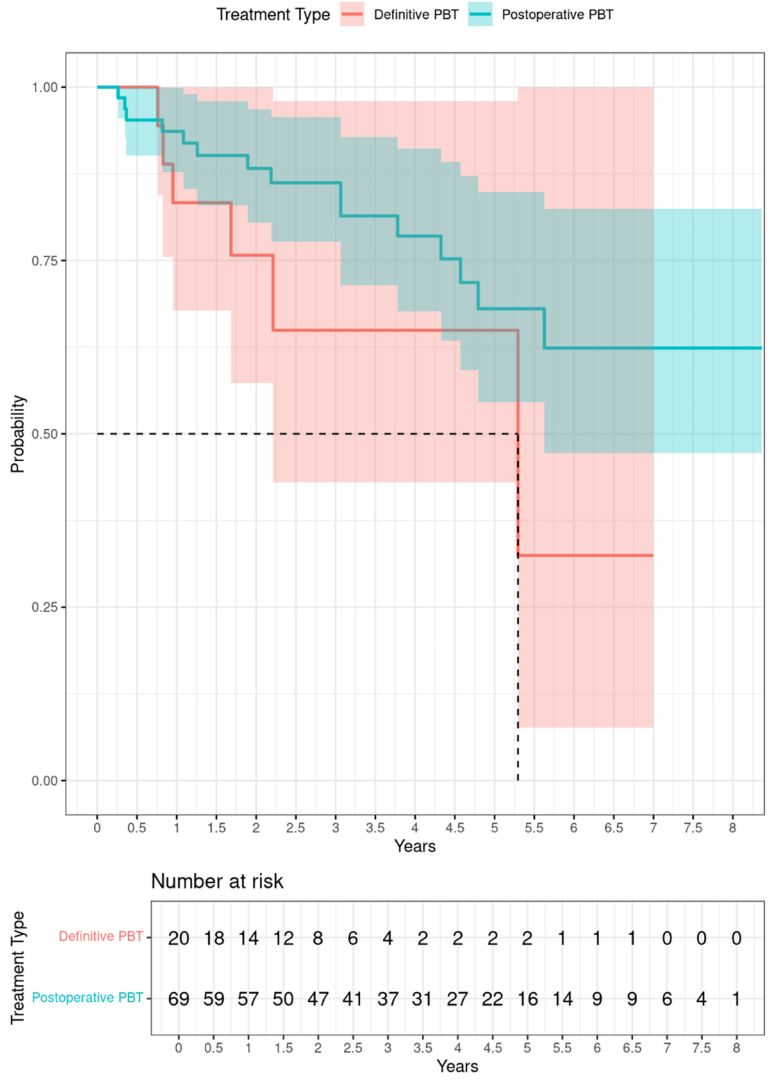


FIGURE 2
Distant-metastasis-free survival was not significantly different between the cohort of patients treated with definitive intent PBT versus postoperative PBT.

lungs. This observation is consistent with the established biology of ACC and highlights an important limitation of local therapy (1, 2, 4, 10, 13, 14). Although advances in RT delivery may improve locoregional disease control, additional progress in systemic therapy will likely be necessary to meaningfully improve long-term survival (35, 36).

Regional nodal failure was uncommon in our cohort, consistent with relatively low propensity of ACC for lymphatic dissemination (2, 4, 9–12). Only three patients developed regional nodal recurrence, all of whom were clinically N0 at presentation and did not receive elective nodal irradiation. These findings support our institutional approach of generally omitting elective nodal coverage in patients with a clinically N0 neck, thereby limiting unnecessary radiation dose to the neck and associated toxicity. Elective nodal treatment may warrant consideration on an individualized basis for patients with primary tumors arising in lymphatic-rich anatomic sites. Given the small number of nodal events in this cohort, these findings should not be interpreted as establishing the benefit or lack of benefit of elective nodal irradiation, and additional studies are needed to better select patients who may benefit from regional nodal treatment.

Our findings are consistent with the growing body of literature supporting PBT for ACC. Published experience remains limited primarily to retrospective institutional series; however, collectively these studies have demonstrated favorable LC and survival despite treating patients with advanced primary tumors, frequent perineural invasion, and high rates of positive surgical margins or gross residual disease (15). The outcomes observed in our cohort compare favorably with these published experiences and further support IMPT using PBS PBT as an effective treatment modality for patients with HN ACC.

Treatment was well tolerated, with no observed grade 4 or 5 acute or late toxicities. Acute grade 3 toxicities were uncommon and consisted primarily of mucositis, oral pain, and dermatitis, while late grade 3 toxicities were limited, with osteoradionecrosis representing the most frequent event (N = 4). Importantly, excellent LC was achieved without excessive treatment-related morbidity, supporting the ability of IMPT using PBS PBT to safely deliver high-dose RT to complex skull base targets while maintaining acceptable

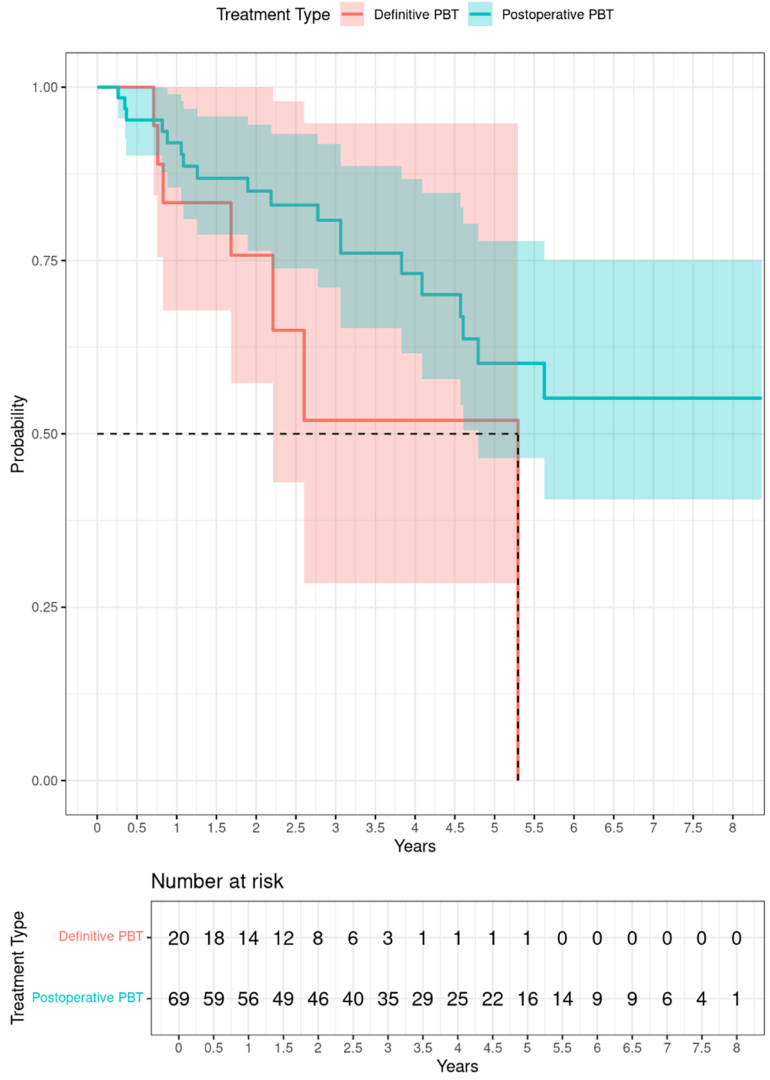


FIGURE 3
Overall Survival was not significantly different between the cohort of of patients treated with definitive-intent PBT versus postoperative PBT.

toxicity profiles. These findings are consistent with previously published PBT series and reinforce the value of PBT in minimizing normal tissue exposure when treating tumors adjacent to critical organs (15).

TABLE 2 Grade 3 toxicity.

Grade 3 toxicity	Patients (N)
Acute	
Dysphagia	4
Mucositis	1
Dermatitis	1
Late	
Osteoradionecrosis	4
Osteomyelitis	1
Vision Loss	1
Lacrimal duct stenosis	1

Several limitations should be considered when interpreting these findings. This study is limited by its retrospective, single-enterprise design, and the inherent selection bias with referral to a tertiary center of excellence with access to PBT. Second, no contemporary photon-treated comparison cohort was available, precluding direct comparison of oncologic outcomes or toxicity between treatment modalities. Although this study represents one of the larger single-institution PBT experiences with ACC, the definitive treatment cohort remained relatively small, limiting statistical power for subgroup analyses. Analyses were limited by the small number of patients and events and may potentially lead to unstable Cox regression estimates and underpowered tests. Thus, results should be considered hypothesis-generating. Next, baseline disease characteristics differed substantially between definitive and postoperative patients as shown in Table 1, confound comparisons between groups. Importantly, the definitive and postoperative cohorts should not be interpreted as comparable treatment groups as patients receiving definitive PBT were selected largely because of unresectable disease and had substantially more

advanced baseline disease characteristics, including higher T stage, more frequent clinical/radiographic PNI, and more advanced overall stage. Consequently, comparisons of outcomes between definitive and postoperative PBT should be interpreted cautiously as nonsignificant associations should not be interpreted as demonstrating equivalence between treatment approaches. Additionally, the propensity of ACC for late recurrence and disease progression, especially distant metastases may result in underestimation of long-term disease control and late treatment-related toxicity due to the relatively short follow up in this cohort of patients. Lastly, the localization of IMPT with PBS PBT at academic centers often predisposes the patient population to non-state residents with many opting for long-term follow-up with local physicians, complicating extended monitoring. Continued long-term longitudinal follow-up will therefore be essential to fully characterize durable outcomes for PBT.

Conclusion

This contemporary single-enterprise two-site institution experience supports curative-intent PBT as a feasible treatment option due to excellent LC and acceptable toxicity for select patients with HN ACC, particularly when normal tissue sparing is clinically desirable because of proximity of critical structures. These findings add to the growing evidence supporting PBT as a treatment option for this anatomically challenging malignancy. Given the rarity of ACC, prospective multi-institutional comparative cohorts using robust adjustment for baseline differences, are needed to define whether the dosimetric advantages of PBT confirm improved toxicity and tumor control compared to contemporary photon RT as well as further refine patient selection and optimize treatment strategies.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Mayo Clinic Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because low risk: retrospective review.

Author contributions

AR: Writing – original draft, Supervision, Project administration, Formal Analysis, Writing – review & editing, Visualization, Investigation, Data curation, Software, Validation, Methodology, Resources, Conceptualization. MV: Software, Investigation, Writing – review & editing, Formal Analysis, Methodology, Writing – original draft. HG: Writing – review & editing, Investigation, Software, Formal Analysis, Methodology, Writing – original draft. DM: Investigation, Writing – review & editing, Writing – original draft. SP: Writing – review & editing, Writing – original draft, Investigation. SL: Writing – original draft, Investigation, Writing – review & editing. JR: Investigation, Writing – review & editing, Writing – original draft. MN: Writing – review & editing, Writing – original draft, Investigation. RF: Writing – review & editing, Writing – original draft, Investigation. DR: Writing – original draft, Investigation, Writing – review & editing. YG: Investigation, Writing – review & editing, Writing – original draft. JW: Investigation, Writing – review & editing, Writing – original draft. DP: Writing – original draft, Investigation, Writing – review & editing. JJ: Writing – original draft, Investigation, Writing – review & editing. MH: Investigation, Writing – review & editing, Writing – original draft. AC: Investigation, Writing – original draft, Writing – review & editing. KP: Writing – review & editing, Writing – original draft, Investigation. PM: Writing – review & editing, Writing – original draft, Investigation. AH: Writing – review & editing, Writing – original draft, Investigation. HM: Writing – original draft, Writing – review & editing, Investigation. LM: Resources, Conceptualization, Project administration, Investigation, Validation, Visualization, Methodology, Writing – review & editing, Supervision, Formal Analysis, Writing – original draft, Data curation.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

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