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Original research

Outcomes of different treatment patterns for adenoid cystic carcinoma of the anterior craniofacial area: A multi-institutional study on 578 patients

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ABSTRACT

Background: Adenoid cystic carcinoma of the anterior craniofacial region (ACF-ACC) is challenging to treat due to extensive subclinical spread and proximity to critical structures. Although surgery followed by radiotherapy (RT) is the current standard, real-world outcomes with modern photon and particle therapy remain insufficiently characterized.

Methods: We retrospectively analyzed 578 patients with ACF-ACC treated at eight international centers (1984–2023). Clinicopathologic features, treatment patterns, and outcomes were assessed. Anatomical extension was classified using hierarchical clustering. Comparative analyses of gross total resection (GTR) and non-surgical treatment (NST) were adjusted using propensity score matching and multivariable Cox and Fine-Gray models. Primary endpoints were local recurrence-free survival (LRFS) and cumulative incidence of local recurrence (LRCI).

Results: Most tumors arose in the sinonasal tract (75.8%) and were low/intermediate grade (68.6%). Long-term outcomes showed high local and distant recurrence (20-year LRCI: 74.1%; cumulative incidence of distant metastasis: 55.6%). GTR followed by adjuvant RT, especially with proton therapy (PT), achieved the best local control. R2 resections provided no advantage over NST. Within the NST cohort (n = 110), PT yielded higher complete response rates than photon RT, while responders demonstrated local control comparable to surgically treated patients. Ten-year ≥G3 toxicity incidence was 36%.

Conclusions: For ACF-ACC, GTR plus modern RT provides the strongest local control, and R2 surgery should be avoided. PT is an effective definitive option for selected patients, supporting future response-guided treatment strategies.

1. Introduction

Adenoid cystic carcinoma (ACC) is one of the most common types of salivary gland carcinomas. It is a biphasic tumor characterized by both epithelial and myoepithelial differentiation and is hypothesized to arise from the junction between the salivary acinus and the intercalated duct. According to cancer registry data, the annual incidence of ACC per milion people has declined from 4.1 in 1975 to 2.5 in 2018 [1]. However, its population prevalence has increased from approximately 2 to 26 cases per million people over the past two decades, with a slight female predominance [1].

Historically, ACC has been subtyped based on the proportion of solid components observed on histopathological examination, following classifications such as those proposed by Perzin *et al.* [2], Szanto *et al.* [3], and Spiro *et al.* [4], which grade ACC from I to III. More recently, metatypical variants characterized by distinct histopathological features have been described, showing a predilection for the sinonasal tract and skull base and harboring molecular alterations such as noncanonical gene fusions and *NOTCH1* mutations [5].

The canonical genetic hallmark of ACC is a fusion involving *MYB* (or, less frequently, *MYBL1*) and *NFIB*, which is found in approximately two-thirds of cases [5,6]. Activating *NOTCH1* mutations are identified in approximately 14% of sinonasal ACC cases and are associated with worse survival compared with tumors harboring non-activating mutations or wild-type *NOTCH1* [5,7].

A recent advance in understanding ACC biology comes from a study by Ferrarotto *et al.*, which identified two distinct ACC subtypes based on proteogenomic profiles [8]. These can be differentiated by the expression of *TP63* (retained in type II, lost in type I) and *MYC* (low in type II, high in type I), which typically show inverse expression. Type II tumors are associated with better prognosis than type I. Additionally, Hanna *et al.* showed that nearly half of ACC cases display an intermediate pattern of TP63 and MYC expression (i.e., TP63-high/MYC-high or TP63-low/MYC-low), which is associated with prognosis more similar to type II ACC [9].

The present study focuses on anterior craniofacial ACC (ACF-ACC), a designation that includes ACCs of minor salivary gland origin with epicenter in the nasal cavity, paranasal sinuses, nasopharynx, hard palate, superior alveolar ridge, or soft palate. According to a recent systematic review of 17,497 ACC cases, ACF-ACC accounts for approximately 64% of all minor salivary gland ACCs, which in turn represent 43% of all head and neck ACCs [10].

The current standard of care for ACF-ACC involves surgical resection followed by adjuvant radiotherapy (RT) [11–13]. However, several nuances in real-world clinical practice challenge this paradigm. Notably, surgical resection is often incomplete, resulting in microscopic (R1) or macroscopic (R2) residual disease in a significant proportion of cases, especially in so-called "borderline resectable" tumors. This raises the question of whether definitive RT could serve as an alternative to upfront surgery in selected cases, and whether this decision should depend on the putative extent of residual disease (R1 *vs.* R2). Furthermore, the foundational studies supporting the current standard of care are dated [14,15], and both surgical and RT techniques have evolved substantially in recent decades. For instance, endoscopic procedures now play an important role in both transnasal and open approaches [16–18], intensity-modulated radiotherapy (IMRT) has become widely adopted [19–22], and particle therapy, including proton therapy (PT) and carbon ion radiotherapy (CIRT), is increasingly available worldwide [23–29].

This study aims at analyzing an international, multicentric, real-world cohort of 578 ACF-ACC to 1) describe clinicopathological characteristics, 2) provide information on survival outcomes and relevant prognostic factors, and 3) infer a recommended strategy of locoregional treatments via comparative analyses adjusted for relevant confounders.

2. Materials and methods

This retrospective, multi-institutional study included patients with ACF-ACC treated at the following centers: University of Padova – "Azienda Ospedale-Università Padova" and "Istituto Oncologico Veneto (IOV) I.R.C.S.S." (Padova, Italy) between 2010 and 2023; University of Brescia – "ASST Spedali Civili di Brescia" (Brescia, Italy) between 1997 and 2022; University of Insubria – "Ospedale di Circolo e Fondazione Macchi" (Varese, Italy) – "Ospedale S. Anna" (Como, Italy) between 2002 and 2021; University of Paris – "Hôpital Lariboisière AP-HP" (Paris, France) between 2000 and 2019; "Institut Gustave Roussy" (Paris, France) between 1998 and 2023; "Centro Nazionale di Adroterapia Oncologica" (Pavia, Italy) between 2016 and 2022; The University of Texas – MD Anderson Cancer Center (Houston, Texas, United States) between 1984 and 2019; University of Cambridge – Cambridge University Hospitals NHS Trust (Cambridge, United Kingdom) between 2015 and 2023.

Inclusion criteria for the multi-institutional database were: histopathological diagnosis of ACC; tumor epicenter in the sinonasal tract, nasopharynx, hard palate, superior alveolar ridge, or soft palate; any disease stage; any clinical presentation (primary, recurrent/persistent); treatment with any intent (curative, non-curative). Exclusion criteria included CIRT and participation in clinical trials involving non-cytotoxic systemic therapies (*e.g.*, NOTCH inhibitors) administered in the curative setting. In both cases, access to the data was restricted to safeguard the intellectual property associated with ongoing clinical trials.

Analysis of data was conducted in accordance with the 1964 Helsinki declaration and its later amendments. Data collection and analysis was approved by local institutional review boards (University of Padova – "Azienda Ospedale-Università Padova", code: 360n/AO/23; University of Brescia – "ASST Spedali Civili di Brescia", code: NP3616; University of Insubria – "Ospedale di Circolo e Fondazione Macchi", code: 0033025/2015; "Ospedale S. Anna", code: 212/2024; University of Paris – "Hôpital Lariboisière AP-HP", codes: REFCOR database approval CNIL #91204 and CCTIR #11.337; "Institut Gustave Roussy", code: 2024–354; "Centro Nazionale di Adroterapia Oncologica", code: CNAO OSS 34/2021; The University of Texas – MD Anderson Cancer Center, code: RCR04–0636; University of Cambridge – Cambridge University Hospitals NHS Trust, code: PRN12291.

Table 1
Summary of clinicopathological variables included in the study. ECOG-PS, Eastern Cooperative Oncology Group performance status.

Clinicopathological variable	Categories
Age	N/A
Gender	Male; Female
ECOG-PS	0; 1; 2
Epicenter	Sinonasal; hard palate or superior alveolar ridge; nasopharynx; soft palate; other
Tumor grade (Perzin-Szanto classification) [2,3]	I; II; III
Tumor grade (Van Weert)	Solid+; solid-
Presentation at referral	Primary; recurrent (defined as evidence of disease after disease-free post-treatment imaging); persistent (defined as evidence of disease at the first post-treatment imaging); disease-free (referred to patients presenting to a participating center with neither clinical nor radiological evidence of disease)
Treatment intent	Curative; non-curative
cT	cT1; cT2; cT3; cT4; cT4a; cT4b
cN	cN0; cN1; cN2; cN2a; cN2b; cN2c; cN3; cN3a; cN3b
Presence of retropharyngeal metastases	Yes; no
Nodal metastases with extranodal extension	Yes; no
cM status	cM0; cM1
pT	pT1; pT2; pT3; pT4; pT4a; pT4b
pN	pN0; pN1; pN2; pN2a; pN2b; pN2c; pN3; pN3a; pN3b
Perineural invasion	Pn0 (absent); Pn1 (only microscopic perineural invasion); Pn2 (gross perineural invasion)
Lymphovascular invasion	LV0 (absent); LV1 (only microscopic lymphovascular invasion); LV2 (gross lymphovascular invasion)
Extent of residual disease post-surgery	R0 (no residual disease); R1 (microscopic residual disease); R2 (macroscopic residual disease).

2.1. Clinicopathological information

Demographic, clinical, and pathological data were retrieved from local archives at each institution, referring to the time of first contact. Collected variables are reported in Table 1. Of note: *i*) clinical and post-surgical staging was defined according to the 8th edition of the TNM Classification of Malignant Tumours (cases originally staged with earlier editions were reclassified accordingly) [30]; *ii*) the Perzin-Szanto grading system was selected for subsequent analysis as it yielded the lowest proportion of missing data, the most consistent reproducibility across institutions, and the best prognostic stratification [2,3]; *iii*) both R0 and R1 resections were considered "gross total resection" (GTR); *iv*) response to non-surgical treatment (NST) was assessed per Response Evaluation Criteria in Solid Tumors v. 1.1 [31].

Pre-treatment tumor extension was evaluated using imaging and anatomical areas were classified as either infiltrated or tumor-free. The anatomical areas assessed (n = 43) included the nasoethmoidal complex, all paranasal sinuses, skull base bones and dura, brain regions, orbital structures, cranial nerves, skull base foramina, major vessels (including ICA by segment), and various soft tissue compartments of the face, nasopharynx, oropharynx, and oral cavity.

2.2. Statistical analysis

Statistical analysis was conducted using RStudio (Version 4.3.1).

Descriptive statistics were presented as frequency and percentage for categorical variables and median and interquartile range (IQR) for continuous variables.

Treatment patterns were analyzed retrospectively and defined as specific combinations of treatment modalities. Comparisons between treatment patterns with respect to clinicopathological features were performed using the Chi-square or Fisher's exact test for categorical

Table 2
Summary of outcomes evaluated in the study.

Outcome	Event/censor definition
Overall survival (OS)	event = death from any cause; censor = alive at last follow-up
Disease-specific survival (DSS)	event = ACC-related death; censor = alive or deceased from non-ACC cause
Recurrence-free survival (RFS)	event = recurrence or death; censor = alive without recurrence
Cumulative incidence of recurrence (RCI)	event = recurrence; censor = no recurrence or death without recurrence;
Local recurrence-free survival (LRFS)	event = local recurrence or death; censor = alive without local recurrence
Cumulative incidence of local recurrence (LRCI)	event = local recurrence; censor = no local recurrence or death without local recurrence
Regional recurrence-free survival (RRFS)	event = regional recurrence or death; censor = alive without regional recurrence
Cumulative incidence of regional recurrence (RRCI)	event = regional recurrence; censor = no regional recurrence or death without regional recurrence
Distant recurrence-free survival (DRFS)	event = distant recurrence or death; censor = alive without distant recurrence
Cumulative incidence of distant metastasis (DMCI)	event = distant recurrence; censor = no distant recurrence or death without distant recurrence
Progression-free survival (PFS)	event = recurrence (in disease-free patients), progression (in patients with residual disease) or death; censor = no recurrence/progression at last follow-up
Cumulative incidence of progression (PCI)	event = recurrence/progression; censor = no recurrence/progression or death without recurrence/progression

variables and Mann-Whitney U or Kruskal-Wallis test for continuous variables.

Survival outcomes were measured separately for primary *vs*. recurrent/persistent ACC and estimated using Kaplan-Meier and cumulative incidence methods, with corresponding 95% confidence intervals (95%-CI). All time-to-event analyses were anchored to the date of treatment start (exact date when available, estimated date otherwise). Where applicable, outcomes definition was consistent with recommendations from the Head and Neck Cancer International Group [32,33]. Outcomes evaluated are reported in Table 2.

Given the study focus on local treatment modalities, local recurrence-free survival (LRFS) and cumulative incidence of local recurrence (LRCI) were defined as primary outcomes, while overall survival (OS), disease-specific survival (DSS), and the other mentioned in Table 2 were considered secondary outcomes.

Univariate analysis was conducted using the log-rank test for Kaplan-Meier data and Gray's test for cumulative incidence curves. To balance treatment sub-cohorts, a three-step process was used: *i*) agglomerative hierarchical clustering (AHC) was used to group anatomical extension patterns into four clusters (missing data were considered "missing at random" and imputed through multivariate imputation by chained equations including the following covariates: age, gender, tumor epicenter, grade, cT category, nodal status, perineural invasion, and lymphovascular invasion); this method ensured balanced clustering of cases into relatively homogeneous groups in terms of anatomical extension; *ii*) a propensity score matching (PSM) method was utilized with the following technical aspects: matching variable was upfront surgery *vs*. NST; distance-determining covariates included age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), tumor epicenter, tumor grade, AHC-generated cluster of anatomical extension, and nodal status; optimal full matching without replacement method was used; propensity score was estimated with logistic regression using a generalized linear model; *iii*) multivariable Cox proportional hazards model was used to compare treatment effects on all outcomes except cumulative incidence-based ones; covariates included: age, gender, ECOG PS, epicenter, grade, AHC cluster, nodal status, perineural invasion, and treatment period (until 1999 *vs*. 2000–2009 *vs*. 2010–2019 *vs*. 2020–2023). Variable inclusion was based on clinical relevance and univariate prognostic significance (with level of significance 0.05). For cumulative incidence outcomes, a multivariable Fine-Gray model was used to measure adjusted hazard ratio (HR) and a multivariable cause-specific Cox model was employed to generate forest plots, using the same covariates reported above. Model diagnostics included: global Schoenfeld test for proportional hazards, deviance residual analysis for influential observations, Martingale residuals for non-linearity, and multicollinearity testing (with a variance inflation factor threshold of $\geq$5 indicating collinearity).

A separate descriptive and survival analysis on patients receiving NST was performed: primary outcomes were measured through univariate analysis with Kaplan-Meier and cumulative incidence methods and assessed with multivariable Cox proportional hazards and Fine-Gray models. Outcomes were compared in terms of presentation to RT (biopsy-only *vs*. R2 cases) and RT modality (photon-based *vs*. PT). Multivariable models included age, gender, ECOG PS, epicenter, grade, AHC cluster, nodal status, treatment period, concomitant/neoadjuvant chemotherapy, presentation to RT, and RT modality as covariates.

3. Results

The entire study cohort included 578 patients, with a median age of 54 years and a slight female predominance (54.5%). Characteristics of the population are summarized in Table 3. Most ACF-ACCs originated from the sinonasal tract (75.8%), were classified as low-to-intermediate grade (68.6%), and occurred in patients with good PS (ECOG-PS 0 in 82.9% of patients). ACC presentation was primary in 65.8%, recurrent in 21.2%, and persistent in 10.2%. Treatment was intended to be curative

Table 3
General demographic and tumor-related information.

Variable	Distribution*	Missing data (%)**
Age (years)	Mean: 52.4 Median: 54 Range: 6-90 IQR: 41-63	None
Gender	Female: 315 (54.5%) Male: 263 (45.5%)	None
ECOG PS	Class 0: 145 (82.9%) Class 1: 24 (13.7%) Class 2: 6 (3.4%)	403 (69.7%)
Site	Sinonasal: 438 (75.8%) Hard palate or superior alveolar ridge: 59 (10.2%) Nasopharynx: 59 (10.2%) Soft palate: 12 (2.1%) Other: 10 (1.7%)	None
Tumor grade (Perzin-Szanto classification)	Grade I: 82 (21.1%) Grade II: 185 (47.6%) Grade III: 122 (31.4%)	189 (32.7%)
Tumor grade (Van Weert)	No solid component: 85 (21.4%) Solid component: 313 (78.6%)	180 (31.1%)
Presentation at referral	Primary: 376 (65.8%) Recurrence: 121 (21.2%) Macroscopic persistence after cure-intended treatment: 39 (6.8%) Macroscopic persistence after non-cure-intended treatment: 14 (2.5%) Macroscopic persistence, NOS: 5 (0.9%) No evidence of disease (referral for follow-up): 16 (2.8%)	7 (1.2%)
Treatment intent	Cure-intended treatment: 489 (89.9%) Non-cure-intended treatment: 55 (10.1%) • M1: 36 (65.5%) • Other reason: 19 (34.5%)	34 (5.9%)
cT category	T1: 32 (5.8%) T2: 65 (11.7%) T3: 75 (13.5%) T4 (nasopharynx): 19 (3.4%) T4 NOS (other sites): 37 (6.7%) T4a: 180 (32.4%) T4b: 147 (26.5%)	23 (4.0%)
cN status	N0: 525 (94.3%) Nodal metastases: 32 (5.7%) • N1: 12 (2.2%) • N2 (nasopharynx): 3 (0.5%) • N2 NOS (sinonasal): 2 (0.4%) • N2a: 1 (0.2%) • N2b: 8 (1.4%) • N2c: 4 (0.7%) • N3b: 2 (0.4%)	21 (3.6%)
Retropharyngeal metastases in cN+ patients (n=32)	No: 17 (94.4%) Yes: 1 (5.6%)	14 (43.8%)
Clinical/pathological ENE in cN+ patients (n=32)	No: 9 (40.9%) Yes: 11 (50.0%) pN0: 2 (9.1%)	10 (31.3%)
cM status	M0: 517 (93.5%) M1: 36 (6.5%) • Lung: 14 (38.9%) • Skeleton: 2 (5.6%) • Liver: 1 (2.8%) • Lung and skeleton: 1 (2.8%) • Not specified: 18 (50.0%)	25 (4.3%)

(*continued on next page*)

Table 3 (*continued*)

Variable	Distribution*	Missing data (%)**
Pattern of metastases	N0M0: 489 (88.6%) N+M0: 27 (4.9%) N0M1: 31 (5.6%) N+M1: 5 (0.9%)	26 (4.5%)
Perineural invasion	Pn0: 88 (23.1%) Pn1: 221 (58.0%) Pn2: 72 (18.9%)	197 (34.1%)
Lymphovascular invasion	LV0: 277 (77.6%) LV1: 58 (16.2%) LV2: 22 (6.2%)	221 (38.2%)
Pattern of neurovascular invasion	Pn0LV0: 85 (23.8%) Pn+LV0: 193 (53.8%) Pn0LV+: 1 (0.3%) Pn+LV+: 79 (22.1%)	221 (38.2%)

*Distribution of non-missing data is reported (i.e., denominator of proportions is the total of non-missing observations); **Proportion of missing data is calculated on the row sample size (n = 578 if not otherwise specified).
Abbreviations: ENE, extranodal extension; LV, lymphovascular invasion (LV0, absent; LV1, only microscopic lymphovascular invasion; LV2, gross lymphovascular invasion; LV+, lymphovascular invasion of any type); IQR, interquartile range; NOS, not otherwise specified; Pn, perineural invasion (Pn0, absent; Pn1, only microscopic perineural invasion; Pn2, gross perineural invasion, Pn+, perineural invasion of any type).

in the large majority of cases (89.9%). Patients were suggested to undergo a lifetime scheduled follow-up including clinical, endoscopic, and radiologic assessment. Type and frequency of assessments varied per period of time and institution. Distribution by year of treatment is reported in Figure S1; distribution by center is detailed in Table S1. Median and mean follow-up duration were 62.8 and 82.9 months in the entire cohort and 70.1 and 89.3 months in patients alive at last follow-up, respectively.

Figure 1 breaks down the series by presentation, treatment intent, local treatment type, residual disease after surgery, response to NST, and local control. Among cases who underwent surgery as primary modality of cure-intended treatment (n = 392), 128 (32.7%) were classified as R0, 158 (40.3%) as R1, 40 as R2 (10.2%), and in 66 (16.8%) post-surgical residual disease could not be classified (*i.e.*, RX). The latter group did not include R2 cases. R1 surgeries included unifocal and multifocal residue in 34/128 (26.6%) and 49/128 (38.3%), respectively, with 45/128 (35.2%) cases of R1 not otherwise specified (NOS). No significant differences in primary outcomes were observed when comparing R0 and R1 surgeries, except for primary ACC treated with GTR without the addition of adjuvant radiation (Figures S2 and S3). R2 surgeries included unifocal and multifocal residue in 9/40 (22.5%) and 14/40 (35.0%), respectively, with 17/40 (42.5%) cases of R2 NOS. Figure S4 summarizes associations between tumor extensions and macroscopic completeness of surgery, highlighting structures that were significantly more frequently involved in patients with a R2 surgery as compared to GTR cases. Patients receiving GTR (n = 352) underwent adjuvant RT in the majority of cases (300, 85.2%), with either photon-based RT (233, 66.2%) or PT (67, 19.0%). In the photon-based RT group, most patients underwent IMRT techniques (157/233, 67.4%), including volumetric modulated arc therapy [VMAT] in 66/157; concomitant chemotherapy [cChT] was used in 7/157 patients. Fifty-two (23.3%) patients underwent 3D conformal RT (cChT in 3/52), and for the remaining (24, 10.3%; cChT in 4/24) this information could not be retrieved. Mean total dose was similar between the aforesaid groups (3D-RT: 66.0 Gy, IMRT/VMAT: 63.6 Gy, PT: 66.9 GyE).

Actuarial survival estimates are reported in Table 4. Substantial

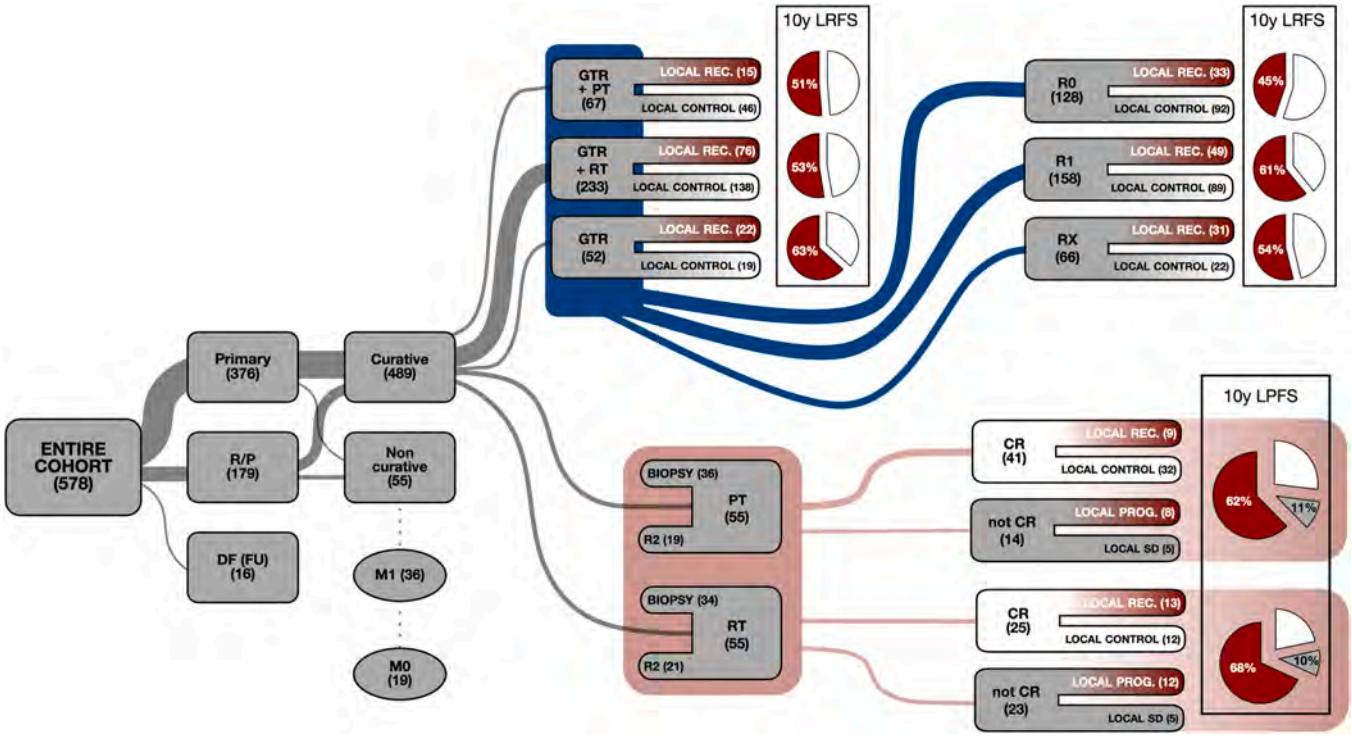


Fig. 1. Flow chart breaking the series down by presentation, treatment intent, type of local treatment and local control. Pie charts show the rate of local recurrence and/or death (red slice), stable local disease (grey slice), and patients alive and local disease-free at 10 years after treatment. CR, complete response; DF (FU), patients referred with no residual disease, for follow-up; GTR, gross total resection; LPFS, local progression-free survival; LRFS, local recurrence-free survival; M0, no distant metastases; M1, presence of distant metastases; P, persistence; PT, Proton therapy; R, recurrence; R0, no residual disease; R1, microscopic residual disease; R2, macroscopic residual disease; RT, radiotherapy; RX, unknown status of residual disease.

Table 4
Five-, 10-, and 20-year survival estimates for the entire cohort, patients treated with curative intent for a primary or recurrent/persistent tumor, and patients treated with non-curative intent. DMCI, cumulative incidence of distant metastasis; DRFS, distant recurrence-free survival; DSS, disease-specific survival; LRCI, cumulative incidence of local recurrence; LRFS, local recurrence-free survival; OS, overall survival; PCI, cumulative incidence of progression; PFS, progression-free survival; RCI, cumulative incidence of recurrence; RFS, recurrence-free survival; RRCI, cumulative incidence of regional recurrence; RRFS, regional recurrence-free survival.

Outcome	Entire cohort (n=569)*	Curative intent – primary presentation (n=324)	Curative intent – non-primary presentation (n=159)	Non-curative intent** (n=55)
OS	5y: 77.1% (73.4–81.0) 10y: 58.1% (53.1–63.5) 20y: 30.9% (24.0–39.7)	5y: 76.9% (72.0-82.1) 10y: 56.5% (49.6-64.3) 20y: 37.9% (29.2-49.4)	5y: 86.0% (80.5–91.7) 10y: 69.9% (62.2–78.6) 20y: 37.0% (26.9–51.1)	5y: 56.3% (43.6–72.7) 10y: 29.4% (17.3–50.0)
DSS	5y: 81.6% (78.0–85.4) 10y: 68.0% (63.0–73.4) 20y: 44.1% (35.4–55.0)	5y: 82.5% (77.8–87.4) 10y: 67.0% (60.0–74.8) 20y: 56.1% (47.1–66.9)	5y: 89.4% (84.2–94.8) 10y: 79.2% (71.6–87.5) 20y: 51.2% (38.6–67.8)	5y: 58.8% (45.5–76.0) 10y: 39.2% (25.2–61.1)
RFS	5y: 58.5% (53.7–63.7) 10y: 34.5% (29.4–40.5) 20y: 11.9% (7.4–19.2)	5y: 55.7% (49.5–62.7) 10y: 34.9% (28.1–43.3) 20y: 21.8% (14.4–33.1)	5y: 64.7% (56.9–73.5) 10y: 33.4% (25.8–43.3) 20y: 7.6% (3.6–16.3)	5y: 38.1% (19.0–76.5) 10y: 38.1% (19.0–76.5)
RCI	5y: 39.6% (34.3–44.4) 10y: 62.7% (56.6–67.9) 20y: 85.5% (77.0–90.9)	5y: 41.2% (34.1–47.5) 10y: 61.3% (52.6–68.4) 20y: 70.7% (59.2–78.9)	5y: 35.3% (26.5–43.1) 10y: 64.8% (54.9–72.6) 20y: 91.4% (81.8–95.9)	5y: 61.9% (23.5–81.0) 10y: 61.9% (23.5–81.0)
PFS	5y: 51.0% (46.6–55.8) 10y: 29.1% (24.7–34.1) 20y: 8.6% (5.3–14.1)	5y: 50.3% (44.5–56.9) 10y: 30.2% (24.3–37.6) 20y: 16.7% (10.6–26.4)	5y: 57.9% (50.5–66.4) 10y: 29.8% (23.0–38.6) 20y: 6.3% (2.9–13.6)	5y: 28.1% (17.2–45.8) 10y: 18.9% (9.7–36.9)
PCI	5y: 45.7% (40.8–50.1) 10y: 67.2% (61.8–71.8) 20y: 88.2% (81.1–92.6)	5y: 45.2% (38.6–51.1) 10y: 65.2% (57.3–71.6) 20y: 73.1% (63.1–80.4)	5y: 41.1% (32.7–48.5) 10y: 67.8% (59.1–74.8) 20y: 92.7% (84.0–96.6)	5y: 69.8% (51.2–81.3) 10y: 76.7% (57.4–87.2)
LRFS	5y: 70.4% (65.8–75.3) 10y: 49.7% (44.1–55.9) 20y: 18.2% (11.9–28.0)	5y: 70.0% (64.1–76.5) 10y: 53.4% (46.0–61.9) 20y: 34.5% (24.0–49.6)	5y: 71.2% (63.8–79.5) 10y: 44.8% (37.0–53.5) 20y: 8.6% (3.5–21.1)	5y: 65.2% (44.4–95.8) 10y: 47.5% (26.4–85.5)
LRCI	5y: 24.3% (19.6–28.7) 10y: 41.4% (35.0–47.2) 20y: 74.1% (61.6–82.6)	5y: 22.7% (16.7–28.3) 10y: 34.0% (25.6–41.4) 20y: 52.2% (34.2–65.3)	5y: 26.7% (20.8–32.6) 10y: 47.5% (39.6–54.6) 20y: 75.7% (62.0–85.7)	5y: 29.4% (0.0–50.3) 10y: 29.4% (0.0–50.3)
RRFS	5y: 73.3% (68.8–78.2) 10y: 55.9% (49.6–62.9) 20y: 29.6% (19.7–44.6)	5y: 80.3% (75.3–85.7) 10y: 62.2% (54.9–70.5) 20y: 44.7% (34.5–58.0)	5y: 83.6% (77.1–89.5) 10y: 66.0% (58.4–73.6) 20y: 41.4% (29.9–53.2)	5y: 93.3% (81.5–100.0) 10y: 46.9% (24.4–90.2)
RRCI	5y: 2.8% (0.9–4.6)	5y: 1.6% (0.0–3.2)	5y: 3.7% (0.9–7.4)	5y: 0.0% (0.0–0.0)

Table 4 (*continued*)

Outcome	Entire cohort (n=569)*	Curative intent – primary presentation (n=324)	Curative intent – non-primary presentation (n=159)	Non-curative intent** (n=55)
	10y: 8.7% (4.2–12.9) 20y: 15.4% (4.8–24.9)	10y: 4.9% (0.8–8.7) 20y: 4.9% (0.8–8.7)	10y: 8.8% (3.8–14.1) 20y: 28.0% (15.7–39.9)	10y: 0.0% (0.0–0.0)
DRFS	5y: 70.1% (65.5–74.9) 10y: 49.5% (44.0–55.7) 20y: 28.8% (22.3–37.3)	5y: 70.8% (65.0–77.2) 10y: 56.1% (48.8–64.5) 20y: 41.9% (31.4–55.9)	5y: 74.8% (69.2–80.4) 10y: 58.3% (50.8–66.0) 20y: 39.1% (30.2–49.1)	5y: 60.0% (39.2–91.9) 10y: 60.0% (39.2–91.9)
DMCI	5y: 25.8% (20.8–30.4) 10y: 43.1% (36.2–49.1) 20y: 55.6% (45.2–64.0)	5y: 25.4% (19.3–31.1) 10y: 38.8% (30.6–46.1) 20y: 47.5% (34.7–57.8)	5y: 25.0% (19.7–30.3) 10y: 38.5% (30.7–45.8) 20y: 51.3% (40.7–60.6)	5y: 40.0% (8.1–60.8) 10y: 40.0% (8.1–60.8)

* 31 patients could not be attributed to any of the following cohorts (in 14 patients treatment intent could not be retrieved; presentation was not defined/applicable in 17 patients).
** All patients died before 240 months of follow-up.

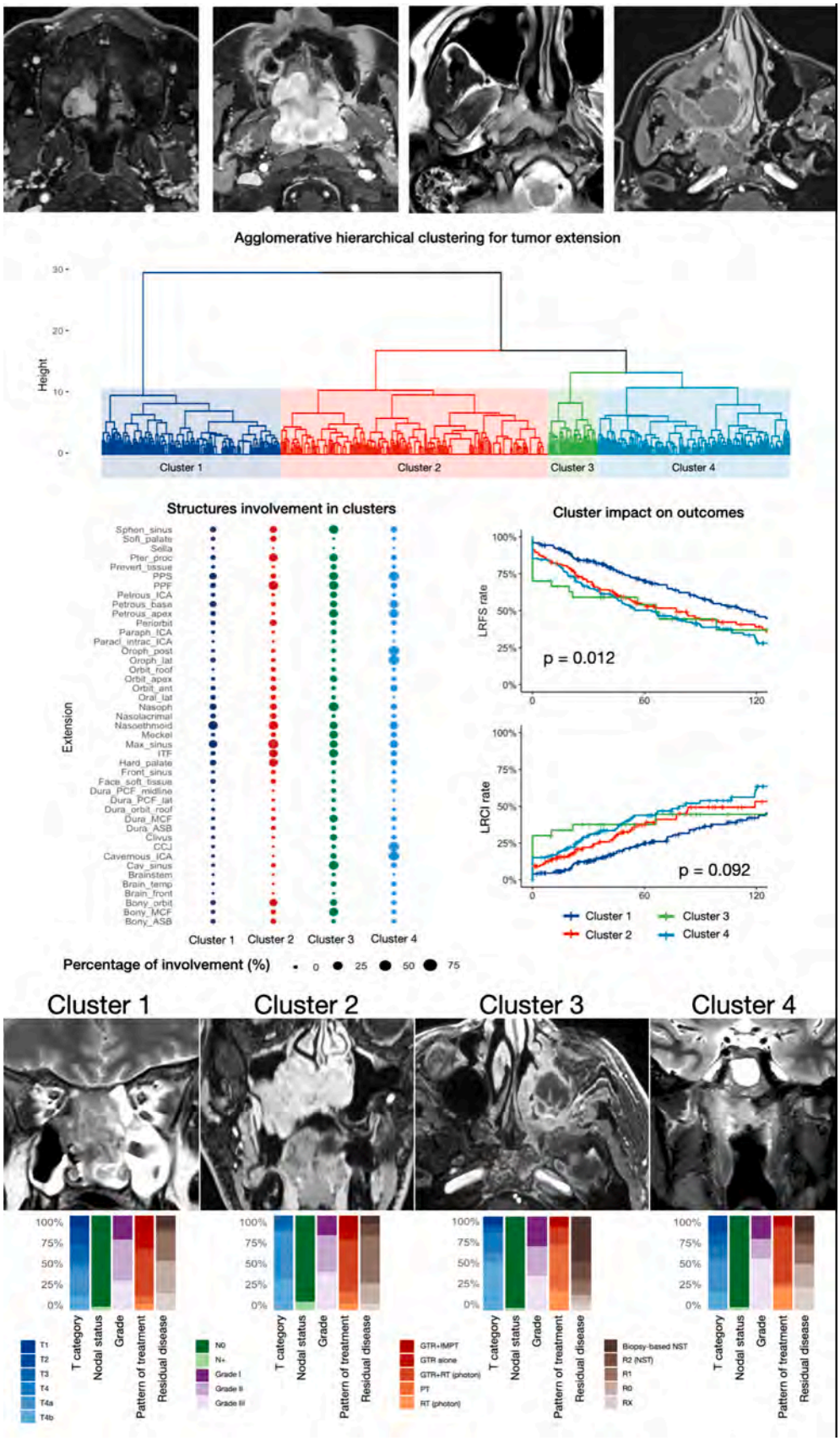
differences in outcomes were observed based on both treatment intent and tumor presentation. Overall, OS and DSS steadily declined over the long term, with more than half of patients dying of ACC within 20 years post-treatment (20-year OS: 30.9%; 20-year DSS: 44.1%). Only a minority were alive and free of disease recurrence at 20 years (20-year RFS: 11.9%). Most recurrences were local or distant, with approximately three-quarters experiencing local recurrence (20-year LRCI: 74.1%; 20-year LRFS: 18.2%) and nearly half developing distant metastases within 20 years (20-year DMCI: 55.6%; 20-year DRFS: 28.8%).

Tumor extension was notably heterogeneous. AHC identified cases with similar anatomical extension, resulting in 4 clusters with relatively homogeneous local extension (Figure 2; Table 5). Cluster 1 involved the sinonasal tract and adjacent bony structures; cluster 2 involved connective spaces (*e.g.*, pterygopalatine and infratemporal fossae) and the oral cavity; cluster 3 showed involvement of the nasopharynx, sphenoid sinus, orbital apex, and middle cranial fossa (including cavernous sinus, Meckel's cave, and dura mater); cluster 4 was characterized by involvement of the oropharynx, parapharyngeal space, craniocervical junction, petrous apex, and internal carotid artery (ICA).

Univariate survival analysis included only patients treated with curative intent and available follow-up (n = 483). Results were analyzed separately for primary (n = 324) and recurrent/persistent cases (n = 159). Several prognostic factors were identified (Tables 6 and 7), including clinical T category (cT), nodal status, tumor grade, and extent of post-surgical residual disease (Figure 3).

Five distinct treatment patterns were identified: 1) GTR + PT; 2) GTR + photon-based RT, 3) GTR; 4) definitive PT; 5) definitive photon-based RT. These groups showed significant differences in some clinicopathological features, particularly in relation to tumor extension (Table 8). For instance, cT4b tumors and AHC-Cluster 4 were more frequently observed in patients treated with NST. Actuarial survival outcomes significantly varied among treatment groups (Figure 4). PSM achieved high balance between the surgery and NST groups (standardized mean difference=0.0057). In the PSM-based, multivariable-adjusted analysis, GTR + PT was associated with the most favorable outcomes, especially in terms of LRFS and LRCI (Figure 5; Table 9).

In patients receiving definitive NST with curative intent (n = 110), 55 (50.0%) underwent photon-based treatment (10 with 3D conformal RT, 34 with IMRT, and 11 with photon-based RT NOS), and 55 (50.0%)



(caption on next page)

Fig. 2. Local extension-based agglomerative hierarchical clustering. Top images exemplify the heterogeneity of local extension of adenoid cystic carcinoma of the anterior craniofacial area. The dendrogram shows the clustering process based on local extension information including 43 anatomical structures (systematically assessed). Bottom radiological images show example of patients included in clusters from 1 to 4, and stacked histograms represent the distribution of relevant clinicopathological features (*i.e.*, cT category, nodal status, grade, pattern of treatment, and residual disease after surgery) into clusters. GTR, gross total resection; LRCI, cumulative incidence of local recurrence; LRFS, local recurrence-free survival: N0, no nodal metastases; N+ , presence of nodal metastases; PT, proton therapy; R0, no residual disease; R1, microscopic residual disease; R2, macroscopic residual disease; RT, radiotherapy; RX, unknown status of residual disease.

Table 5
Frequency of involvement of anatomical subunits of the anterior craniofacial area, for the entire cohort and for agglomerative hierarchical clustering-generated groups. P-value indicates if significant difference exists among clusters.

Anatomical structure	Frequency of involvement					
	Entire cohort	*Cluster 1*	*Cluster 2*	*Cluster 3*	*Cluster 4*	*P-value*
Nasoethmoidal complex	323 (56.8%)	130 (68.4%)	102 (74.5%)	17 (48.6%)	74 (58.3%)	**0.005**
Maxillary sinus	318 (55.9%)	96 (50.5%)	130 (94.9%)	16 (45.7%)	76 (59.8%)	**< 0.001**
Pterygopalatine fossa	194 (34.1%)	26 (13.7%)	108 (78.8%)	24 (68.6%)	36 (28.3%)	**< 0.001**
Hard palate – alveolar process	157 (27.6%)	38 (20.0%)	85 (62.0%)	5 (14.3%)	29 (22.8%)	**< 0.001**
Sphenoid sinus/body	144 (25.3%)	36 (18.9%)	49 (35.8%)	25 (71.4%)	34 (26.8%)	**< 0.001**
Pterygoid process	149 (26.2%)	18 (9.5%)	89 (65.0%)	19 (54.3%)	23 (18.1%)	**< 0.001**
Nasopharyngeal walls	152 (26.7%)	51 (26.8%)	41 (29.9%)	28 (80.0%)	32 (25.2%)	**< 0.001**
Infratemporal fossa	143 (25.1%)	13 (6.8%)	79 (57.7%)	22 (62.9%)	29 (22.8%)	**< 0.001**
Orbital bony walls	105 (18.5%)	19 (10.0%)	61 (44.5%)	11 (31.4%)	14 (11.0%)	**< 0.001**
Periorbit	80 (14.1%)	14 (7.4%)	44 (32.1%)	5 (14.3%)	17 (13.4%)	**< 0.001**
Meckel's cave	72 (12.7%)	6 (3.2%)	15 (10.9%)	20 (57.1%)	31 (24.4%)	**< 0.001**
Cavernous sinus	131 (23.0%)	3 (1.6%)	0 (0.0%)	7 (20.0%)	121 (95.3%)	**< 0.001**
Parapharyngeal space	215 (37.8%)	61 (32.1%)	20 (14.6%)	21 (60.0%)	113 (89.0%)	**< 0.001**
Nasolacrimal system (sac, duct)	61 (10.7%)	20 (10.5%)	32 (23.4%)	1 (2.9%)	8 (6.3%)	**< 0.001**
Anterior orbital content	80 (14.1%)	14 (7.4%)	26 (19.0%)	2 (5.7%)	38 (29.9%)	**< 0.001**
Central anterior cranial fossa (bone)	47 (8.3%)	16 (8.4%)	21 (15.3%)	2 (5.7%)	8 (6.3%)	0.072
Middle cranial fossa (bone)	57 (10.0%)	9 (4.7%)	14 (10.2%)	23 (65.7%)	11 (8.7%)	**< 0.001**
Middle cranial fossa (dura)	47 (8.3%)	5 (2.6%)	9 (6.6%)	17 (48.6%)	16 (12.6%)	**< 0.001**
Facial soft tissues	53 (9.3%)	19 (10.0%)	16 (11.7%)	2 (5.7%)	16 (12.6%)	0.696
Lateral wall of the oral cavity (buccal area, retromolar trigone)	39 (6.9%)	19 (10.0%)	18 (13.1%)	2 (5.7%)	0 (0.0%)	**< 0.001**
Soft palate	44 (7.7%)	11 (5.8%)	29 (21.2%)	0 (0.0%)	4 (3.1%)	**< 0.001**
Posterior orbital content (orbital apex)	43 (7.6%)	4 (2.1%)	17 (12.4%)	11 (31.4%)	11 (8.7%)	**< 0.001**
Lateral oropharyngeal wall	154 (27.1%)	20 (10.5%)	7 (5.1%)	1 (2.9%)	126 (99.2%)	**< 0.001**
Central anterior skull base (dura)	24 (4.2%)	6 (3.2%)	10 (7.3%)	3 (8.6%)	5 (3.9%)	0.199
Clivus (middle, inferior)	27 (4.7%)	4 (2.1%)	1 (0.7%)	11 (31.4%)	11 (8.7%)	**< 0.001**
Petrous apex/petroclival junction	135 (23.7%)	21 (11.1%)	2 (1.5%)	21 (60.0%)	91 (71.7%)	**< 0.001**
Posterior oropharyngeal wall	141 (24.8%)	5 (2.6%)	7 (5.1%)	3 (8.6%)	126 (99.2%)	**< 0.001**
Petrous bone (excl. apex)	153 (26.9%)	46 (24.2%)	11 (8.0%)	12 (34.3%)	84 (66.1%)	**< 0.001**
Frontal sinus	20 (3.5%)	4 (2.1%)	10 (7.3%)	1 (2.9%)	5 (3.9%)	0.137
Internal carotid artery (petrous tract)	25 (4.4%)	8 (4.2%)	2 (1.5%)	11 (31.4%)	4 (3.1%)	**< 0.001**
Orbital roof (bone)	18 (3.2%)	0 (0.0%)	12 (8.8%)	2 (5.7%)	4 (3.1%)	**< 0.001**
Prevertebral muscles	17 (3.0%)	4 (2.1%)	1 (0.7%)	6 (17.1%)	6 (4.7%)	**< 0.001**
Internal carotid artery (paraclival-parasellar tracts)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9 %)	0 (0.0%)	0.071
Internal carotid artery (parapharyngeal tract)	15 (2.6%)	4 (2.1%)	1 (0.7%)	5 (14.3%)	5 (3.9%)	**0.002**
Brain (temporal lobe)	22 (3.9%)	1 (0.5%)	0 (0.0%)	5 (14.3%)	16 (12.6%)	**< 0.001**
Orbital roof (dura)	9 (1.6%)	2 (1.1%)	3 (2.2%)	2 (5.7%)	2 (1.6%)	0.285
Brain (frontal lobe)	6 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (4.7%)	**0.001**
Craniocervical junction and adjacent soft tissues	129 (22.7%)	3 (1.6%)	0 (0.0%)	2 (5.7%)	124 (97.6%)	**< 0.001**
Lateral posterior cranial fossa (dura)	5 (0.9%)	2 (1.1%)	1 (0.7%)	2 (5.7%)	0 (0.0%)	**0.048**
Midline posterior cranial fossa (dura)	7 (1.2%)	2 (1.1%)	0 (0.0%)	3 (8.6%)	2 (1.6%)	**0.006**
Brainstem	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0.072
Sella turcica	1 (0.2%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
Internal carotid artery (paraclinoid-intracranial tracts)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0.072

PT. Mean total dose was similar between the aforesaid groups (3D-RT: 68.9 Gy, IMRT: 69.2 Gy, PT: 70.0 GyE). Chemotherapy was administered in 20/55 (36.4%; concomitant in 13, neoadjuvant in 7) of the photon group, and in 10/55 (18.2%; concomitant in all cases) of the IMPT group (p = 0.028). Patterns of presentation to the RT team were similar between these two subgroups (i.e., photon *vs*. PT), with 34/55 (61.8%) and 36/55 (65.4%) patients presenting with a biopsy-only ACC, respectively, and the remaining presenting after R2 resection. Complete response at first imaging after RT was observed in 25 (52.1% out of 48 with known response) patients after photon-based RT and in 41 (74.5%) after PT (p = 0.023). Figure S5 shows the rate of response by RT type and addition of concomitant CT. Ten-year LRFS was not significantly different between biopsy-only and R2 patients (16.5% [95%-CI: 7.3–37.7] and 28.0% [95%-CI: 15.1–52.0], respectively, p = 0.220; Figure S6), nor when stratified by RT modality (photon: 18.8% [95%-CI: 10.2–34.6], PT: 26.5% [95%-CI: 11.8–59.3], p = 0.303). Similarly, 10-year LRCI did not significantly differ by presentation status (biopsy-only: 68.3% [95%-CI: 50.5–79.7]; R2: 68.4% [95%-CI: 43.1–82.5], p = 0.588) or RT modality (photon: 73.0% [95%-CI: 54.7–83.9], PT: 68.2% [95%-CI: 34.5–84.6], p = 0.289). Compared to biopsy-only cases, R2 status was not associated with a different multivariable-adjusted LRFS (HR: 0.68 [95%-CI: 0.4–1.3], p = 0.213) or LRCI (HR: 0.90 [95%-CI: 0.4–1.9], p = 0.800) (Figure S7). LRFS and LRCI were not significantly impacted by RT modality when adjusting by potential confounders (photon-HR: 0.88 [95%-CI: 0.4–1.8], p = 0.716, and 0.84 [95%-CI: 0.4–1.9], p = 0.700, respectively) (Figure S7). The overall cumulative incidence of ≥G3 adverse events at 10 years in patients treated with NST was 36.0% (95%-CI: 21.8–47.6) and did not

Table 6
Univariate survival analysis in patients receiving treatment with curative intent for a ***primary adenoid cystic carcinoma*** of the anterior craniofacial area (n = **324**). CRT, Chemoradiation; DMCI, Distant metastasis-cumulative incidence; DRFS, Distant recurrence-free survival; DSS, Disease-specific survival; ECOG-PS, Eastern Cooperative Oncology Group performance status; GTR, Gross total resection; LRCI, Local recurrence-cumulative incidence; LRFS, Local recurrence-free survival; NOS, Not otherwise specified; NST, Definitive non-surgical treatment; OS, Overall survival; PT, Proton therapy; RCI, Recurrence-cumulative incidence; RFS, Recurrence-free survival; RRCI, Regional recurrence-cumulative incidence; RRFS, Regional recurrence-free survival; RT, Radiotherapy.

Variable	Category	10y OS (%)	P-value	10y DSS (%)	P-value	10y RFS (%)	P-value	10y RCI (%)	P-value	10y LRFS (%)	P-value	10y LRCI (%)	P-value	10y RRFS (%)	P-value	10y RRCI (%)	P-value	10y DRFS (%)	P-value	10y DMCI (%)	P-value
Age	**>threshold (years)**	(>71)		(>71)		(>71)		(>71)		(>71)		(>71)				(>38)		(>71)		(>49)	
	≤threshold (years)	22.8% (≤71)	**<0.001**	37.8 (≤71)	**<0.001**	6.7 (≤71)	**0.010**	86.9 (≤71)	**0.024**	6.7 (≤71)	**<0.001**	42.5 (≤71)	**0.004**	(>71) 7.6 (≤71) 60.3	**<0.001**	1.2 (≤38)	**0.002**	7.6 (≤71)	**<0.001**	30.9 (≤49)	
		61.4%		72.6		32.8		62.8		47.9		76.3				6.8		45.6		42.4	0.155
Gender	**Male**	57.4		67.6		24.2		58.9		40.6		43.3		51.2		4.5		37.0		35.7	
	Female	55.7	0.549	69.5	0.703	34.4	0.303	72.2	0.492	43.9	0.839	32.4	0.637	55.5	0.538	0	**0.037**	44.6	0.342	35.1	0.939
ECOG-PS	**0**	55.3		66.9		32.3		62.3		47.7		31.2		57.7		1.9		41.6		40.8	
	1-2	58.2	0.964	70.6	0.987	26.9	0.986	68.7	0.847	36.4	0.389	45.2	0.249	48.6	0.526	2.0	0.519	40.2	0.873	35.9	0.124
Site (simplified)	**Nasopharynx**	55.6		77.5		32.2		65.6		49.0		43.2		62.3		0		41.9		30.2	
	Sinonasal	53.7	0.460	64.3	0.143	28.0	0.305	67.0	0.224	39.2	0.152	38.5	0.108	50.5	0.402	1.6	0.757	38.5	0.424	38.0	0.379
	Other	68.8		81.7		34.6		58.0		54.7		30.1		62.2		5.6		49.4		31.4	
cT	**T1**	100		100		85.0		14.8		85.2		14.8		100		0		100		0	
	T2	67.6		95.2		43.2		49.6		59.6		14.3		64.9		3.3		56.3		30.8	
	T3	56.1	**0.001**	72.6	**0.001**	31.8	**<0.001**	57.3	**<0.001**	41.9	**<0.001**	34.1	**<0.001**	48.5	**<0.001**	2.4	0.814	33.2	**<0.001**	36.9	**0.039**
	T4a	59.6		66.4		29.5		69.0		46.3		34.2		58.1		3.1		43.1		42.2	
	T4b	39.0		54.2		13.4		83.0		20.4		62.9		31.3		0		22.0		36.7	
cN (simplified)	**N0**	57.7		70.3		30.0		64.9		43.1		37.1		54.8		2.2		41.5		34.7	
	N+	37.5	**0.048**	40.2	**0.005**	28.0	**0.016**	68.5	**0.007**	34.0	**0.012**	44.7	**0.048**	49.2	0.125	0	0.644	35.0	**0.012**	52.7	**0.004**
Grade	**I**	71.5		79.8		44.4		48.8		58.5		32.2		66.3		0		55.3		27.1	
	II	56.6	**<0.001**	78.2	**<0.001**	33.1	**<0.001**	63.0	**<0.001**	50.0	**<0.001**	38.9	**0.014**	62.5	**<0.001**	2.5	0.426	47.2	**<0.001**	30.8	**<0.001**
	III	30.1		41.6		14.5		80.4		19.5		46.0		28.5		2.9		21.8		51.0	
Grade (simplified)	**I-II**	67.3	**<0.001**	78.6	**<0.001**	36.5	**<0.001**	58.8	**<0.001**	52.5	**<0.001**	44.1	**0.019**	54.2	**<0.001**	1.7	0.291	49.0	**<0.001**	29.8	**<0.001**
	III	30.1		41.6		14.5		80.4		19.5		46.0		28.5		2.9		21.8		51.0	
pT	**NST**	28.6		48.0		9.3*		90.2*		25.6*		62.3*		26.0*		0*		21.2*		50.5*	
	T1	100	**<0.001**	100	**<0.001**	80.8	**<0.001**	19.2	**<0.001**	92.3	**<0.001**	7.7	**<0.001**	100	**<0.001**	0	0.855	88.9	**<0.001**	11.1	**0.047**
	T2-T3	64.1		86.3		44.1		45.9		51.3		24.2		60.0		2.1		53.9		28.8	
	T4-T4a-T4b	56.1		64.5		26.5		68.7		41.6		37.6		52.2		2.6		37.4		38.9	
Surgery	**Yes**	60.3	**0.024**	71.0	0.153	32.8	**<0.001**	61.3	**<0.001**	46.3	**<0.001**	33.0	**<0.001**	56.0	**<0.001**	0	0.515	43.5	**<0.001**	35.2	0.994
	No	28.6		48.0		9.3*		90.2*		12.9*		62.3		26.0		2.3		21.2		50.5	
Definitive radiotherapy	**No**	59.4		70.9		33.6		59.7		46.9		30.2		57.1		2.5		44.4		35.8	
	RT	49.1	0.221	56.8	0.181	16.7	**<0.001**	82.9	**<0.001**	23.6	**<0.001**	62.3	**<0.001**	37.7	**0.018**	0	0.661	29.6	**0.015**	32.6	0.720
	CRT	38.6		68.6		14.9		84.5		40.1		58.2		48.1		0		20.1		56.2	
Adjuvant radiotherapy	**No**	43.2		65.4		28.8		48.8		28.8		35.6		44.2		0		36.2		26.2	
	RT	62.2	**0.026**	72.9		19.3	**<0.001**	60.2		50.4	**<0.001**	29.5		59.7	**0.005**	2.4	0.765	45.3	**0.009**	36.0	0.233
	CRT	41.7		46.3	0.053	21.9		74.4	**<0.001**	35.1		41.7	**<0.001**	52.6		0		43.8		38.6	
	NST	45.8		59.8		15.3		84.3		27.1		61.8		39.6		0		25.9		38.5	
Residue	**Biopsy-based RT (photon)**	0		26.3^		0		100		0		75.0^		0		0		0		28.6^	
	Biopsy-based PT	60.0	**0.003**	71.1	**0.004**	13.6*	**<0.001**	74.0*	**<0.001**	17.1*	**<0.001**	54.4*	**<0.001**	36.6*	**<0.001**	0	0.933	32.6	**<0.001**	50.2	0.300
	R0	70.1		80.5		46.4		39.8		55.8		23.2		64.4		4.1		57.7		26.7	
	R1, unifocal	72.0		66.2		26.8		56.2		53.0		37.1		64.6		0		26.8		67.4	

(*continued on next page*)

Table 6 (*continued*)

Variable	Category	10y OS (%)	P-value	10y DSS (%)	P-value	10y RFS (%)	P-value	10y RCI (%)	P-value	10y LRFS (%)	P-value	10y LRCI (%)	P-value	10y RRFS (%)	P-value	10y RRCI (%)	P-value	10y DRFS (%)	P-value	10y DMCI (%)	P-value
	R1, multifocal	55.6		64.9		25.7		71.4		43.1		41.8		58.4		0		40.7		34.4	
	R1, NOS	48.4		59.3		20.3		66.0		34.7		40.1		48.5		3.0		37.3		41.4	
	R2, unifocal	75.0		75.0		0		52.4		47.6		52.4**		71.4**		0		0		50.0**	
	R2, multifocal	55.6		55.6		22.2		71.8		22.2		72.2		22.2		0		22.2		20.0	
	R2, NOS	63.0		78.7		28.1		53.2		42.2		53.2		68.2		0		51.1		25.0	
	RX	39.7		74.0		28.1		56.3		37.4		14.3		37.4		0		28.1		41.7	
Residue (simplified)	**Biopsy-based RT (photon)**	0	**<0.001**	26.3^	**0.003**	0	**<0.001**	100	**<0.001**	0	**<0.001**	75.0^	**<0.001**	0	**<0.001**	0	0.668	0	**<0.001**	28.6^	0.221
	Biopsy-based PT	60.0		71.1		13.6*		74.0*		17.1*		54.4*		36.6*		0		32.6		50.2	
	R0	70.1		80.5		46.4		48.4		55.8		26.0		64.4		4.1		57.7		26.7	
	R1	53.0		62.0		23.6		71.5		41.4		46.3		54.8		1.0		35.8		44.2	
	R2	63.3		67.2		4.2		74.8		38.4		61.8		51.2		0		33.2		28.5	
	RX	39.7		74.0		8.1		56.3		37.4		14.3		37.4		0		28.1		41.7	
Pattern of treatment	**GTR alone**	45.5	**0.017**	69.8	0.070	31.9	**<0.001**	45.6	**<0.001**	31.9	**<0.001**	31.6	**<0.001**	46.5	**0.015**	0	0.692	38.0	0.002	36.2	0.544
	GTR+RT (photon)	44.0		68.8		32.6		62.3		46.7		29.9		55.3		3.1		43.1		38.8	
	GTR+PT	85.5		87.5		51.3^^		47.1^^		64.3^^		33.8^^		77.8^^		0		65.1^^		13.4	
	RT (photon)	38.5		55.5		32.6		84.6		46.7		67.1		33.7		0		20.3		38.3	
	PT	53.0		60.3		15.3*		84.7*		18.5*		53.7*		35.8*		0		32.7*		39.6*	

*10-year estimate was not available, 108-month rate is reported;
**10-year estimate was not available, 110-month rate is reported;
^10-year estimate was not available, 82-month rate is reported;
^^10-year estimate was not available, 102-month rate is reported.

Table 7

Univariate survival analysis in patients receiving treatment with curative intent for a ***recurrent/persistent adenoid cystic carcinoma*** of the anterior craniofacial area (n = **159**). CRT, Chemoradiation; DMCI, Distant metastasis-cumulative incidence; DRFS, Distant recurrence-free survival; DSS, Disease-specific survival; ECOG-PS, Eastern Cooperative Oncology Group performance status; GTR, Gross total resection; LRCI, Local recurrence-cumulative incidence; LRFS, Local recurrence-free survival; NOS, Not otherwise specified; NST, Definitive non-surgical treatment; OS, Overall survival; PT, Proton therapy; RCI, Recurrence-cumulative incidence; RFS, Recurrence-free survival; RRCI, Regional recurrence-cumulative incidence; RRFS, Regional recurrence-free survival; RT, Radiotherapy.

Variable	Category	10y OS (%)	P-value	10y DSS (%)	P-value	10y RFS (%)	P-value	10y R-CI (%)	P-value	10y LRFS (%)	P-value	10y LR-CI (%)	P-value	10y RRFS (%)	P-value	10y RR-CI (%)	P-value	10y DRFS (%)	P-value	10y DM-CI (%)	P-value
Age (years)	>threshold (years)	(>66) 22.7	**<0.001**	(>66) 52.8	**0.008**	(>47) 28.6	0.087	(>50) 67.0	**0.049**	(>50) 38.1	0.142	(>32) 58.8	0.203	(>28) 53.7	0.082	(>35) 3.5	0.079	(>32) 41.9	0.076	(>60) 0	**0.013**
	≤threshold (years)	(≤66) 72.8		(≤66) 82.2		(≤47) 20.7		(≤50) 79.2		(≤50) 27.5		(≤32) 47.2		(≤28) 77.8		(≤35) 12.1		(≤32) 68.2		(≤60) 33.0	
Gender	Male	64.6	0.326	81.8	0.954	25.1	0.739	72.8	0.695	30.3	0.476	59.3	0.306	56.0	0.951	14.3	0.069	49.1	0.850	26.4	0.997
	Female	72.2		77.5		24.5		74.8		33.5		54.6		56.8		10.1		44.5		31.4	
ECOG-PS	0	69.8	0.979	80.0	0.599	25.1	**<0.001**	74.3	0.379	32.5	**<0.001**	56.6	**0.013**	56.8	**<0.001**	7.3	-	46.9	**<0.001**	41.3	-
	1-2	0		75.0		0		72.7		0		100		0		-		0		-	
Site (simplified)	Nasopharynx	62.5	0.667	62.5	0.696	14.3	0.968	85.7	0.934	38.1	0.742	61.9	0.994	71.4	0.870	0	0.570	35.7	0.808	50.0	0.679
	Sinonasal	68.4		80.6		25.6		73.1		31.5		56.0		56.4		11.6		46.9		27.1	
	Other	75.0		75.0		25.0		75.0		33.3		66.7		47.6		14.3		57.1		42.9	
cT	T1	90.0	0.184	100	0.319	46.7	**0.005**	53.3	**<0.001**	70.0	**0.005**	30.0	**0.009**	80.0	0.060	0	0.403	57.1	0.348	25.0	0.957
	T2	71.6		79.9		21.3		75.1		21.3		50.2		38.4		5.6		38.4		30.9	
	T3	77.2		82.0		30.2		69.8		34.1		57.7		56.7		8.3		45.5		22.2	
	T4a	72.2		82.9		34.6		64.5		47.6		47.3		72.4		2.6		56.8		32.2	
	T4b	59.0		78.6		7.7		92.3		12.0		83.6		44.9		6.7		40.9		29.8	
cN (simplified)	N0	68.9	0.495	80.1	0.916	25.3	0.382	73.4	0.389	32.3	0.905	57.0	0.526	56.8	0.692	4.7	0.069	46.2	0.303	29.1	0.525
	N+	66.7		66.7		0		100		33.3*		50.0*		33.3*		33.3*		66.7*		33.3*	
Grade	I	69.9	0.266	87.9	0.075	42.6	**0.019**	57.4	**0.043**	34.5	0.471	49.9	0.848	54.9	0.379	3.3	0.207	46.1	**0.048**	22.1	**0.023**
	II	74.0		85.3		19.3		77.9		33.4		58.4		61.5		2.9		53.1		28.3	
	III	53.0		68.1		18.0		81.4		25.2		62.1		45.8		16.5		31.1		45.3	
Grade (simplified)	I-II	72.4	0.103	87.0	**0.026**	30.4	**0.023**	68.2	**0.019**	33.9	0.261	55.3	0.567	58.9	0.165	3.2	0.099	50.3	**0.014**	25.5	0.188
	III	53.0		68.1		18.0		81.4		25.2		62.1		45.8		16.5		31.1		45.3	
pT	NST	28.2	**0.001**	55.4	**0.034**	5.9	**<0.001**	94.2	0.139	5.9	**<0.001**	88.2	**<0.001**	19.2	**<0.001**	11.1	0.463	22.4	**0.034**	14.3	0.791
	T1	100		100		45.5		54.5		62.3		28.4		81.8		9.1		54.5		27.3	
	T2-T3	82.2		89.1		30.9		67.1		37.1		51.5		62.7		0		51.4		26.7	
	T4-T4a-T4b	62.4		73.3		23.1		76.5		32.3		59.7		59.8		5.1		51.1		28.2	
Surgery	Yes	72.5	**0.005**	81.4	**0.048**	27.2	**0.004**	71.4	**<0.001**	35.5	**<0.001**	53.0	**<0.001**	59.6	**0.002**	11.0	0.516	48.1	0.088	30.6	0.216
	No	36.7		61.3		7.6		92.4		7.6		87.1		30.8		8.3		34.2		11.1	
Definitive radiotherapy	No	74.9	**<0.001**	83.9	**<0.001**	29.3	**<0.001**	69.5	0.070	37.7	**<0.001**	49.8	**<0.001**	62.5	**<0.001**	11.1	0.734	51.1	**<0.001**	30.0	0.721
	RT	38.2		59.9		4.6		95.2		5.5		88.1		20.7		8.3		20.5		17.5	
	CRT	53.3****		53.3****		21.4****		78.6****		21.4****		78.6****		60.0****		0****		60.0****		0****	
Adjuvant radiotherapy	No	78.5	**<0.001**	93.1	**<0.001**	34.2	**<0.001**	65.8	0.081	34.2	**<0.001**	61.3	**<0.001**	81.2	**<0.001**	4.2	0.934	76.9	**<0.001**	16.4	0.195
	RT	79.9		84.9		27.8		70.2		40.8		40.1		57.2		6.6		42.0		35.3	
	CRT	60.6		60.6		29.3		70.7		39.1		60.9		63.5		0		52.9		27.8	
	NST	29.0		54.4		4.0		95.6		4.4		91.8		18.8		5.6		18.8		19.5	

(*continued on next page*)

Table 7 (*continued*)

Variable	Category	10y OS (%)	P-value	10y DSS (%)	P-value	10y RFS (%)	P-value	10y R-CI (%)	P-value	10y LRFS (%)	P-value	10y LR-CI (%)	P-value	10y RRFS (%)	P-value	10y RR-CI (%)	P-value	10y DRFS (%)	P-value	10y DM-CI (%)	P-value
Residue	Biopsy-based RT (photon)	42.4		53.3		7.7		92.3		7.7		84.6		26.7		16.7		33.3		0	
	Biopsy-based PT	100**		100**		- 44.9		- 55.1		- 44.9		- 45.6		- 58.3		-		- 58.3		- 26.9	
	R0	76.4		80.2		43.8		50.0		58.3		33.3		87.5		5.0		72.9		16.7	
	R1, unifocal	76.2		100		18.2		81.8		18.2		48.9		68.6		0		57.1		21.3	
	R1, multifocal	78.7	**<0.001**	78.7	**<0.001**	6.4	**<0.001**	87.2	**<0.001**	26.1	**<0.001**	30.9	**<0.001**	29,6	**<0.001**	0	0.646	7.3	**<0.001**	70.9	**0.006**
	R1, NOS	56.0		79.8		0		100		0		100		0		18.5		0		0	
	R2, unifocal	50.0***		50.0***		0		100		0		100		0		0		0		0	
	R2, multifocal	53.3		53.3		9.1		90.0		12.1		82.2		16.0		0		12.0		38.5	
	R2, NOS	29.1		61.4		32.5		67.5		43.3		49.4		75.7		0		61.3		25.5	
	RX	87.0		88.9												3.9					
Residue (simplified)	Biopsy-based RT (photon)	42.4		53.3		7.7		92.3		7.7		84.6		26.7		16.7		33.3		0	
	Biopsy-based PT	100**	**<0.001**	100**	**<0.001**	- 44.9	**<0.001**	- 55.1	**<0.001**	- 44.9	**<0.001**	- 45.6	**<0.001**	- 58.3	**<0.001**	-	0.725	- 58.3	**<0.001**	- 20.3	0.122
	R0	76.4		80.2		18.0		78.5		30.0		48.9		54.5		5.0		36.3		44.7	
	R1	66.7		84.0		6.3*****		93.4****		8.3***		78.0*****		12.3****		8.0		9.2***		31.4	
	R2	27.1		51.9		32.5		* 67.5		** 43.3		49.4		* 75.7		0		** 61.3		25.5	
	RX	87.0		88.9												3.9					
Pattern of treatment	GTR alone	84.7		96.3		40.1		59.9		40.1		66.5		87.8		4.0		83.4		25.4	
	GTR+RT (photon)	75.1		79.0		25.7		72.2		35.9		47.2		49.5		8.1		38.6		41.4	
	GTR+PT	75.7	**<0.001**	91.7	**<0.001**	20.0	**<0.001**	80.0	**<0.001**	38.1	**<0.001**	49.0	**<0.001**	70.7	**<0.001**	0	0.606	44.4	**<0.001**	73.0	**0.032**
	RT (photon)	31.9		43.0		5.6		94.1		6.9		84.3		22.9		11.1		22.5		20.0	
	PT	37.0		74.1		0		100		0		100		0		0		0		0	

*10-year estimate was not available, 78-month rate is reported;
**10-year estimate was not available, 81-month rate is reported;
***10-year estimate was not available, 31-month rate is reported;
****10-year estimate was not available, 63-month rate is reported;
*****10-year estimate was not available, 96-month rate is reported.

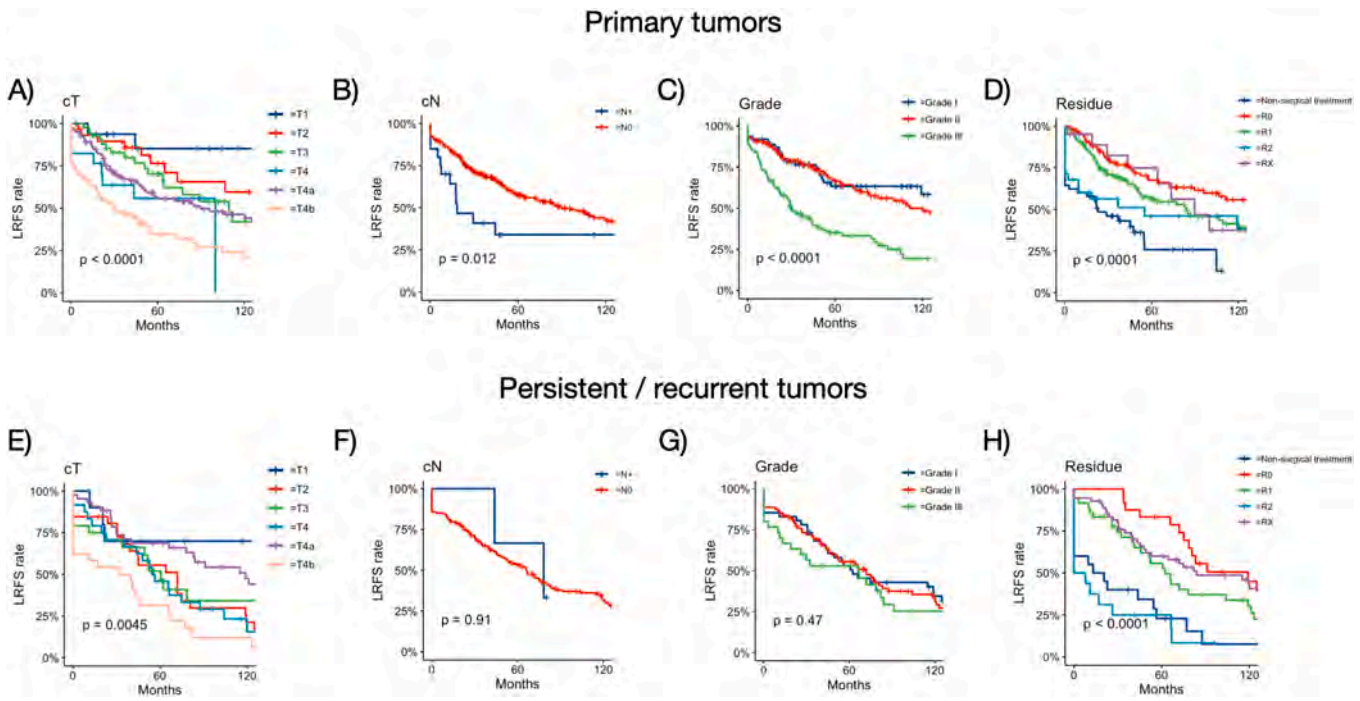


Fig. 3. Univariate effect on local recurrence-free survival (LRFS) of relevant clinicopathological factors (cT category, nodal status, grade, and residual disease) in primary and persistent/recurrent adenoid cystic carcinoma of the anterior craniofacial area.

significantly vary according to presentation (biopsy-only: 37.8% [95%-CI: 18.1–52.8]; R2: 32.8% [95%-CI:12.5–48.4], p = 0.865; Figure S6), RT modality (photon: 28.7% [95%-CI: 13.2–41.4], PT: 48.4% [95%-CI: 13.7–69.1], p = 0.383), or cChT (RT+cChT: 27.5% [95%-CI: 5.4–44.5], RT: 38.5% [95%-CI: 21.1–52.2], p = 0.919; photon-RT+cChT: 20.3% [95%-CI: 0–38.6], photon-RT: 32.9% [95%-CI: 22.5–48.5], p = 0.492; PT+cChT: 44.4% [95%-CI: 0–72.6], PT: 49.8% [95%-CI 5.7–73.2], p = 0.121). Most frequent ≥G3 adverse events were mucositis (10-year CI: 10.3%; 4.6% in photon-based RT, 17.8% in PT, p = 0.205), maxillary bone necrosis (10-year CI: 9.1%; 8.2% in photon-based RT, 11.1% in PT, p = 0.705), ocular complications including blurred vision, diplopia, and corneal abscess (10-year CI: 5.8%; 5.1% in photon-based RT, 8.3% in PT, p = 0.885), facial deformity (10-year CI: 2.4%; 5.1% in photon-based RT, 0% in PT, p = 0.142), and myelosuppression (10-year CI: 2.1%; 2.2% in photon-based RT, 2.1% in PT, p = 0.951).

4. Discussion

The present study analyzed a large, multi-institutional cohort of ACC involving the ACF area, focusing on differences in local control among various therapeutic strategies. The main finding is that GTR followed by RT is associated with the highest achievable local control, which is consistent with previous reports highlighting the relevance of including surgery into treatment [34,35]. Although PT yielded better outcomes than photon-based RT in the adjuvant setting, imbalances in subgroup sizes and the lack of statistically significant differences in multivariable analysis preclude drawing firm conclusions regarding the superiority of PT over state-of-the-art photon-based RT in this context. Macroscopically incomplete surgery resulted in outcomes comparable to those achieved with PT alone, confirming that R2 resections may be unnecessary if the patient can be referred to a particle therapy center [36]. Therefore, surgery should primarily be considered when there is a reasonably high likelihood of achieving resection without macroscopic residual disease. Since the rate of R2 significantly increased with involvement of some anatomical extensions including infratemporal fossa, parapharyngeal space, middle cranial fossa, orbital apex, petrous bone, orbital roof, cavernous ICA, and dura of the posterior cranial fossa, then surgery should be considered carefully in those cases.

Interestingly, this prognostic stratification was less pronounced in the recurrent/persistent ACC cohort. In this group, differences in primary outcomes among the GTR-including cohorts were more subtle (Figure 4) and did not reach statistical significance after adjustment for potential confounders (Table 9). Nevertheless, the prognostic gap between the GTR-including and NST cohorts was even more evident in patients with recurrent/persistent ACC. These presentation-dependent differences may be attributable to several factors, including limited therapeutic options, the selection of radioresistant clones, and an increased risk of adverse events. Further targeted studies are warranted to clarify treatment-specific outcome differences.

The clustering patterns observed in this cohort indicate that ACF-ACC manifests in distinct anatomic phenotypes. In particular, clusters 2–4 demonstrate characteristic routes of spread, ranging from classic V2 pathways to more central skull base spread and to predominantly inferior or lateral extension involving the cavernous sinus and petrous apex as well as the cranio-cervical junction area. These patterns may have practical implications for multidisciplinary treatment planning, potentially informing more tailored preoperative assessments and radiation target volume.

In general, local residual disease is a critical issue for ACC, which becomes even more relevant with an extraordinary density of functional tissues such as in the ACF area. ACC is among the epithelial cancers with the highest rate of microscopic positive margins [10,22,34,37], which are synonymous with R1. For instance, a large national cancer database study on 870 sinonasal ACC reported a rate of positive margins as high as

Table 8
Clinicopathological characteristics of the five patterns of treatment.

Variable	Categories	GTR + PT (n=67)		GTR + RT (photon) (n=233)		GTR (n=52)		PT (n=55)		RT (photon) (n=55)		P-value	
		Primary (n=53)	R/P (n=14)	Primary (n=171)	R/P (n=62)	Primary (n=21)	R/P (n=31)	Primary (n=43)	R/P (n=12)	Primary (n=37)	R/P (n=18)	Primary	R/P
Median age (IQR)		57 (44.2-64.8)	44.8 (35.2-56.9)	57 (44.1-64.8)	49 (36.9-56.7)	56 (41.7-65.1)	48 (36.8-56.7)	57 (44.5-64.8)	53 (36.1-61.8)	57 (44.5-64.8)	48 (36.9-57.3)	0.681	0.333
Gender (%)	Male	29 (54.7%)	6 (42.9%)	85 (49.7%)	24(38.7%)	12 (57.1%)	16(51.6%)	15 (34.9%)	8 (66.7%)	11 (29.7%)	9 (50%)	0.051	0.431
	Female	24 (45.3%)	8 (57.1%)	86 (50.3%)	38(61.3%)	9 (42.9%)	15(48.4%)	28 (65.1%)	4 (33.3%)	26 (70.3%)	9 (50%)		
ECOG PS (%)	0	36 (67.9%)	14 (100%)	105 (61.4%)	61 (98.4%)	14 (66.6%)	30 (96.8%)	25 (58.1%)	12 (100%)	17 (45.9%)	18 (100%)	0.297	1
	1-2	17 (32.1%)	0 (0%)	66 (38.6%)	1 (1.6%)	7 (33.3%)	1 (3.2%)	18 (41.9%)	0 (0%)	20 (54.1%)	0 (0%)		
Grade (Perzin-Szanto) (%)	Grade I	7 (13.2%)	2 (14.3%)	39 (22.8%)	22 (35.5%)	3 (14.3%)	7 (22.6%)	9 (20.9%)	1 (8.3%)	9 (24.3%)	6 (33.3%)	0.612	0.452
	Grade II	30 (56.6%)	10 (71.4%)	79 (46.2%)	27 (43.5%)	10 (47.6%)	18 (58.1%)	25 (58.1%)	8 (66.7%)	16 (37.3%)	10 (55.6%)		
	Grade III	16 (30.2%)	2 (14.3%)	53 (31.0%)	12 (20.0%)	8 (38.1%)	6 (19.3%)	9 (20.9%)	3 (25.0%)	12 (32.4%)	2 (11.1%)		
cT category (%)	T1	5 (9.4%)	0 (0%)	5 (2.9%)	4 (6.5%)	7 (33.3%)	2 (6.5%)	0 (0.0%)	0 (0%)	1 (2.7%)	1 (5.6%)	**<0.001**	**<0.001**
	T2	6 (11.3%)	0 (0%)	18 (10.5%)	18 (29.0%)	3 (14.3%)	5 (16.1%)	0 (0.0%)	1 (8.3%)	4 (10.8%)	0 (0%)		
	T3	4 (7.6%)	4 (28.6%)	33 (19.3%)	10 (16.1%)	3 (14.3%)	4 (12.9%)	2 (4.6%)	1 (8.3%)	2 (5.4%)	1 (5.6%)		
	T4 NOS	4 (7.6%)	0 (0.0%)	3 (1.8%)	9 (14.5%)	0 (0.0%)	5 (16.1%)	11 (25.6%)	1 (8.3%)	4 (10.8%)	8 (44.4%)		
	T4a	20 (37.7%)	6 (42.8%)	84 (49.1%)	16 (25.8%)	4 (19.1%)	12 (38.7%)	10 (23.3%)	0 (0%)	10 (27.0%)	3 (16.7%)		
	T4b	14 (26.4%)	4 (28.6%)	28 (16.4%)	5 (8.1%)	4 (19.1%)	3 (9.7%)	20 (46.5%)	9 (75.1%)	16 (43.3%)	5 (27.7%)		
AHC-generated cluster (%)	Cluster 1	27 (50.9%)	4 (28.6%)	59 (34.5%)	27 (43.5%)	15 (71.4%)	20 (64.6%)	13 (30.2%)	3 (25.0%)	7 (18.9%)	4 (22.1%)	**<0.001**	**0.003**
	Cluster 2	21 (39.6%)	3 (21.4%)	63 (36.9%)	9 (14.5%)	5 (23.8%)	5 (16.1%)	11 (25.6%)	6 (50.0%)	8 (21.6%)	1 (5.6%)		
	Cluster 3	2 (3.8%)	1 (7.1%)	5 (2.9%)	1 (1.6%)	0 (0.0%)	1 (3.2%)	15 (34.9%)	1 (8.3%)	6 (16.2%)	1 (5.6%)		
	Cluster 4	3 (5.7%)	6 (42.9%)	44 (25.7%)	25 (40.4%)	1 (4.8%)	5 (16.1%)	4 (9.3%)	2 (16.7%)	16 (43.3%)	12 (66.7%)		
Nodal status (%)	N0	51 (96.2%)	14 (100%)	159 (93.0%)	61 (98.4%)	19 (90.5%)	30 (96.8%)	42 (97.7%)	12 (100%)	34 (91.9%)	18 (100%)	**<0.001**	1
	N+	2 (3.8%)	0 (0%)	12 (7.0%)	1 (1.6%)	2 (9.5%)	1 (3.2%)	1 (2.3%)	0 (0%)	3 (8.1%)	0 (0%)		
Pattern of neurovascular invasion (%)	Pn0V0	12 (22.6%)	2 (14.3%)	34 (19.9%)	27 (43.5%)	4 (19.1%)	9 (29.0%)	8 (18.6%)	2 (16.7%)	9 (24.3%)	6 (33.3%)	0.175	0.262
	Pn+V0	27 (50.9%)	8 (57.1%)	103 (60.2%)	24 (38.7%)	10 (47.6%)	18 (58.1%)	27 (62.8%)	9 (75.0%)	13 (35.2%)	9 (50.0%)		
	Pn0V+	0 (0.0%)	0 (0%)	0 (0.0%)	0 (0%)	0 (0.0%)	0 (0%)	0 (0.0%)	0 (0%)	0 (0.0%)	0 (0.0%)		
	Pn+V+	14 (26.5%)	4 (28.6%)	34 (19.9%)	11 (17.8%)	7 (33.3%)	4 (12.9%)	8 (18.6%)	1 (8.3%)	15 (40.5%)	3 (16.7%)		
Residual disease (%)	R0	19 (35.8%)	2 (14.3%)	73 (42.7%)	11 (17.8%)	11 (52.4%)	12 (38.7%)	0 (0.0%)	0 (0%)	0 (0.0%)	0 (0%)	**<0.001**	**<0.001**
	R1	32 (60.4%)	8 (57.1%)	83 (48.5%)	19 (30.6%)	7 (33.3%)	9 (29.0%)	0 (0.0%)	0 (0%)	0 (0.0%)	0 (0%)		
	R2	0	0 (0%)	0 (0.0%)	0 (0%)	0 (0.0%)	0 (0%)	10 (23.3%)	9 (75.0%)	16 (43.2%)	5 (27.8%)		
	Biopsy only	0	0 (0%)	0 (0.0%)	0 (0%)	0 (0.0%)	0 (0%)	33 (76.7%)	3 (25.0%)	21 (56.8%)	13 (72.2%)		
	RX	2 (3.8%)	4 (28.6%)	15 (8.8%)	32 (51.6%)	3 (14.3%)	10 (32.3%)	0 (0.0%)	0 (0%)	0 (0.0%)	0 (0%)		

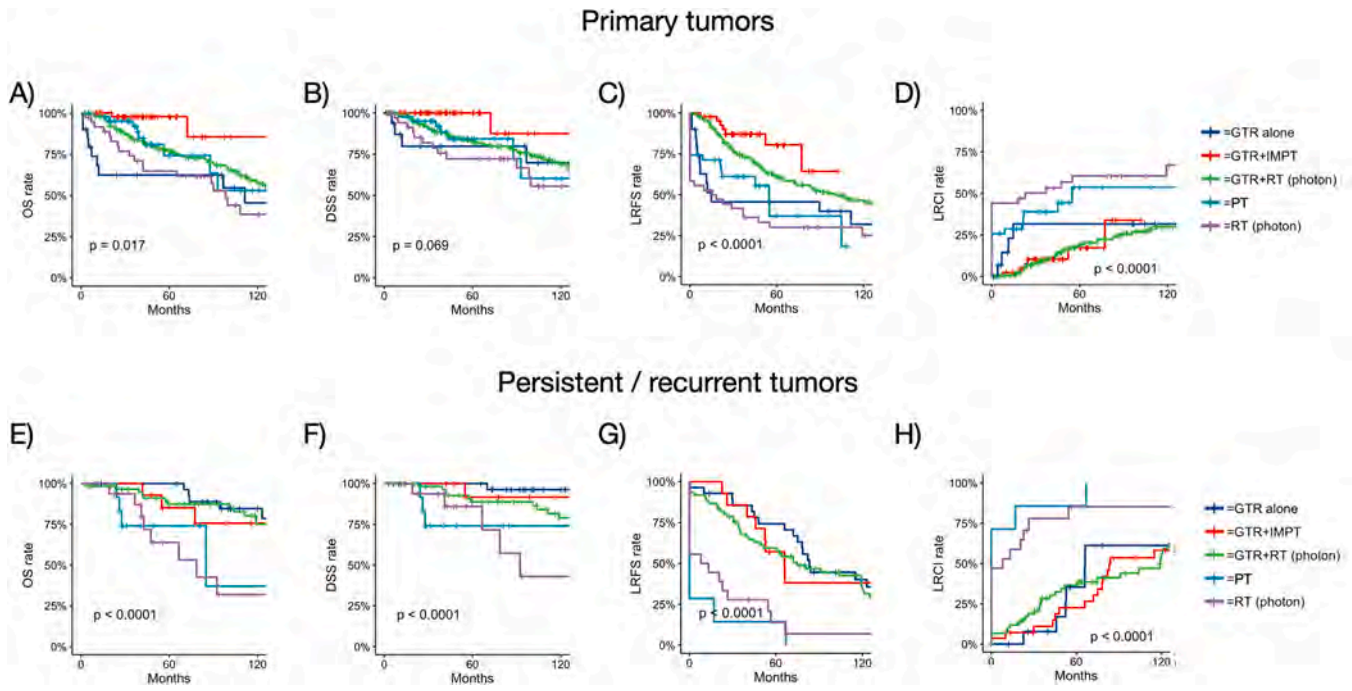
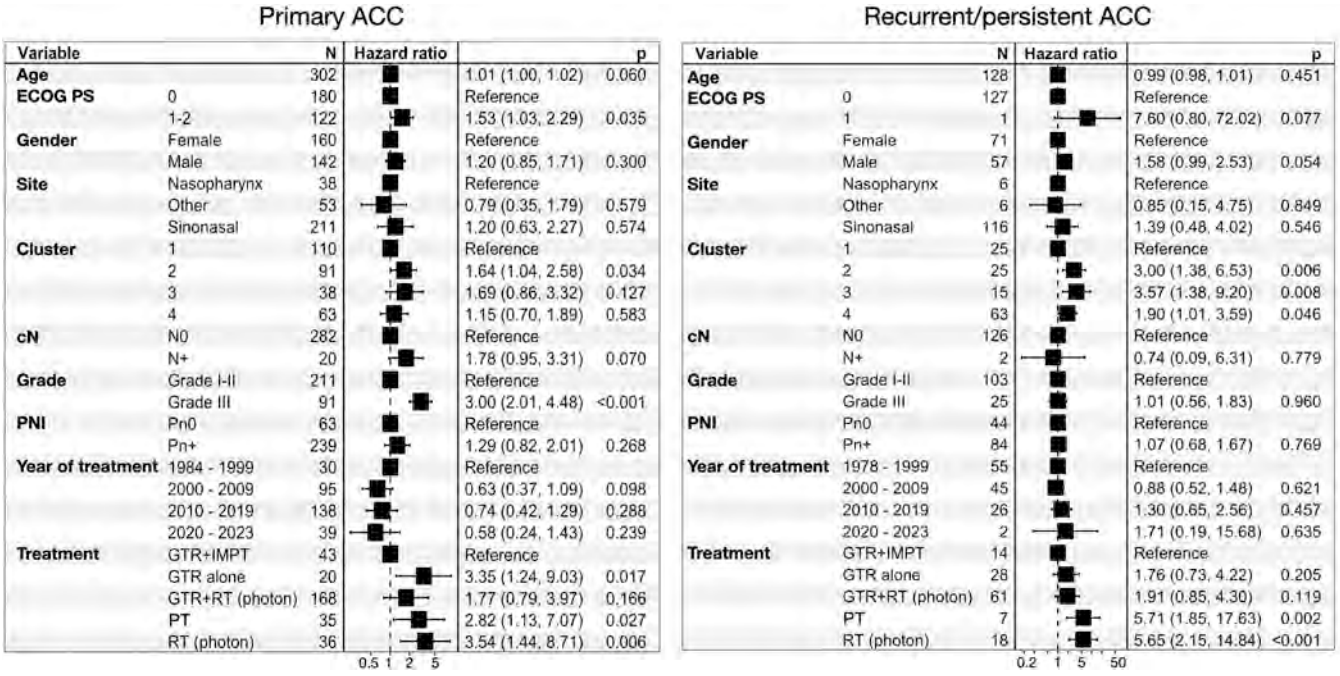


Fig. 4. Univariate effect of treatment pattern on overall survival, disease-specific survival, local recurrence-free survival, and cumulative incidence of local recurrence. DSS, disease-specific survival; GTR, gross total resection; LRCI, cumulative incidence of local recurrence; LRFS, local recurrence-free survival; OS, overall survival; PT, Proton therapy; RT, radiotherapy.



Primary ACC

Variable		N	Hazard ratio	p
Age		302	1.01 (1.00, 1.02)	0.060
ECOG PS	0	180	Reference	
	1-2	122	1.53 (1.03, 2.29)	0.035
Gender	Female	160	Reference	
	Male	142	1.20 (0.85, 1.71)	0.300
Site	Nasopharynx	38	Reference	
	Other	53	0.79 (0.35, 1.79)	0.579
	Sinonasal	211	1.20 (0.63, 2.27)	0.574
Cluster	1	110	Reference	
	2	91	1.64 (1.04, 2.58)	0.034
	3	38	1.69 (0.86, 3.32)	0.127
	4	63	1.15 (0.70, 1.89)	0.583
cN	N0	282	Reference	
	N+	20	1.78 (0.95, 3.31)	0.070
Grade	Grade I-II	211	Reference	
	Grade III	91	3.00 (2.01, 4.48)	<0.001
PNI	Pn0	63	Reference	
	Pn+	239	1.29 (0.82, 2.01)	0.268
Year of treatment	1984 - 1999	30	Reference	
	2000 - 2009	95	0.63 (0.37, 1.09)	0.098
	2010 - 2019	138	0.74 (0.42, 1.29)	0.288
	2020 - 2023	39	0.58 (0.24, 1.43)	0.239
Treatment	GTR+IMPT	43	Reference	
	GTR alone	20	3.35 (1.24, 9.03)	0.017
	GTR+RT (photon)	168	1.77 (0.79, 3.97)	0.166
	PT	35	2.82 (1.13, 7.07)	0.027
	RT (photon)	36	3.54 (1.44, 8.71)	0.006

0.5 1 2 5

Recurrent/persistent ACC

Variable		N	Hazard ratio	p
Age		128	0.99 (0.98, 1.01)	0.451
ECOG PS	0	127	Reference	
	1	1	7.60 (0.80, 72.02)	0.077
Gender	Female	71	Reference	
	Male	57	1.58 (0.99, 2.53)	0.054
Site	Nasopharynx	6	Reference	
	Other	6	0.85 (0.15, 4.75)	0.849
	Sinonasal	116	1.39 (0.48, 4.02)	0.546
Cluster	1	25	Reference	
	2	25	3.00 (1.38, 6.53)	0.006
	3	15	3.57 (1.38, 9.20)	0.008
	4	63	1.90 (1.01, 3.59)	0.046
cN	N0	126	Reference	
	N+	2	0.74 (0.09, 6.31)	0.779
Grade	Grade I-II	103	Reference	
	Grade III	25	1.01 (0.56, 1.83)	0.960
PNI	Pn0	44	Reference	
	Pn+	84	1.07 (0.68, 1.67)	0.769
Year of treatment	1978 - 1999	55	Reference	
	2000 - 2009	45	0.88 (0.52, 1.48)	0.621
	2010 - 2019	26	1.30 (0.65, 2.56)	0.457
	2020 - 2023	2	1.71 (0.19, 15.68)	0.635
Treatment	GTR+IMPT	14	Reference	
	GTR alone	28	1.76 (0.73, 4.22)	0.205
	GTR+RT (photon)	61	1.91 (0.85, 4.30)	0.119
	PT	7	5.71 (1.85, 17.63)	0.002
	RT (photon)	18	5.65 (2.15, 14.84)	<0.001

0.2 1 5 50

Fig. 5. Forest plots showing propensity score-matched, multivariable-adjusted effect of the pattern of treatment on local recurrence-free survival. ECOG PS, Eastern Cooperative Oncology Group performance status; GTR, gross total resection; N0, no nodal metastases; N + , presence of nodal metastases; Pn0, absence of perineural invasion; Pn+ , presence of perineural invasion; PNI, perineural invasion; PT, Proton therapy; RT, radiotherapy.

53.5% [37]. Moreover, local recurrence following surgery with negative margins unveils an unrecognized R1, a phenomenon observed in a high proportion of patients receiving "clear margin surgery" in this and other studies [22,38]. Preliminary unpublished data from our research groups suggest that microscopic foci of ACC are found with a roughly 15% likelihood at 3 cm from the clinically and radiologically appreciable tumor volume. PNI is certainly the driving mechanism of local extension [38–40], but other subtle modality of growth including permeative bone invasion and periosteal involvement have been reported [41,42]. Moreover, ACC can grow extensively while remaining non- or pauci-symptomatic. This is possibly related to the minimal tendency to elicit inflammation and related symptoms [43]. Overall, this unique

Table 9
Propensity score matching-based, multivariable-adjusted effect of the pattern of treatment on prognostic outcomes. NA, not available; REF, reference.

Treatment		OS		DSS		RFS		RCI		LRFS		LRCI		RRFS		DRFS		DMCI	
		HR (95%-CI)	P-value	HR (95%-CI)	P-value	HR (95%-CI)	P-value	HR (95%-CI)	P-value	HR (95%-CI)	P-value	HR (95%-CI)	P-value	HR (95%-CI)	P-value	HR (95%-CI)	P-value	HR (95%-CI)	P-value
Primary ACC	**GTR+PT**	REF		REF		REF		REF		REF		REF		REF		REF		REF	
	GTR alone	5.3 (1.3–21.1)	0.189	3.1 (0.5–18.5)	0.210	6.9 (2.1–22.6)	**0.001**	3.2 (0.8–13.1)	0.094	3.4 (1.2–9.0)	**0.017**	1.4 (0.4–4.9)	0.620	3.9 (1.0–15.3)	0.054	2.8 (1.0–7.4)	**0.044**	1.2 (0.2–6.1)	0.850
	GTR+RT (photon)	3.3 (1.0–10.9)	0.051	3.5 (0.8–14.9)	0.096	2.6 (1.0–6.6)	0.054	2.9 (1.0–8.4)	**0.049**	1.8 (0.8–4.0)	0.166	1.0 (0.4–2.5)	0.970	3.1 (0.9–10.3)	0.063	1.6 (0.7–3.3)	0.253	1.6 (0.6–4.9)	0.360
	PT	2.5 (0.6–9.3)	0.185	2.2 (0.4–11.5)	0.337	3.7 (1.2–11.1)	**0.022**	4.9 (1.5–16.6)	**0.009**	2.8 (1.1–7.1)	**0.027**	3.2 (1.2–8.4)	**0.016**	3.4 (0.9–12.6)	0.073	1.5 (0.6–3.9)	0.383	1.1 (0.3–4.9)	0.860
	RT (photon)	4.3 (1.2–15.8)	**0.030**	5.0 (1.0–24.5)	**0.048**	2.9 (1.0–8.9)	0.056	3.8 (1.1–13.3)	**0.034**	3.6 (1.4–8.8)	**0.006**	3.9 (1.5–9.9)	**0.004**	5.6 (1.5–20.3)	**0.009**	2.8 (1.2–6.9)	**0.019**	1.4 (0.3–5.2)	0.650
Recurrent/ persistent ACC	**GTR+PT**	REF		REF		REF		REF		REF		REF		REF		REF		NA	
	GTR alone	0.3 (0.1–1.1)	0.074	0.6 (0.0–8.3)	0.689	1.1 (0.5–2.4)	0.857	0.8 (0.4–1.8)	0.650	1.8 (0.7–4.2)	0.205	2.3 (0.9–5.7)	0.074	0.5 (0.1–1.8)	0.293	0.3 (0.1–0.8)	**0.015**	NA	NA
	GTR+RT (photon)	0.9 (0.3–2.8)	0.896	4.6 (0.5–45.8)	0.194	1.6 (0.8–3.4)	0.176	1.4 (0.7–2.7)	0.360	1.9 (0.8–4.3)	0.119	1.8 (0.7–4.2)	0.200	1.2 (0.4–3.5)	0.750	1.0 (0.4–2.2)	0.927	NA	NA
	PT	2.2 (0.6–8.1)	0.252	4.8 (0.4–54.6)	0.204	3.2 (1.1–9.3)	**0.031**	3.1 (1.0–9.1)	**0.044**	5.7 (1.9–17.6)	**0.002**	10.3 (3.2–33.4)	**< 0.001**	8.8 (2.1–37.2)	**0.003**	3.3 (0.9–11.6)	0.062	NA	NA
	RT (photon)	3.5 (1.0–12.4)	**0.048**	15.0 (1.3–178.1)	**0.031**	4.3 (1.8–10.4)	**0.001**	3.9 (1.5–10.1)	**0.004**	5.7 (2.2–14.8)	**< 0.001**	7.3 (2.7–20.4)	**< 0.001**	3.2 (0.9–11.5)	**0.077**	1.6 (0.6–4.7)	0.367	NA	NA

propensity for subclinical local extension makes ACC unlikely to be completely resected irrespective of how much grossly uninvolved tissues are electively taken as margins. Thus, the present study embraces the hypothesis that a large proportion of surgeries labeled as with negative margins may in fact leave behind microscopic disease, thereby justifying the application of the "cumulative" concept of GTR, where the distinction between R0 and R1 loses clinical significance. This interpretation aligns with findings from studies where margin status did not impact prognosis [36,44,45]. Aforesaid principles constitute the rationale for proposing GTR as the reasonable type of ablation for the large majority of ACF-ACC. Other groups have previously highlighted the importance of appropriately weighing morbidity of surgery and modulating extent of ablation given the near-certainty of local R1 [19,44,46,47]. On the other hand, patients who received resections labeled as R0 had a more favorable prognosis, including LRFS and LRCI, as observed in other studies [15,22]. These findings might be related to a less critical local extent in the R0 sub-group, but one cannot exclude that these patients benefitted from a genuinely complete resection. Thus, for the cases of low-volume and favorably located tumors surrounded by resectable tissues, seeking microscopically negative margins might be beneficial.

Patients with primary ACC who received GTR followed by adjuvant PT demonstrated improved LRFS compared with those treated with GTR alone. A less pronounced, statistically non-significant benefit was also observed in patients receiving GTR and adjuvant photon-based RT. Nonetheless, LRCI did not significantly change across these treatment groups. Overall, given the characteristic local infiltrative behavior of ACC and the benefits observed in this study, adjuvant RT should be strongly considered for all primary ACF-ACC cases, with PT potentially offering clinically meaningful advantages in this setting. These findings are consistent with those of Kaki *et al.* and Patel *et al.*, who reported a significant improvement in OS with adjuvant RT in both pT1–2N0M0 [48] ACC and pT3–4N0M0 [49] salivary gland carcinomas lacking other adverse features (ACC representing 13.6% of their series), respectively. In the recurrent/persistent setting, evidence supporting the benefit of adjuvant treatment is less definitive, likely due to multiple confounding factors and the heterogeneity of prior therapies within this cohort.

In patients receiving NST, complete response to treatment was significantly more frequent following PT compared to photon-based RT, largely represented by IMRT. Overall, addition of cChT to definitive RT was significantly related to the response rate, PT with cChT being associated with the highest response rate (90%). Thus, this finding aligns with the evidence from the postoperative setting that cChT could be beneficial in selected cases [50–52], and suggests that it might play a role in definitive NST too. Although the heterogeneity of techniques within the photon-based RT group and the differential use of chemotherapy may have influenced response rates, to our knowledge this is the first retrospective comparative study suggesting a potential advantage of PT over photon-based RT in terms of initial tumor response to NST for ACF-ACC. Although detailed information on doses and treatment volumes is lacking, these findings support the growing evidence for the benefit of PT, and particle therapy in general, over photons as definitive NST for skull base tumors. This benefit may be attributed to the higher linear energy transfer, the intrinsic biological properties, and to the superior dose conformality of protons, which enables more optimal high-dose coverage of the target compared with photons. Focusing on responders to RT, no significant differences were observed in terms of LRFS and LRCI, which implies that the local control following a complete response to NST appears independent of RT modality. Similarly, no significant differences were found in terms of the cumulative incidence of ≥G3 adverse events within 10 years from treatment. The cumulative incidence of ≥G3 adverse events in patients receiving definitive PT was 48.3%, which is consistent with another study [53]. Augustin *et al.* reported a lower cumulative incidence at 5 years (15%) in a series grouping adjuvant and definitive PT, suggesting that late adverse events occur even beyond 5 years of follow-up [36]. These results should be compared to outcomes of other particle therapy modalities such as CIRT.

Studies involving CIRT-treated head and neck ACC have reported a 5-year local control rate ranging between 73% and 79% [26,54], which favorably compares with 5-year LRCI of photon RT- and PT-treated cohorts in the present study (68.5% and 57.6%, implying 5-year local control rate of 31.5% and 42.4%, respectively). Thus, CIRT and carbon ion-including mixed beam RT might qualify as preferred strategies for NST of ACF-ACC.

Another interesting finding of the present study comes from the analysis of LRCI curves' slope across treatment types (Figure 4). Interestingly, the pace of local failures appears similar in patients receiving NST *vs*. those treated bimodally with GTR and adjuvant treatment. This suggests that the difference in local control between these groups is intimately related to the initial response to NST. In other words, it is caused by non-responders, while the clinical course of responders is similar to the group treated with GTR and adjuvant RT. Therefore, one could hypothesize that if factors reliably predicting response to NST are available, then patients identified as likely responders could have a non-inferior chance of having their ACF-ACC controlled even without surgery. This hypothesis highlights the urgent need for reliable strategies to predict ACC response to NST. In this context, we advocate for further research into the molecular classification of ACC to enable more accurate prognostic and predictive stratification. Specifically, comprehensive characterization of the transcriptomic, proteomic, and mutational profiles, as well as epigenetic alterations, could improve baseline prognostic assessment and ultimately guide a more tailored therapeutic approach [8].

Given the retrospective nature of the study and the non-comparability of treatment pattern-specific sub-cohorts, any comparison between patients undergoing NST and those receiving upfront surgery is inherently subject to selection bias, which represents the main limitation of the present study. In addition, both surgical and RT approaches were heterogeneous across cohorts, reflecting the evolution of techniques, technologies, and strategies incorporating chemotherapy over the study period. Moreover, given the indolent yet relentless natural history of ACC, the median follow-up may be insufficient to fully capture late recurrences and long-term outcomes. To mitigate these sources of bias, a rigorous methodological strategy, including machine learning methods, PSM, and multivariable analysis, was implemented. Nevertheless, it should be acknowledged that such an approach cannot provide evidence equivalent to that derived from prospective, comparative clinical trials.

5. Conclusions

For ACC of the ACF area, GTR followed by state-of-the-art adjuvant RT is associated with the highest achievable local control. R2 surgery should be avoided, since it provides no measurable prognostic advantages for patients while delaying definitive NST. Responders to NST show a similar rate of local failures compared to patients receiving GTR and adjuvant treatment, suggesting potential changes in treatment paradigms once reliable response-predicting strategies are available.

Authors' contributions

MF is responsible for study conception and design, analysis and interpretation, and drafting of the manuscript. GS is responsible for study design, data acquisition, analysis and interpretation, and drafting of the manuscript.

PG, SS, EO, DM, MTZ, DL, BV, GA, ADA, DB, FC, NC, FD, AD, RF, FF, MGG, GG, MK, MKr, AL, ML, LDL, VJL, JP, VR, SR, AR, RS, ST, GT, MT, AV, EZ, PB, AMP, PH, PBa, MB, PC, BV and CP contributed to data collection and critical revision of the manuscript.

PN and EYH equally share the last authorship. PN and EYH supervised the study, provided critical intellectual input, and revised the manuscript.

All authors read and approved the final manuscript.

CRediT authorship contribution statement

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.116680.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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