Clinical and Translational Radiation Oncology 53 (2025) 100945

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Concurrent chemoradiotherapy versus radiotherapy alone in postoperative high-risk adenoid cystic carcinoma of the head and neck: A propensity score matched analysis

Shengjin Dou [a,f,g,h,i,1], Xin Wang [b,1], Ying Xiao [c], Lin Zhang [a,f,g,h,i], Wen Jiang [a,f,g,h,i], Lulu Ye [a,f,g,h,i], Yu Wang [d], Yining He [e], Shengwen Liu [a,f,g,h,i], Rongrong Li [a,f,g,h,i,*], Guopei Zhu [a,f,g,h,i,*]

[a] Department of Oral and Maxillofacial-Head Neck Oncology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[b] Department of Radiation Oncology, Shanghai Second People's Hospital, Shanghai, China
[c] Department of Oncology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
[d] Department of Oral Pathology, Ninth People's Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China
[e] Biostatistics Office of Clinical Research Unit, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[f] College of Stomatology, Shanghai Jiao Tong University, Shanghai, China
[g] National Center for Stomatology& National Clinical Research Center for Oral Diseases, Shanghai, China
[h] Shanghai Key Laboratory of Stomatology& Shanghai Research Institute of Stomatology, Shanghai, China
[i] Shanghai Center of Head and Neck Oncology Clinical and Translational Science, China

A B S T R A C T

Background: The role of concurrent chemoradiotherapy (CCRT) in postoperative head and neck adenoid cystic carcinoma (ACC) remains controversial due to the limited evidence from randomized trials. This study assessed the effectiveness of CCRT by comparing a prospective CCRT group with a retrospective radiation (RT) alone group using propensity score matching (PSM).

Methods and materials: Postoperative head and neck ACC patients with T3-4/N1-3 M0 disease or after R1/R2 resection were enrolled. All patients underwent intensity-modulated radiation therapy (IMRT), and CCRT group received two cycles of concurrent docetaxel and nedaplatin. To ensure comparability, PSM were utilized. Following PSM, survival outcomes were analyzed using Kaplan-Meier curves and compared using the log-rank test.

Results: A prospective CCRT group of 55 patients and a retrospective RT alone group of 160 patients were included. The multivariate Cox regression analysis showed no association between CCRT and overall survival (OS) (hazard ratio [HR] = 0.71, 95 %CI: 0.24–2.08, p = 0.537), or other survival outcomes. To mitigate potential confounding factors, a 1: 1 PSM analysis was performed. With a median follow-up of 51 months, post-PSM analysis (including 48 patients in each group) indicated no significant differences in OS (estimated 5-year OS rates: 90.7 % versus 84.3 %, p = 0.331), locoregional recurrence-free survival (LRRFS) (p = 0.261), distant metastasis-free survival (DMFS) (p = 0.425), or disease-free survival (DFS) (p = 0.600) between two groups. The multivariate Cox regression analysis also showed no association between CCRT and OS (HR = 0.29, 95 %CI: 0.06–1.38, p = 0.119), or other survival outcomes.

Conclusion: The addition of concurrent chemotherapy to postoperative IMRT did not confer a survival benefit in terms of LRRFS, DMFS, DFS, or OS in patients with head and neck ACC. Upcoming results from randomized studies are anticipated to shed more light on this debated issue. CCRT should be avoided outside of clinical trials.

Abbreviations: ACC, adenoid cystic carcinoma; CCRT, concurrent chemoradiotherapy; SGC, salivary gland carcinoma; RT, radiotherapy; TP, docetaxel and nedaplatin; PSM, propensity score matching; IMRT, Intensity-modulated radiotherapy; KPS, Karnofsky performance status; CTV, clinical target volume; PTV, planning target volumes; IQR, interquartile range; ENE, extranodal extension; LRRFS, locoregional recurrence-free survival; DMFS, distant metastasis-free survival; DFS, disease-free survival; OS, overall survival.

* Corresponding authors at: No.639 Zhizaoju Road, Shanghai 200011, China.
E-mail addresses: rongrli2003@163.com (R. Li), antica@gmail.com (G. Zhu).

[1] These two authors contributed equally to this work.

https://doi.org/10.1016/j.ctro.2025.100945
Received 3 December 2024; Received in revised form 21 February 2025; Accepted 9 March 2025
Available online 17 March 2025

Introduction

The primary therapeutic approach for adenoid cystic carcinoma (ACC) of the head and neck involves adequate and appropriate surgical resection followed by postoperative radiotherapy, even for stage I-II disease [1]. Despite important advances in radiotherapy techniques, patients with T3-4 stages, lymph node metastasis, positive margin and high histological grade still face a high risk of recurrence and have a poor prognosis [2–4].The efficacy of concurrent chemoradiotherapy (CCRT) in high-risk head and neck squamous cell carcinoma patients has been demonstrated in several multicenter randomized trials [5–7], yet evidence supporting its use in high-risk ACC patients remains scarce. Given the limited availability of high-quality prospective trials on chemotherapy or targeted therapy for advanced ACC, uncertainty persists regarding the optimal treatment approach [8–11]. Two ongoing randomized phase III trials (ClinicalTrials.gov identifiers: NCT01220583 and NCT02998385) are currently investigating the use of adjuvant radiation (RT) with or without concurrent cisplatin in patients with salivary gland carcinoma. However, due to the rarity and complexity of the disease, obtaining unequivocal results from randomized studies may prove challenging.

In an effort to improve the survival outcomes of postoperative high-risk salivary gland cancer patients, a single center, non-randomized, phase II trial was initiated, including an adenoid cystic carcinoma (ACC) cohort and a non-ACC cohort to investigate the effectiveness of CCRT. (ClinicalTrials.gov identifiers: NCT02776163). Given the prevalent occurrence of distant site recurrence [12,13], a combined treatment regimen involving docetaxel and nedaplatin (TP) was chosen to address micrometastases and enhance the sensitivity of radiotherapy. Propensity score matching (PSM) serves as a statistical tool to mitigate biases in non-randomized studies, facilitating more objective comparative analyses [14,15]. In this study, the prospective cohort was derived from the ACC cohort of the above phase II trial and will be compared with a retrospective RT alone cohort using PSM, aiming to provide deeper insights into the efficacy of CCRT in postoperative high-risk ACC patients.

Methods

Patients

The study was approved by the Local Ethics Committee and conducted according to the principles of the Declaration of Helsinki. The clinical trial was registered with ClinicalTrials.gov. Postoperative patients with pathologically confirmed ACC of the head and neck treated from 2015 to 2023 were enrolled. The primary inclusion criteria are as follows: ① Age between 18 and 75 years; ② T3-4/N1-3 or post R1/R2 resection (according to the 7th edition of the AJCC staging system 2017); ③ Karnofsky performance status (KPS) score $\geq$ 70; ④ Absence of distant metastasis; ⑤ Expected survival of at least 6 months. Patients who underwent only biopsy, had a history of malignant cancer (excluding non-melanomatous skin cancer) within the past 5 years, or had significant medical comorbidities were excluded from participation in this study. Evaluation of residual disease was conducted through intraoperative observations, assessment of surgical margins, and postoperative MRI, CT or ^{18}F-FDG PET/CT scans of the head and neck.

Study treatment

Intensity-modulated radiotherapy (IMRT) commenced 4–6 weeks post-surgery. Patients underwent simulation for treatment using computed tomography, and custom thermoplastic head-neck-shoulder masks were employed for immobilization. Clinical target volume 1 (CTV1) included radiographic residual disease, areas with positive surgical margins, and any imaging evidence of perineural tumor spread. CTV2 encompassed CTV1, the tumor bed, typical pathways of spread along cranial nerves, and elective high-risk cervical nodes. CTV3 electively covered the low-risk cervical nodes. Planning target volumes (PTVs) were generated by uniformly expanding CTV1 by 5 mm and CTV2 by 3 mm. The prescribed doses for PTV1, PTV2, and PTV3 were 66–70 Gy, 60 Gy, and 54 Gy, respectively, delivered over 33 to 35 treatment fractions. In the prospective CCRT cohort, patients underwent two cycles of concurrent chemotherapy administered at 3-week intervals concurrently with IMRT. Docetaxel was administered intravenously at a dose of 70 mg/m2 on day 1, and nedaplatin was administered intravenously at a dose of 35 mg/m2 on days 1–2. Standard prophylactic antiemetic medications were administered to all patients receiving docetaxel therapy. Prior to chemotherapy administration, dexamethasone at a dose of 8 mg was orally administered twice daily for a total of six doses to prevent hypersensitivity reactions and mitigate skin-related toxicities and fluid retention.

Evaluation

Before initiating IMRT, each patient underwent a comprehensive assessment to ascertain eligibility. This assessment included obtaining a detailed medical history, conducting physical examinations, performing a full blood count, biochemical laboratory tests, contrast-enhanced MRI or CT scans of the head and neck, and other staging procedures as deemed necessary. The evaluation of resection status (R0, R1, or R2) was conducted by a multidisciplinary team comprising surgeons, pathologists, radiologists, and radiation oncologists. This collaborative approach ensured a comprehensive assessment, drawing on expertise from various medical specialties to accurately determine the extent of tumor resection and the presence of any residual disease. Throughout the treatment course, patients were examined at least once weekly. Follow-up appointments were scheduled at least every 3 months during the first 2 years following radiotherapy, and then every 6 months thereafter up to 5 years.

Statistical analysis

The sample size calculation for the ACC cohort was as follows: We assume that for the ACC arm, the DFS rate will be similar to that reported by previous studies for the stage III-IV patients or R1/R2 resection, or an estimated 5-year disease-free survival (DFS) rate 40 % for radiotherapy alone. To detect whether CCRT would increase the 5-year DFS rate to 65 %, a sample size of 53 achieves 80 % power to detect an improvement from 40 % to 65 % using a two-sided log-rank test. The target significance level is 0.05. Considering 10 % loss in two years, 58 evaluable patients were required in this ACC arm. At the end of study, 55 patients were enrolled. The sample size for the PSM analysis was determined primarily to balance the baseline characteristics between the two groups and secondarily to ensure sufficient power to detect an improvement in the 5-year DFS rate from 40 % to 65 %, using a two-sided log-rank test. After PSM, each subgroup consisting of 48 patients. The baseline characteristics were well-balanced, and the power was estimated to be 77 %.

The statistical analysis was conducted using R version 4.3.2. Categorical variables were presented as counts (proportions) and compared using either the chi-square test or Fisher's exact test. Continuous variables were expressed as medians with interquartile ranges (IQRs) and compared using the Wilcoxon test. PSM was employed to balance demographic and tumor characteristics between the CCRT group and the RT alone group. Factors included in the matching process were age, sex, site, T stage, N stage, extranodal extension (ENE), surgery status and pathology type. Matching was performed at a 1:1 ratio with a caliper value of 0.2. Following PSM, various endpoints including locoregional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS), DFS, and overall survival (OS) were analyzed using Kaplan-Meier curves and compared using the log-rank test. All intervals were calculated from the date of surgery to the date of event or death. To account for potential confounding factors, multivariable Cox proportional hazards models were utilized before and after PSM. This approach

helped to assess the impact of concurrent chemotherapy on outcomes while controlling for other variables. A two-sided P-value of less than 0.05 was considered statistically significant in all analyses. This comprehensive statistical approach aimed to reduce bias and provide robust insights into the effectiveness of concurrent chemotherapy in the treatment of the patients.

Results

Patient characteristics

The prospective CCRT group comprised 55 patients, while the retrospective RT alone group consisted of 160 patients (as shown in Table 1). Significant differences in various baseline characteristics were observed between the two groups.

Specifically, the CCRT group had a higher proportion of female patients compared to the RT alone group ($p = 0.022$). Additionally, there was a higher prevalence of T4b disease in the CCRT group compared to the RT alone group ($p = 0.020$). Furthermore, patients in the CCRT group were more likely to have undergone R2 resection ($p = 0.002$) and had a higher proportion of solid-type pathology ($p = 0.002$) compared to the RT alone group.

These differences in demographic and clinical characteristics highlight the importance of employing PSM to balance the groups and minimize potential confounding effects when comparing outcomes between the CCRT and RT alone groups. PSM ensures that baseline characteristics are similar between groups, thereby enhancing the validity of the comparative analysis.

Survival outcomes and confounding factors analysis before propensity score matching

With a median follow-up of 44 months, the Kaplan-Meier curve revealed no significant differences between the CCRT group and the RT alone group in terms of OS, with estimated 5-year OS rates of 85.1 % versus 92.1 % ($p = 0.366$). Similarly, there were no significant differences in LRRFS, with estimated 5-year rates of 80.2 % versus 84.4 %($p = 0.368$), distant metastasis-free survival (DMFS), with estimated 5-year rates of 51.5 % versus 63.6 % ($p = 0.135$), or disease-free survival (DFS), with estimated 5-year rates of 50.8 % versus 63.2 % ($p = 0.089$). (Fig. S1). To further explore the potential benefit of CCRT and confounding effects of other factors, both univariate and multivariate Cox regression analyses were conducted. These analyses revealed no significant association between CCRT and overall survival (OS), with hazard ratios (HR) of 1.56 (95 % CI: 0.59–4.13, $p = 0.370$) in the univariate analysis and 0.71 (95 % CI: 0.24–2.08, $p = 0.537$) in the multivariate analysis. Similar results were observed for other survival outcomes, as detailed in Tables 2 and 3.

Table 1
Demographic and clinical characteristics before propensity score matching.

Variables	Levels	No (N = 160)	Yes (N = 55)	*P*
Sex	Female	60 (37.5 %)	31 (56.4 %)	0.022
	Male	100 (62.5 %)	24 (43.6 %)	
Age	Median (IQR)	51.0 (37.5 to 59.0)	52.0 (42.0 to 58.0)	0.708
Site	Major	70 (43.8 %)	16 (29.1 %)	0.079
	minor	90 (56.2 %)	39 (70.9 %)	
T Stage	T1-2	38 (23.8 %)	8 (14.5 %)	0.020
	T3-4a	88 (55 %)	25 (45.5 %)	
	T4b	34 (21.2 %)	22 (40 %)	
N Stage	N0	143 (89.4 %)	47 (85.5 %)	0.671
	N1-2	12 (7.5 %)	5 (9.1 %)	
	N3	5 (3.1 %)	3 (5.5 %)	
ENE	No	151 (94.4 %)	51 (92.7 %)	0.909
	Yes	9 (5.6 %)	4 (7.3 %)	
Surgery status	R0	46 (28.8 %)	6 (10.9 %)	0.002
	R1	70 (43.8 %)	21 (38.2 %)	
	R2	44 (27.5 %)	28 (50.9 %)	
Pathology type	Nonsolid	152 (95 %)	44 (80 %)	0.002
	Solid	8 (5 %)	11 (20 %)	

Abbreviations: IQR, ENE, extranodal extension.

Univariate analyses identified that variables including sex, T stage, N stage, ENE, and pathology type were significantly associated with different survival outcomes (Table 2 and Table 3). All significant factors identified in the univariate analysis were included in the multivariate Cox regression model. Since CCRT was the primary factor under investigation in this study, we also included it in the multivariate Cox regression model to further assess whether CCRT affects survival outcomes. The multivariate analysis revealed that pathology type remained significantly associated with OS (HR = 12.97, 95 % CI: 4.03–41.76, $p < 0.001$), LRRFS (HR = 9.85, 95 %CI:4.08–23.81, $p < 0.001$), DMFS (HR = 2.26, 95 %CI: 1.12–4.57, $p = 0.023$), and DFS (HR = 2.45, 95 %CI: 1.16–5.15, $p = 0.018$) outcomes. Additionally, sex was found to be significantly associated with OS (HR = 0.20, 95 %CI: 0.06–0.65, $p = 0.008$) and LRRFS (HR = 0.40, 95 %CI: 0.18–0.90, $p = 0.027$) outcomes, while T stage was significantly associated with LRRFS (T4b, HR = 3.33, 95 %CI = 1.02–10.83, $p = 0.045$), DMFS (T3-4a, HR = 3.64, 95 %CI = 1.50–8.84, $p = 0.004$; T4b, HR = 5.14, 95 %CI = 0.02–13.08, $p = 0.001$), and DFS (T3-4a, HR = 2.59, 95 %CI: 1.14–5.88, $p = 0.023$; T4b, HR = 4.35, 95 %CI = 1.86–10.15, $p = 0.001$) outcomes. Moreover, ENE was identified as significantly associated with DMFS (HR = 9.35, 95 % CI: 2.28–38.35, $p = 0.002$) and DFS (HR = 2.45, 95 %CI: 1.16–5.15, $p = 0.018$) outcomes (Table 2 and Table 3).

These findings indicate that while CCRT didn't demonstrate a significant impact on survival outcomes compared to RT alone, other factors like pathology type, sex, T stage, and ENE significantly influence prognosis. These factors could potentially confound the comparison of outcomes between the CCRT and RT alone groups.

Propensity score matching

Performing PSM between the groups of patients is a crucial step to minimize bias and ensure comparability. In our study, a 1:1 PSM analysis was conducted, where the factors used for matching included age, site, factors with significant P-values from both univariate and multivariate Cox analyses (as listed in Tables 2 and 3), and surgery status. The decision to include surgery status was based on findings from a multicenter, retrospective study indicating that the addition of concurrent chemotherapy to postoperative radiotherapy was associated with improved 10-year local control rates in patients with salivary gland carcinomas (SGCs) who underwent R2 resection [16].

After matching, 96 patients were assessed and each subgroup included 48 patients. The P values for all covariates were greater than 0.05, indicating that propensity scores for the two groups significantly overlapped (Table 4). This suggests that after matching, the characteristics of the patients in the CCRT and RT alone groups were well-balanced, minimizing potential biases.

Survival outcomes and subgroup analysis after PSM

With a median follow-up of 51 months, the Kaplan-Meier curve revealed no significant differences between the CCRT group and the RT alone group in terms of OS, with estimated 5-year OS rates of 90.7 % versus 84.3 % ($p = 0.331$). Similarly, there were no significant differences in LRRFS, with estimated 5-year rates of 84.0 % versus 72.8 %($p = 0.261$), DMFS, with estimated 5-year rates of 55.9 % versus 44.1 % ($p = 0.426$), or DFS, with estimated 5-year rates of 54.9 % versus 46.2 % ($p = 0.600$). (Fig. 1).

After matching, both univariate and multivariate Cox regression analyses still revealed no significant association between CCRT and OS, with HR of 0.53 (95 % CI: 0.15–1.93, $p = 0.337$) in the univariate analysis and 0.29 (95 % CI: 0.06–1.38, $p = 0.119$) in the multivariate

Table 2
Univariate and multivariate analysis of OS and DFS before PSM.

Characteristics		OS		DFS	
		HR (univariable)	HR (multivariable)	HR (univariable)	HR (multivariable)
CCRT	No	Ref	Ref	Ref	Ref
	Yes	1.56 (0.59–4.13, p = 0.370)	0.71 (0.24–2.08, p = 0.537)	1.50 (0.94–2.42, p = 0.092)	1.10 (0.67–1.82, p = 0.711)
Age	Median (IQR)	1.00 (0.97–1.04, p = 0.789)		1.01 (0.99–1.03, p = 0.277)	
Sex	Female	Ref	Ref	Ref	
	Male	0.23 (0.07–0.70, p = 0.010)	0.20 (0.06–0.65, p = 0.008)	0.79 (0.50–1.25, p = 0.319)	
Site	Major	Ref		Ref	
	minor	1.00 (0.38–2.64, p = 0.996)		1.35 (0.83–2.19, p = 0.224)	
T Stage	T1-2	Ref		Ref	Ref
	T3-4a	1.02 (0.25–4.09, p = 0.978)		2.98 (1.33–6.68, p = 0.008)	2.59 (1.14–5.88, p = 0.023)
	T4b	2.69 (0.71–10.18, p = 0.144)		5.01 (2.18–11.52, p < 0.001)	4.35 (1.86–10.15, p = 0.001)
N Stage	N0	Ref	Ref	Ref	
	N1-2	3.94 (1.09–14.17, p = 0.036)	0.78 (0.15–4.17, p = 0.770)	2.01 (1.00–4.06, p = 0.051)	
	N3	6.62 (1.45–30.28, p = 0.015)	1.13 (0.05–23.50, p = 0.937)	1.95 (0.71–5.39, p = 0.195)	
Pathology type	Nonsolid	Ref	Ref	Ref	Ref
	Solid	11.46 (4.15–31.63, p < 0.001)	12.97 (4.03–41.76, p < 0.001)	3.53 (1.92–6.48, p < 0.001)	2.64 (1.40–5.00, p = 0.003)
ENE	No	Ref	Ref	Ref	Ref
	Yes	5.91 (1.66–21.11, p = 0.006)	6.39 (0.46–88.29, p = 0.166)	2.70 (1.29–5.63, p = 0.008)	2.45 (1.16–5.15, p = 0.018)
Surgery status	R0	Ref		Ref	
	R1	1.02 (0.24–4.30, p = 0.983)		0.64 (0.35–1.19, p = 0.160)	
	R2	1.94 (0.53–7.18, p = 0.320)		1.21 (0.69–2.14, p = 0.506)	

Abbreviations: CCRT, concurrent chemoradiotherapy; ENE, extranodal extension.

Table 3
Univariate and multivariate analysis of LRRFS and DMFS before PSM.

Characteristics		LRRFS		DMFS	
		HR (univariable)	HR (multivariable)	HR (univariable)	HR (multivariable)
CCRT	No	Ref	Ref	Ref	Ref
	Yes	1.41 (0.66–3.00, p = 0.370)	0.50 (0.21–1.20, p = 0.122)	1.45 (0.89–2.37, p = 0.137)	1.17 (0.70–1.97, p = 0.544)
Age	Median (IQR)	1.01 (0.98–1.04, p = 0.447)		1.01 (0.99–1.03, p = 0.340)	
Sex	Female	Ref	Ref	Ref	
	Male	0.38 (0.18–0.81, p = 0.013)	0.40 (0.18–0.90, p = 0.027)	0.87 (0.54–1.40, p = 0.573)	
Site	Major	Ref		Ref	
	minor	1.60 (0.73–3.51, p = 0.244)		1.30 (0.79–2.13, p = 0.303)	
T Stage	T1-2	Ref	Ref	Ref	Ref
	T3-4a	1.12 (0.34–3.65, p = 0.851)	0.84 (0.25–2.87, p = 0.779)	3.53 (1.49–8.37, p = 0.004)	3.64 (1.50–8.84, p = 0.004)
	T4b	4.27 (1.42–12.79, p = 0.010)	3.33 (1.02–10.83, p = 0.045)	5.07 (2.07–12.41, p < 0.001)	5.14 (2.02–13.08, p = 0.001)
N Stage	N0	Ref		Ref	Ref
	N1-2	1.94 (0.58–6.51, p = 0.282)		2.15 (1.06–4.36, p = 0.033)	0.94 (0.35–2.47, p = 0.894)
	N3	2.94 (0.69–12.56, p = 0.146)		2.16 (0.78–5.97, p = 0.138)	0.18 (0.03–1.03, p = 0.054)
Pathology type	Nonsolid	Ref	Ref	Ref	Ref
	Solid	9.20 (4.12–20.53, p < 0.001)	9.85 (4.08–23.81, p < 0.001)	2.93 (1.52–5.62, p = 0.001)	2.26 (1.12–4.57, p = 0.023)
ENE	No	Ref		Ref	Ref
	Yes	2.83 (0.85–9.44, p = 0.091)		2.96 (1.41–6.21, p = 0.004)	9.35 (2.28–38.35, p = 0.002)
Surgery status	R0	Ref		Ref	
	R1	0.84 (0.27–2.66, p = 0.766)		0.68 (0.36–1.26, p = 0.219)	
	R2	2.35 (0.87–6.38, p = 0.093)		1.11 (0.62–2.01, p = 0.718)	

Abbreviations: CCRT, concurrent chemoradiotherapy; ENE, extranodal extension.

analysis. Similar results were observed for other survival outcomes, as detailed in Tables 5 and 6.

The results of the multivariate analysis showed that: pathology type remained significantly associated with OS (HR = 5.42, 95 %CI: 1.17–25.01, p = 0.030) and LRRFS (HR = 5.32, 95 %CI: 1.68–16.83, p = 0.004), indicating its independent predictive value for these endpoints; T4b stage (HR = 5.16, 95 %CI: 1.46–18.28, p = 0.011) and ENE (HR = 231.46, 95 %CI: 12.91–4149.69, p < 0.001) significantly associated with DFS; T stage(T3-4a, HR = 8.16, 95 %CI: 1.73–38.49, p = 0.008; T4b, HR = 8.33, 95 %CI: 1.79–38.82, p = 0.007) and N3 stage(HR = 0.00, 95 %CI 0.00–0.00, p < 0.001) significantly associated with DMFS (Table 5 and Table 6).

To investigate the potential benefits of CCRT in specific subgroups of patients, the effects of CCRT were analyzed across various demographic and clinical characteristics, including sex, site, T stage, N stage, pathology type, ENE status, and surgery status. However, the analysis revealed that no survival benefit associated with CCRT could be derived within any of these subgroups (Fig. 2). These findings suggest that, regardless of patient demographics or disease characteristics, CCRT did not confer a survival advantage in the studied population.

Discussion

The role of CCRT in postoperative high-risk head and neck ACC patients remains a subject of debate and uncertainty. This uncertainty stems from the rarity and complexity of ACC, as well as the limited availability of high-quality clinical evidence from randomized controlled trials. In this study, PSM analysis was employed to compare outcomes between a prospective CCRT group and a retrospective RT alone group. The results of this analysis revealed that the addition of concurrent chemotherapy with TP regimen did not confer improvements in LRRFS, DMFS DFS or OS in postoperative head and neck ACC patients.

The role of CCRT in postoperative high-risk head and neck ACC patients has been relatively understudied. Similarly, in patients with SGCs, including ACC, the use of CCRT in the postoperative setting remains a topic of debate and uncertainty [11,17–24]. Several studies have

Table 4
Demographic and clinical characteristics after propensity score matching.

Variables	Levels	No (N = 48)	Yes (N = 48)	*P*
Sex	Female	22 (45.8 %)	25 (52.1 %)	0.683
	Male	26 (54.2 %)	23 (47.9 %)	
Age	Median (IQR)	53.5 (36.5 to 59.5)	53.0 (41.0 to 58.5)	0.878
Site	Major	13 (27.1 %)	12 (25 %)	1.000
	minor	35 (72.9 %)	36 (75 %)	
T Stage	T1-2	8 (16.7 %)	8 (16.7 %)	0.798
	T3-4a	19 (39.6 %)	22 (45.8 %)	
	T4b	21 (43.8 %)	18 (37.5 %)	
N Stage	N0	43 (89.6 %)	42 (87.5 %)	0.842
	N1-2	4 (8.3 %)	4 (8.3 %)	
	N3	1 (2.1 %)	2 (4.2 %)	
ENE	No	46 (95.8 %)	45 (93.8 %)	1.000
	Yes	2 (4.2 %)	3 (6.2 %)	
Surgery status	R0	6 (12.5 %)	6 (12.5 %)	0.668
	R1	14 (29.2 %)	18 (37.5 %)	
	R2	28 (58.3 %)	24 (50 %)	
Pathology type	Nonsolid	42 (87.5 %)	42 (87.5 %)	1.000
	Solid	6 (12.5 %)	6 (12.5 %)	

Abbreviations: ENE, extranodal extension.

examined the impact of adjuvant CCRT compared to RT alone in patients with major SGCs. For instance, a retrospective study evaluated survival outcomes in a large cohort of major SGC patients using data from the National Cancer Database [23]. This study included 368 patients who received adjuvant CCRT and 1842 patients who received RT alone. Despite the large sample size, adjuvant CCRT did not demonstrate improvements in OS, even in a propensity-matched cohort consisting of 350 pairs of patients. It's worth noting that ongoing multi-center, randomized trials, such as RTOG 1008 and the GORTEC SANTAL trial, are currently investigating the role of postoperative CCRT in high-risk SGCs patients. These trials are randomizing high-risk postoperative patients to receive either RT alone or RT combined with concurrent cisplatin. The aim is to evaluate whether the addition of concurrent cisplatin to radiotherapy improves outcomes compared to radiotherapy alone in patients with various histological subtypes of SGCs, including adenocarcinoma, mucoepidermoid carcinoma, salivary duct carcinoma, and ACC, et.al. However, due to the inherent complexity and heterogeneity of SGCs, it remains uncertain whether the findings from these trials will be directly applicable to patients specifically diagnosed with ACC. ACC, in particular, presents unique characteristics and treatment responses that may differ from other subtypes of SGCs. Since the level of evidence supporting the addition of chemotherapy to radiotherapy in postoperative high-risk ACC is low, this treatment is not recommended outside of a clinical trial [1,25]. Given this uncertainty, our study focusing specifically on postoperative head and neck ACC patients could provide valuable evidence.

Our study demonstrated high OS and local control rates in both groups, with a 5-year OS rates of 90.7 % in the CCRT group compared to

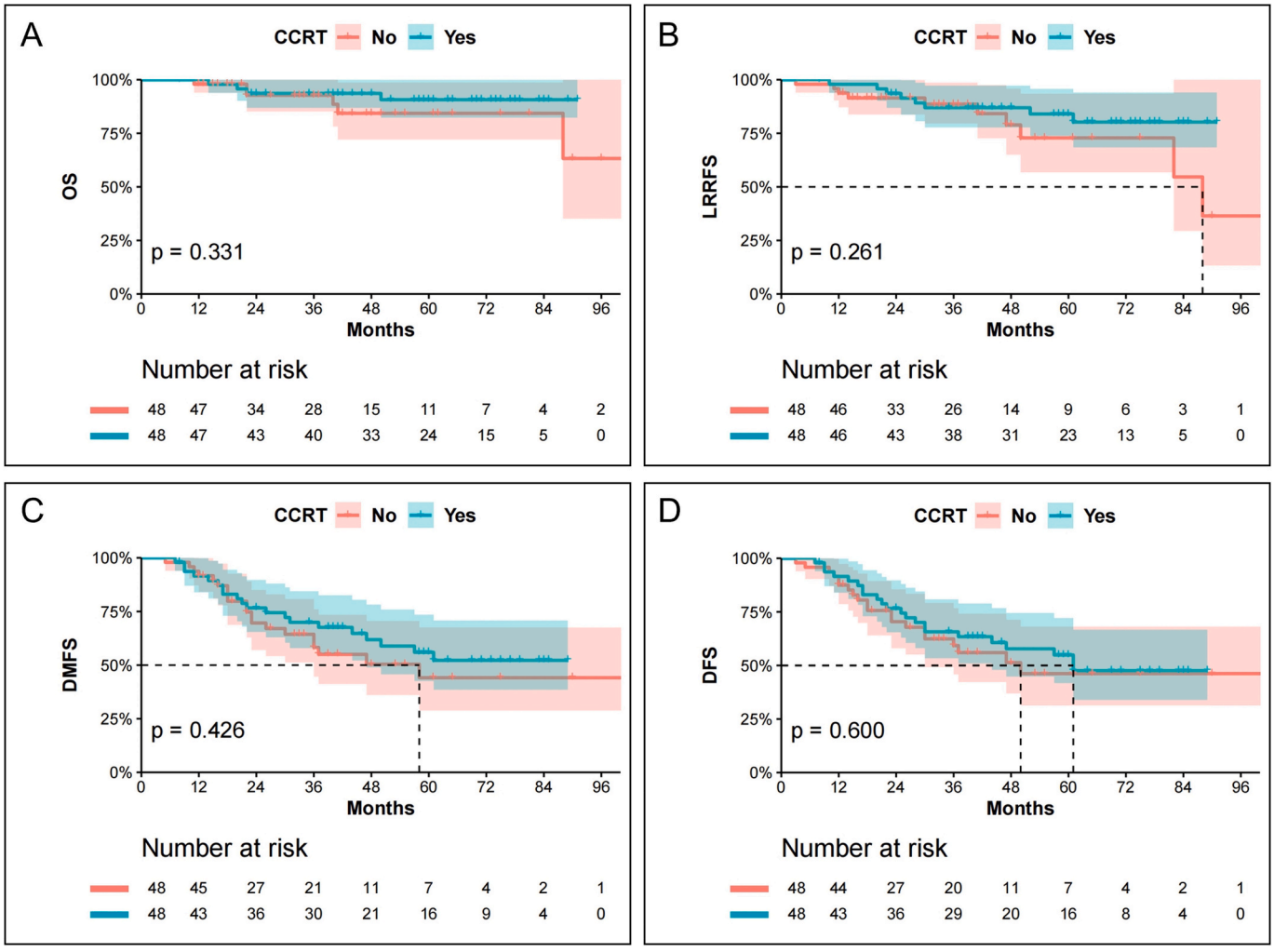

Fig. 1. Survival outcomes between the CCRT group and the RT alone group after PSM. Abbreviations: OS, overall survival; DFS, disease-free survival; LRRFS, localregional recurrence-free survival; DMFS, distant metastasis-free survival; CCRT, concurrent chemoradiotherapy; PSM, propensity score matching.

Table 5
Univariate and multivariate analysis of OS and DFS after PSM.

Characteristics		OS		DFS	
		HR (univariable)	HR (multivariable)	HR (univariable)	HR (multivariable)
CCRT	No	Ref	Ref	Ref	Ref
	Yes	0.53 (0.15–1.93, p = 0.337)	0.29 (0.06–1.38, p = 0.119)	0.85 (0.46–1.56, p = 0.601)	0.79 (0.42–1.48, p = 0.466)
Age	Median (IQR)	1.01 (0.96–1.06, p = 0.645)		1.01 (0.98–1.03, p = 0.593)	
Sex	Female	Ref		Ref	
	Male	0.24 (0.05–1.14, p = 0.073)		0.89 (0.48–1.63, p = 0.698)	
Site	Major	Ref		Ref	
	minor	0.94 (0.24–3.63, p = 0.924)		1.74 (0.80–3.77, p = 0.162)	
T Stage	T1-2	Ref		Ref	Ref
	T3-4a	1.41 (0.15–13.61, p = 0.767)		3.21 (0.94–10.97, p = 0.063)	3.68 (0.99–13.66, p = 0.051)
	T4b	2.65 (0.32–22.07, p = 0.369)		4.17 (1.24–14.05, p = 0.021)	5.16(1.46–18.28, p = 0.011)
N Stage	N0	Ref	Ref	Ref	Ref
	N1-2	6.11 (1.15–32.48, p = 0.034)	2.36 (0.23–23.73, p = 0.466)	1.63 (0.58–4.60, p = 0.353)	0.61 (0.14–2.75, p = 0.523)
	N3	39.00 (6.27–242.49, p < 0.001)	9.61 (0.25–366.24, p = 0.223)	9.15 (2.62–31.91, p < 0.001)	0.08(0.00–1.71, p = 0.107)
Pathology type	Nonsolid	Ref	Ref	Ref	Ref
	Solid	7.98 (2.09–30.48, p = 0.002)	5.42 (1.17–25.01, p = 0.030)	2.72 (1.25–5.93, p = 0.012)	2.14(0.88–5.24, p = 0.095)
ENE	No	Ref	Ref	Ref	Ref
	Yes	31.12 (6.01–161.01, p < 0.001)	8.60 (0.39–191.48, p = 0.174)	15.40 (5.42–43.78, p < 0.001)	231.46(12.91–4149.69. p < 0.001)
Surgery status	R0	Ref		Ref	
	R1	0.34 (0.05–2.49, p = 0.290)		0.38 (0.14–1.01, p = 0.052)	
	R2	0.59 (0.12–2.92, p = 0.516)		0.77 (0.33–1.77, p = 0.537)	

Abbreviations: CCRT, concurrent chemoradiotherapy; ENE, extranodal extension.

Table 6
Univariate and multivariate analysis of LRRFS and DMFS after PSM.

Characteristics		LRRFS		DMFS	
		HR (univariable)	HR (multivariable)	HR (univariable)	HR (multivariable)
CCRT	No	Ref	Ref	Ref	Ref
	Yes	0.59 (0.23–1.51, p = 0.267)	0.47 (0.17–1.30, p = 0.145)	0.77 (0.41–1.45, p = 0.421)	0.64 (0.33–1.22, p = 0.174)
Age	Median (IQR)	1.00 (0.97–1.04, p = 0.974)		1.01 (0.98–1.03, p = 0.530)	
Sex	Female	Ref		Ref	
	Male	0.46 (0.17–1.22, p = 0.119)		1.02 (0.55–1.90, p = 0.948)	
Site	Major	Ref		Ref	
	minor	1.54 (0.51–4.71, p = 0.446)		1.58 (0.73–3.45, p = 0.248)	
T Stage	T1-2	Ref		Ref	Ref
	T3-4a	1.20 (0.23–6.25, p = 0.828)		4.96 (1.15–21.49, p = 0.032)	8.16 (1.73–38.49, p = 0.008)
	T4b	2.66 (0.59–12.04, p = 0.204)		5.81 (1.35–24.95, p = 0.018)	8.33 (1.79–38.82, p = 0.007)
N Stage	N0	Ref	Ref	Ref	Ref
	N1-2	2.57 (0.57–11.63, p = 0.219)	0.98 (0.12–8.26, p = 0.987)	1.67 (0.59–4.73, p = 0.333)	0.79 (0.19–3.34, p = 0.753)
	N3	17.90 (3.33–96.10, p < 0.001)	3.27 (0.11–93.79, p = 0.488)	10.69 (3.02–37.85, p < 0.001)	0.00 (0.00–0.00, p < 0.001)
Pathology type	Nonsolid	Ref	Ref	Ref	
	Solid	6.73 (2.40–18.87, p < 0.001)	5.32 (1.68–16.83, p = 0.004)	2.16 (0.95–4.92, p = 0.066)	
ENE	No	Ref	Ref	Ref	Ref
	Yes	15.85 (3.51–71.63, p < 0.001)	4.86 (0.26–91.90, p = 0.292)	18.89 (6.53–54.66, p < 0.001)	NA (NA, NA)
Surgery status	R0	Ref		Ref	
	R1	0.31 (0.06–1.55, p = 0.153)		0.37 (0.14–1.01, p = 0.052)	
	R2	0.81 (0.23–2.88, p = 0.744)		0.68 (0.29–1.57, p = 0.362)	

Abbreviations: CCRT, concurrent chemoradiotherapy; ENE, extranodal extension.

84.3 % in the non-CCRT group (p = 0.331) and 5-year LRRFS of 84.0 % versus 72.8 % (p = 0.261). These rates are comparable to those reported in previous studies [8,16], particularly noteworthy given the inclusion of more patients with locally advanced disease in our study cohort. The advancements in RT techniques and improvements in the standardization of target volume delineation [26] have led to remarkable advancements in achieving excellent local control rates for head and neck ACC [3,27]. Despite the achievement of excellent locoregional control with surgery and precision radiation, the long-term outcomes for ACC patients remain poor, often characterized by the development of distant metastasis [12,27]. Given the observed failure pattern in the era IMRT, the potential of CCRT to substantially improve survival outcomes may be limited. Heish et al.[8] presented findings from a study involving 91 postoperative ACC patients, among whom 58 underwent adjuvant RT alone, while 33 received RT concurrent with cisplatin. Following PSM analysis, the study observed significantly higher 5-year and 8-year local control rates in the CCRT group compared to the RT alone group (97 %, 97 % vs. 79 %, 67 %, respectively; p = 0.017). However, no statistically significant disparities were noted in DMFS, DFS, or OS between the two groups. Consequently, although CCRT demonstrated an enhancement in local control rates among ACC patients compared to RT alone, the study did not reveal a clear survival advantage associated with this approach. Recently, Heish et al [16]. conducted a multicenter, retrospective study to explore the long-term outcomes of postoperative SGC patients who received either RT alone or CCRT. The study focused on 148 ACC patients, with 43 undergoing RT alone and 105 receiving CCRT. The findings indicated that CCRT was linked to significantly improved 10-year local control rates in ACC patients, with figures showing 97.6 % for CCRT compared to 83.6 % for RT alone (P = 0.039). The differences observed in the outcomes of CCRT between the study by Hsieh et al.[8 16] and the current study could indeed stem from variations in several key factors, including radiation techniques, target volume delineation standards, and chemotherapy regimens. Firstly, various radiotherapy techniques such as 3D conformal radiotherapy (3DCRT), IMRT, and

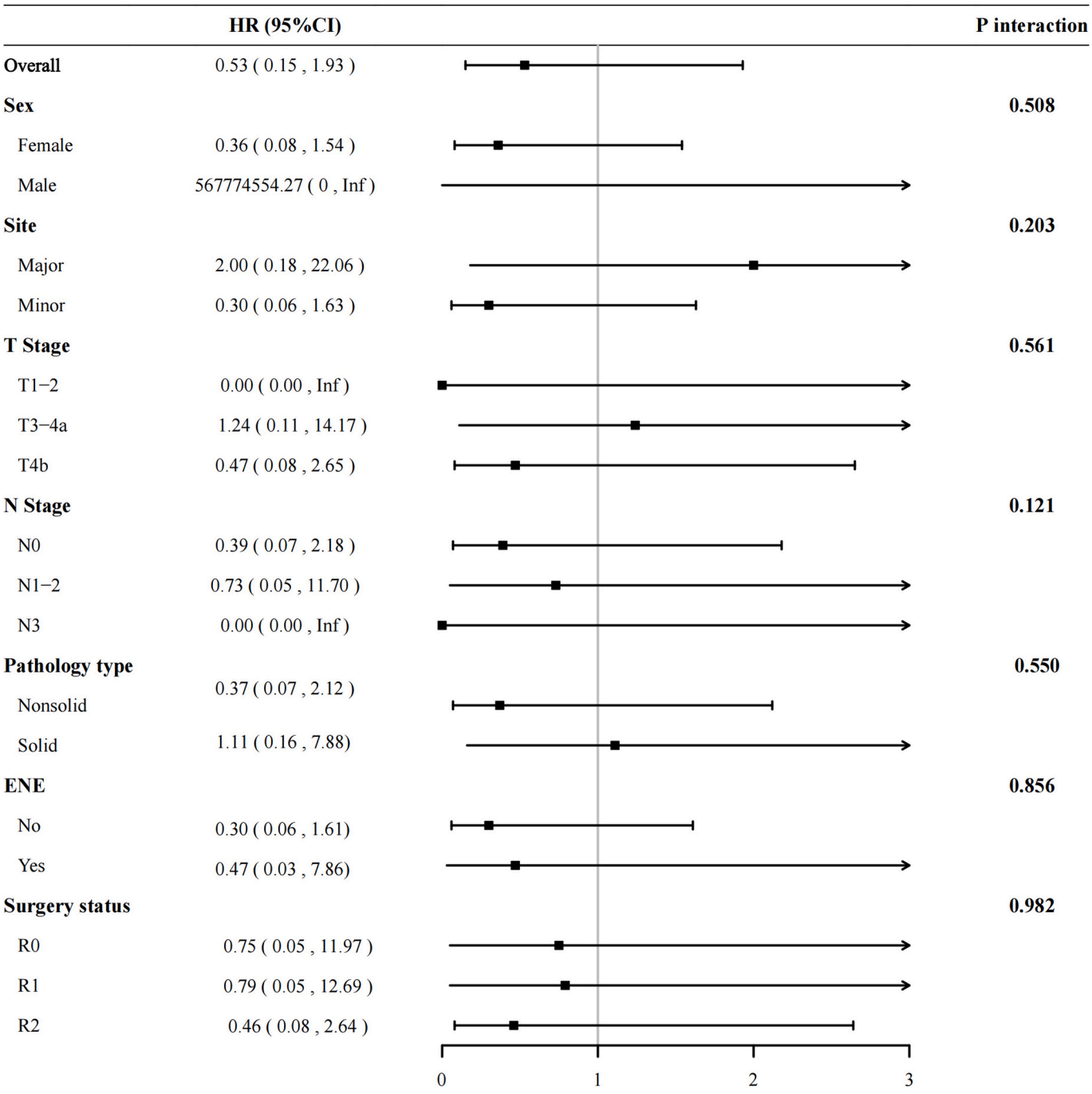

Fig. 2. Forrest plot showed the result of subgroup analysis. Abbreviations: ENE, extranodal extension.

volumetric modulated arc therapy (VMAT) were employed in two studies by Hsieh et al.[8 16], while in the current study, IMRT was uniformly employed, ensuring precise dose coverage, particularly to critical structures like nerve pathways. Additionally, variations in target volume delineation standards could impact treatment efficacy. While previous studies lacked a unified standard for target volume delineation, the current study adhered to a predefined protocol, potentially leading to more consistent and effective treatment delivery. Moreover, various chemotherapy regimens, such as the use of cisplatin-based single-agent or combined regimens in previous studies [8 16] compared to a unified TP regimen in the current study, could also contribute to disparate findings. Despite favorable local control rates observed in Heish et al [16], further validation through randomized controlled trials is warranted to definitively establish the added benefit of CCRT in the postoperative management of ACC.

The study indeed presents several limitations that warrant consideration. Firstly, the relatively short follow-up time may restrict the ability to fully assess survival outcomes, particularly in the context of ACC, characterized by its indolent yet relentless growth pattern. Given the slow progression of ACC, longer follow-up periods are essential to capture meaningful data on survival endpoints. Secondly, the nedaplatin regimen may have influenced the observed differences in outcomes. Given that nedaplatin has demonstrated non-inferior efficacy in treating various tumors [28–30], and considering that the regimen also included docetaxel, we believe the impact of the chemotherapy is likely to be minimal. Thirdly, the limited number of patients included in the study poses challenges in conducting subgroup analyses to further elucidate the role of CCRT in specific patient subsets, such as patients with solid

type, ENE, T4b, R2 resection, etc. The solid subtype consistently harbors notch mutations and shows a high degree of overlap with ACC-I, which is associated with a distinct poor prognosis and need treatment escalation [31,32]. The rarity of ACC contributes to the difficulty in recruiting large cohorts for research purposes, thereby limiting the statistical power and generalizability of findings. Addressing these limitations necessitates collaborative efforts across multiple institutions to accrue larger patient cohorts with extended follow-up periods. Additionally, innovative study designs, such as multi-institutional collaborations and prospective data collection, may help overcome the challenges posed by the rarity of ACC and facilitate comprehensive evaluation of treatment outcomes.

Conclusion

In summary, the findings of our study suggest that the addition of concurrent chemotherapy to postoperative IMRT did not confer significant advantages in terms of LRRFS, DMFS, DFS or OS in high-risk head and neck ACC patients. As such, the incorporation of CCRT into the treatment regimen for postoperative ACC patients should be approached with caution outside the context of a clinical trial. The results underscore the need for further investigation and validation through ongoing and future studies, such as the RTOG 1008 and GORTEC SANTAL trials.

CRediT authorship contribution statement

Shengjin Dou: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xin Wang:** Writing – review & editing, Resources, Investigation, Data curation. **Ying Xiao:** Writing – review & editing, Resources, Investigation. **Lin Zhang:** Writing – review & editing, Resources. **Wen Jiang:** Writing – review & editing, Resources. **Lulu Ye:** Writing – review & editing, Resources. **Yu Wang:** Writing – review & editing, Resources. **Yining He:** Writing – original draft, Visualization, Methodology, Formal analysis, Software. **Shengwen Liu:** Writing – review & editing, Resources. **Rongrong Li:** Writing – review & editing, Validation, Supervision, Resources, Methodology. **Guopei Zhu:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

Funding

This work is partially supported by the Adenoid Cystic Carcinoma Research Foundation

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used chat8 in order to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of Competing Interest

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.

Acknowledgements

We would like to express gratitude to all those colleagues who contributed to this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2025.100945.

References

[1] Geiger JL, Ismaila N, Beadle B, Caudell JJ, Chau N, Deschler D, et al. Management of Salivary Gland Malignancy: ASCO Guideline. J Clin Oncol 2021;39:1909–41.
[2] Atallah S, Casiraghi O, Fakhry N, Wassef M, Uro-Coste E, Espitalier F, et al. A prospective multicentre REFCOR study of 470 cases of head and neck Adenoid cystic carcinoma: epidemiology and prognostic factors. Eur J Cancer 2020;130:241–9.
[3] Gao RW, Routman DM, Harmsen WS, Ebrahimi S, Foote RL, Ma DJ, et al. Adenoid cystic carcinoma of the head and neck: Patterns of recurrence and implications for intensity-modulated radiotherapy. Head Neck 2023;45:187–96.
[4] Shimoda H, Teshima M, Murase T, Nagao T, Kusafuka K, Nakaguro M, et al. Prognostic scores for patients with salivary adenoid cystic carcinoma without lymph node metastasis. Oral Oncol 2023;145:106491.
[5] Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 2005;27:843–50.
[6] Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937–44.
[7] Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–52.
[8] Hsieh CE, Lin CY, Lee LY, Yang LY, Wang CC, Wang HM, et al. Adding concurrent chemotherapy to postoperative radiotherapy improves locoregional control but Not overall survival in patients with salivary gland adenoid cystic carcinoma-a propensity score matched study. Radiat Oncol 2016;11:47.
[9] Joshi NP, Broughman JR. Postoperative Management of Salivary Gland Tumors. Curr Treat Options Oncol 2021;22:23.
[10] Coca-Pelaz A, Rodrigo JP, Bradley PJ, Vander Poorten V, Triantafyllou A, Hunt JL, et al. Adenoid cystic carcinoma of the head and neck–An update. Oral Oncol 2015;51:652–61.
[11] Cheraghlou S, Kuo P, Mehra S, Agogo GO, Bhatia A, Husain ZA, et al. Adjuvant therapy in major salivary gland cancers: Analysis of 8580 patients in the National Cancer Database. Head Neck 2018;40:1343–55.
[12] Fang Y, Peng Z, Wang Y, Gao K, Liu Y, Fan R, et al. Current opinions on diagnosis and treatment of adenoid cystic carcinoma. Oral Oncol 2022;130:105945.
[13] Nightingale J, Lum B, Ladwa R, Simpson F, Panizza B. Adenoid cystic carcinoma: a review of clinical features, treatment targets and advances in improving the immune response to monoclonal antibody therapy. Biochim Biophys Acta Rev Cancer 2021;1875:188523.
[14] Liang J, Hu Z, Zhan C, Wang Q. Using Propensity Score Matching to Balance the Baseline Characteristics. J Thorac Oncol 2021;16:e45–6.
[15] Wu Z, Wang W, Zhang K, Fan M, Lin R. The impact of surgery and survival prediction in patients with gastroenteropancreatic neuroendocrine tumors: a population-based cohort study. Int J Surg 2023;109:1629–38.
[16] Hsieh RC, Chou YC, Hung CY, Lee LY, Venkatesulu BP, Huang SF, et al. A multicenter retrospective analysis of patients with salivary gland carcinoma treated with postoperative radiotherapy alone or chemoradiotherapy. Radiother Oncol 2023;188:109891.
[17] Cerda T, Sun XS, Vignot S, Marcy PY, Baujat B, Baglin AC, et al. A rationale for chemoradiation (vs radiotherapy) in salivary gland cancers? On behalf of the REFCOR (French rare head and neck cancer network). Crit Rev Oncol Hematol 2014;91:142–58.
[18] Gebhardt BJ, Ohr JP, Ferris RL, Duvvuri U, Kim S, Johnson JT, et al. Concurrent Chemoradiotherapy in the Adjuvant Treatment of High-risk Primary Salivary Gland Malignancies. Am J Clin Oncol 2018;41:888–93.
[19] Schoenfeld JD, Sher DJ, Norris Jr CM, Haddad RI, Posner MR, Balboni TA, et al. Salivary gland tumors treated with adjuvant intensity-modulated radiotherapy with or without concurrent chemotherapy. Int J Radiat Oncol Biol Phys 2012;82:308–14.
[20] Rosenberg L, Weissler M, Hayes DN, Shockley W, Zanation A, Rosenman J, et al. Concurrent chemoradiotherapy for locoregionally advanced salivary gland malignancies. Head Neck 2012;34:872–6.
[21] Aro K, Ho AS, Luu M, Kim S, Tighiouart M, Yoshida EJ, et al. Survival Impact of Adjuvant Therapy in Salivary Gland Cancers following Resection and Neck Dissection. Otolaryngology–head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck. Surgery 2019;160:1048–57.
[22] Mifsud MJ, Tanvetyanon T, McCaffrey JC, Otto KJ, Padhya TA, Kish J, et al. Adjuvant radiotherapy versus concurrent chemoradiotherapy for the management of high-risk salivary gland carcinomas. Head Neck 2016;38:1628–33.
[23] Amini A, Waxweiler TV, Brower JV, Jones BL, McDermott JD, Raben D, et al. Association of Adjuvant Chemoradiotherapy vs Radiotherapy Alone With Survival in Patients With Resected Major Salivary Gland Carcinoma: Data From the National Cancer Data Base. JAMA Otolaryngol Head Neck Surg 2016;142:1100–10.
[24] Tanvetyanon T, Qin D, Padhya T, McCaffrey J, Zhu W, Boulware D, et al. Outcomes of postoperative concurrent chemoradiotherapy for locally advanced major

salivary gland carcinoma. Archives of Otolaryngology–head & Neck Surgery 2009; 135:687–92.
[25] van Herpen C, Vander Poorten V, Skalova A, Terhaard C, Maroldi R, van Engen A, et al. Salivary gland cancer: ESMO-European Reference Network on Rare Adult Solid Cancers (EURACAN) Clinical Practice Guideline for diagnosis, treatment and follow-up. ESMO Open 2022;7:100602.
[26] Bakst RL, Glastonbury CM, Parvathaneni U, Katabi N, Hu KS, Yom SS. Perineural Invasion and Perineural Tumor Spread in Head and Neck Cancer. International Journal of Radiation Oncology*biology*physics 2019;103:1109–24.
[27] Xu P, Wang S, Luo Y, Yin J, Belkacemi Y, Lu S, et al. Outcome of Adenoid Cystic Carcinoma of Head and Neck After Postoperative Intensity Modulation Radiotherapy: A Single Institution Study. Cancer Manag Res 2021;13:2411–7.
[28] Tang LQ, Chen DP, Guo L, Mo HY, Huang Y, Guo SS, et al. Concurrent chemoradiotherapy with nedaplatin versus cisplatin in stage II-IVB nasopharyngeal carcinoma: an open-label, non-inferiority, randomised phase 3 trial. Lancet Oncol 2018;19:461–73.
[29] Yang X, Ren H, Li Z, Zhang L, Shao Y, Li H, et al. A phase III randomized, controlled trial of nedaplatin versus cisplatin concurrent chemoradiotherapy in patients with cervical cancer. ESMO Open 2022;7:100565.
[30] Shukuya T, Yamanaka T, Seto T, Daga H, Goto K, Saka H, et al. Nedaplatin plus docetaxel versus cisplatin plus docetaxel for advanced or relapsed squamous cell carcinoma of the lung (WJOG5208L): a randomised, open-label, phase 3 trial. Lancet Oncol 2015;16:1630–8.
[31] Ferrarotto R, Mitani Y, McGrail DJ, Li K, Karpinets TV, Bell D, et al. Proteogenomic Analysis of Salivary Adenoid Cystic Carcinomas Defines Molecular Subtypes and Identifies Therapeutic Targets. Clin Cancer Res 2021;27:852–64.
[32] Ferrarotto R, Mitani Y, Diao L, Guijarro I, Wang J, Zweidler-McKay P, et al. Activating NOTCH1 Mutations Define a Distinct Subgroup of Patients With Adenoid Cystic Carcinoma Who Have Poor Prognosis, Propensity to Bone and Liver Metastasis, and Potential Responsiveness to Notch1 Inhibitors. J Clin Oncol 2017; 35:352–60.