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Results of a combination treatment with intensity modulated radiotherapy and active raster-scanning carbon ion boost for adenoid cystic carcinoma of the minor salivary glands of the nasopharynx

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A R T I C L E I N F O

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A B S T R A C T

Objectives: We aimed to present the first clinical results for adenoid cystic carcinoma (ACC) of the nasopharynx after primary radiotherapy (RT) with the focus on local control (LC) and patterns of recurrence.
Materials and methods: We retrospectively analyzed 59 patients with ACC of the nasopharynx, who were treated with bimodal radiotherapy (RT) consisting of intensity modulated radiotherapy and carbon ion boost at the Heidelberg Ion-Beam Therapy Center between 2009 and 2018. The patients had predominantly inoperable (n = 42, 72%) or incompletely resected (n = 17, 29%) tumors. Kaplan-Meier estimates and the log-rank (Mantel-Cox) test were used for univariate and multivariate analyses.
Results: The median follow-up was 32 months. At last follow-up, 67% of the patients were still alive (n = 39/58), of whom 74% were free of progression (n = 29/39). The 2-year LC, distant progression-free survival (DPFS) and overall survival (OS) were 83%, 81%, 87% and the estimated 5-year LC, DPFS and OS were 49%, 54%, 69%, respectively. LC was significantly inferior in patients with large tumor volumes (gross tumor volume, GTV > 100 cc, $p = 0.020$) and T4 tumors ($p = 0.021$). The majority of the recurrences occurred at the margin, where critical structures were spared (n = 11/19, 58%). Overall, grade 3 toxicity was moderate with 12% acute and 8% late side effects.
Conclusion: Bimodal RT including active raster-scanning carbon ion boost for nasopharyngeal ACC resulted in adequate LC and OS rates with moderate toxicity. T4 stage, large tumor volume and the necessary dose sparing in critical structures, i.e. optic nerves, brain stem and orbit, negatively affected LC.

Background

Tumors of adenoid cystic histology (ACC) are mostly diagnosed in the major salivary glands of the head and neck, but can also arise from the minor salivary glands of the larynx, hypopharynx, oropharynx, lips, tonsils, oral cavity, nasopharynx and paranasal sinuses. Overall, ACC accounts for 25–30% of all malignant salivary gland tumors and the incidence predominantly depends on the location of the tumor [1–4].

While malignant salivary gland tumors of other histologies, e.g. early-stage, low-grade mucoepidermoid carcinomas, acinic cell carcinomas and adenocarcinomas, have an adequate local control (LC) after surgery alone with 10-year LC rates of up to 85%, complete resection of

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ACC is often impossible due its locally infiltrative character [5]. Therefore, postoperative radiotherapy (RT) is considered in the majority of ACC patients and should also be recommended for advanced stages (T3/4), lymphovascular spread (L1), perineural spread (Pn), incomplete resection margins (R+) and high-grade (G3) tumors [6–8]. In several studies, no benefit in the LC and survival could be shown for patients with ACC of the head and neck, who received postoperative RT for grossly incompletely resected tumors (R2), when compared with patients, who underwent primary RT [9]. Thus, patients with inoperable ACCs should be treated with primary RT in order to minimize treatment-related morbidity [7,10–13].

Modern RT techniques, i.e. intensity modulated radiotherapy (IMRT), can lead to a notable decrease of acute and late treatment-related side effects. Especially in the area of the nasopharynx, less toxicity could be achieved with IMRT compared to two- and three-dimensional conformal RT [14–17]. Nevertheless, considerable treatment-related side effects are still reported and toxicity after RT remains challenging due to the proximity of nasopharyngeal tumors to surrounding critical structures (brain stem, skull base, optic system) [18–25]. Thus, more conformal RT techniques are required to minimize toxicity. Dosimetric comparisons between IMRT and proton beam radiotherapy have shown promising results for nasopharyngeal tumors, but clinical data are still missing [26,27].

Currently, there are few data available on treatment results for nasopharyngeal ACC. In the current study, we aimed to analyze the first patient cohort with ACC of the nasopharynx after bimodal RT with IMRT and active raster-scanning carbon ion radiotherapy (CIRT), which is known for its conformal dose distribution and increased biological effectiveness, with a focus on local control and recurrence patterns.

Methods

Evaluation

We reviewed medical records of fifty-nine consecutive patients with nasopharyngeal ACC, who were treated with IMRT via TomoTherapy® (Accuray, Sunnyvale, California) and carbon ion boost in a bimodal setting at the Heidelberg Ion-Beam Therapy Center (HIT) between 2009 and 2018. Tumors, which infiltrated the paranasal sinuses solely, were classified as paranasal sinus ACCs and were excluded from analysis. Locally advanced tumors infiltrating the paranasal sinuses besides the nasopharynx with a main tumor load in the nasopharynx were classified as T3/T4 nasopharynx ACCs and were included into analysis. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the University Hospital Heidelberg (S-421/2015). All data generated or analysed during the current study are included in this published article. The dataset is available from the corresponding author on reasonable request.

Initial work up included a clinical examination, a magnetic resonance imaging (MRI) scan of the primary tumor and a computed tomography (CT) scan of the chest. Patients were followed-up every three months for the first two years after RT, every six months during the next two years and then, once a year with a contrast-enhanced MRI and an annually repeated CT of the chest at our institution or at the referring center. Treatment response according to the current Response Evaluation Criteria in Solid Tumors (RECIST) was assessed during each follow-up and was based on the performed MRI scans and the clinical examinations by an ENT specialist [28]. Toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5. TNM and UICC stage were adjusted to the eight edition of the tumor, node, metastasis (TNM) staging system of the Union International Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) [29]. T and N stage were evaluated with an initial MRI scan at the first diagnosis and N stage was clarified with an additional sonography of the bilateral cervical nodal levels.

For statistical analysis, IBM SPSS Statistics version 24 (International Business Machines Corporation, Armonk, New York, USA) was used. Time-to-event data were either assessed from the first diagnosis (overall survival (OS), distant progression-free survival (DPFS)) or the first day of RT (local control (LC)) to the last follow-up information, death or time of event (local or distant failure) by using the Kaplan-Meier method. LC was defined as the absence of tumor growth based on the best response after RT. Prognostic factors for survival outcome were determined using the log-rank test for univariate and the cox-regression model for multivariate analyses (2-tailed) with a significance level of $\alpha < 0.05$.

Patient characteristics

Patients, who received re-RT, were excluded from the analysis. Overall, fifty-nine patients (73% females) with a median age of 50 years (range 19–77 years) at treatment start could be identified, who received bimodal RT for an ACC of the nasopharynx. Fifty-six patients were available for survival analysis due to missing data of three patients (loss to follow-up). At the first diagnosis, the majority of patients showed locally advanced tumors with skull base infiltration (T4, n = 48, 81%). Overall, 72% of the patients received primary RT for inoperable tumors (n = 42) and 29% postoperatively (n = 17), while R0 resection was not possible in any patient, R1 resection in only 5% (n = 3) and Rx resection in 7% of the patients (n = 4). Detailed patients' characteristics are shown in Table 1.

Treatment features

Patients were immobilized with individual performed thermoplastic head masks with shoulder fixation. A contrast-enhanced CT in 3-mm slices and a MRI scan was matched with a natively performed planning CT for better tumor demarcation. CTV1 including the macroscopic tumor or the tumor bed after surgery and CTV2 including CTV1, the operating area and the prophylactic cervical lymph drainage were outlined on the native CT scan. Unilateral cervical nodal levels II-III in case of N0 (n = 27, 46%), bilateral cervical nodal levels II-III in case of N0 and midline infiltrating tumors (n = 28, 47%) and cervical nodal levels II-IV in case of N+ (n = 4, 7%) were included into the CTV2. CTV1 received ≥ 95% (C12 boost) and CTV2 ≥ 90% (IMRT base plan) of the prescribed isodose. All patients received bimodal RT with IMRT at 50 Gy to 56 Gy in 2 Gy fractions (5 fractions/wk) and CIRT boost at 18 Gy (relative biological effectiveness, RBE) to 21 Gy (RBE) in 3 Gy (RBE) fractions (5–6 fractions/wk). The cumulative median total dose was 74 Gy (RBE) (range 72–74 Gy (RBE)), which corresponded a median EQD2 (equivalent dose in 2 Gy fractions) of 80 Gy (range 76.5–80 Gy). Dose constraints for the spinal cord, brain stem, temporal lobe, eyes and optic nerves were defined according the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) data [30,31]. Detailed treatment characteristics are depicted in Table 1. A bimodal treatment plan for a patient with a T4N0 skull base infiltrating ACC of the nasopharynx is shown in Fig. 1.

Results

Survival analysis

The median follow-up was 32 months (range 7–106 months). At last follow-up, 67% of the patients were still alive (n = 39/58, one patient was lost of follow-up for survival analysis), of whom 74% were free of progression (n = 29/39). Overall, progressive disease was seen in 45% of the patients (n = 25/56, 3 patients were lost to follow-up for statistical analysis, Fig. 2). Local failure occurred after a median time period of 28 months (range 7–74 months) after RT and distant failure after a median time period of 36 months (range 8–152 months) after the first diagnosis. The corresponding 2-year LC, DPFS and OS were 83%,

Table 1
Patient, disease, and treatment characteristics.

Characteristic	Overall, *n = 59* No. (%)
Median age	50 years (19–77 years)
Gender	
Male	16 (27)
Female	43 (73)
Karnofsky performance score in %	
100	17 (29)
90	24 (41)
80	12 (20)
70	3 (5)
60	3 (5)
Histology	
Solid	14 (24)
Tubulous	6 (10)
Cribriform	17 (29)
Mixed	9 (15)
Unknown	13 (22)
TNM stage	
T1	2 (3)
T2	1 (2)
T3	5 (8)
T4	48 (81)
Tx	3 (5)
N0	52 (88)
N1	1 (2)
N2b	2 (3)
N2c	1 (2)
Nx	3 (5)
M0	59 (100)
Definitive RT	42 (72)
Postoperative RT	17 (29)
Rx	4 (7)
R1	3 (5)
R2	10 (17)
Therapy regimes	
50 Gy IMRT + 24 Gy (RBE) C12	40 (68)
54 Gy IMRT + 18 Gy (RBE) C12	10 (17)
56 Gy IMRT + 18 Gy (RBE) C12	9 (15)
Median total dose	74 Gy (RBE) (72–74 Gy (RBE))
Median GTV	87 cc (13–158 cc)
Median CTV1	131 cc (50–321 cc)
Median CTV2	329 cc (121–754 cc)
Concomitant immunotherapy	3 (5)

Abbreviations: GTV = gross tumor volume, CTV = clinical target volume, C12 = carbon ions, IMRT = intensity modulated radiotherapy, RT = radiotherapy, TNM = tumor, nodal, metastasis stage, RBE = relative biological effectiveness.

81%, 87% and the estimated 5-year LC, DPFS and OS were 49%, 54%, 69%, respectively (Fig. 3). Distant metastases involved the lung in 77% (n = 10/13), while polytopic metastases occurred in 38% of the patients with metastases (n = 5/13). Patients with distant metastases predominantly received a palliative chemotherapy with CAP (cyclophosphamide, adriamycin, cisplatin, n = 4/13, 31%) or best supportive care (n = 7/13, 54%). For local relapse, re-RT was conducted in 11/19 patients (58%), surgery in 2/19 patients (11%), best supportive care in 3/19 patients (16%) and palliative CAP chemotherapy in 3/19 patients (16%). We identified progressive disease ($p = 0.020$, HR 5.03, 95%-CI 1.11–22.87) as an independent negative prognostic factor for OS (Fig. 4). While local relapse did not influence OS ($p = 0.514$, HR 1.44, 95%-CI 0.47–4.40), distant relapse showed a non-statistically significant impact on OS ($p = 0.059$, HR 2.47, 95%-CI 0.90–6.78). Nevertheless, subgroup analyses showed a considerable OS benefit for patients, who received re-RT for local recurrence, compared to patients, who did not ($p = 0.019$, HR 5.65, 95%-CI 0.00–10.89). Further, we identified a higher tumor volume (GTV > 100 cc vs. GTV ≤ 100 cc) as a significant risk factor for decreased OS ($p = 0.018$, HR 3.96, 95%-CI 13.87), LC ($p = 0.020$, HR 3.16, 95%-CI 1.12–8.97) and DPFS ($p = 0.023$, HR 2.46, 95%-CI 0.96–6.31) as well as T4 stage (with skull base infiltration) vs. T1-3 stage ($p = 0.021$, HR 8.63, 95%-CI 1.06–70.20) for LC solely (Figs. 5 and 6). UICC stage, Karnofsky performance status (KPS), histological subtype (solid vs. non-solid) and treatment setting (definitive RT vs. postoperative RT) had no significant impact on the survival outcome.

Patterns of recurrence

An analysis of the recurrence patterns showed, that the majority of local recurrences occurred close to critical organs, i.e. orbit, optic system, brain stem and temporal lobe (n = 11/18, 58%), while 42% of the patients with local recurrence showed an in-field recurrence (n = 8/19). 73% of the patients with local relapse, who received re-RT locally, were still alive at last follow-up (n = 8/11). Patients, who received another therapy than re-RT for recurrence, died within a median time of 32 months (range 10–70 months). Fig. 1 shows a combined radiation treatment plan with CIRT (a) and IMRT (b) for a female patient, who developed a local relapse into the brain stem, where the dose was initially spared. In Fig. 7, the initial MRI scan at the first diagnosis (1a-c), the MRI scan before RT (2a-d) and the MRI scan at recurrence (3a-d) are depicted.

Toxicity

The RT was tolerated well without any grade 4 and 5 side effects. Overall, grade 3 acute toxicity was observed in 12% (n = 7/59) and grade 3 late toxicity in 7% (n = 4/56) of the patients. The most frequently observed grade 3 acute side effects were mucositis, dysphagia and odynophagia (each n = 4/59, 7%). 3 months after RT, the majority of these symptoms resolved. 15% of the patients were dependent on a gastric tube during RT as a consequence of acute dysphagia, odynophagia and appetite loss (n = 9/59). 3–6 months after completion of the RT, no patient was further dependent on a gastric tube. An overview of the acute and chronic toxicity is shown in Table 2. 3 Patients had a mild affection of the abducent nerve (cranial nerve (CN) IV) 6 months, 14 months and > 24 months post RT (n = 3/56, 5%), 2 patients of the hypoglossal nerve (CN XII) 12 months and > 24 months post RT (n = 2/56, 4%), one patient of the facial nerve (CN VII) 3 months post RT (n = 1/56, 2%) and two patients of the trigeminal nerve (CN V) 3 months and 12 months after RT (n = 2/56, 4%; overall n = 8/56, 14%). In 3 cases, the symptoms disappeared within 8 months (5%) and in one case within 12 months (2%). One patient developed a grade 3 osteoradionecrosis of the maxillary bone 3 months after the completion of RT and received surgical treatment (2%). An asymptomatic temporal lobe reaction was seen in 3 patients and a temporal lobe reaction with mild symptoms was observed in 2 patients (headache, dizziness, nausea) 18–36 months after RT (8%). In only one patient with a grade 2 temporal lobe necrosis, a cortisone therapy was obligatory due to dizziness (2%). A hearing aid was required by 2 patients for severe hearing impairment due to tympanic effusion 6 months and 12 months after RT (4%) and hypopituitarism grade 3 occurred in only one patient 30 months after RT (2%), all in patients with large RT volumes (CTV2 > 250 cc) and tumors with skull base infiltration.

Discussion

For the current patient collective with predominantly locally advanced high-risk ACCs of the nasopharynx, a 2-year LC, DPFS and OS of 83%, 81%, 87% and a 5-year LC, DPFS and OS of 49%, 54%, 69% were achieved with bimodal treatment including CIRT despite unfavorable patient characteristics (T4 stage, n = 48/59, 81%), respectively. Especially T1-3 stage tumors profited from bimodal RT resulting in an excellent 5-year LC of 68% according to the Kaplan-Meier estimates ($p = 0.021$). Results for T4 cases were felt to be acceptable, with a 5-year LC of 35%, given the typical skull base infiltration and proximity to critical structures. Additionally, we found gross tumor volume

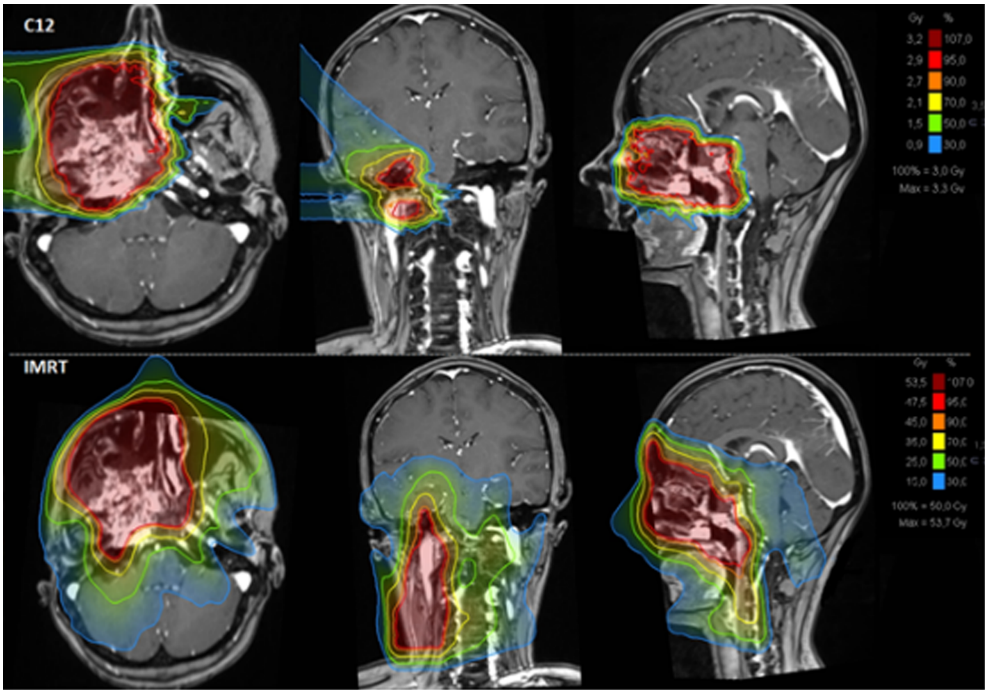

Fig. 1. Bimodal treatment plan with active raster-scanning carbon ion radiotherapy (CIRT) and intensity modulated radiotherapy (IMRT) of a patient with nasopharyngeal ACC. CIRT was applied with two beams up to 24 Gy (RBE) in 3 Gy (RBE) fractions. From left to right, axial dose distribution, coronal dose distribution and sagittal dose distribution are depicted.

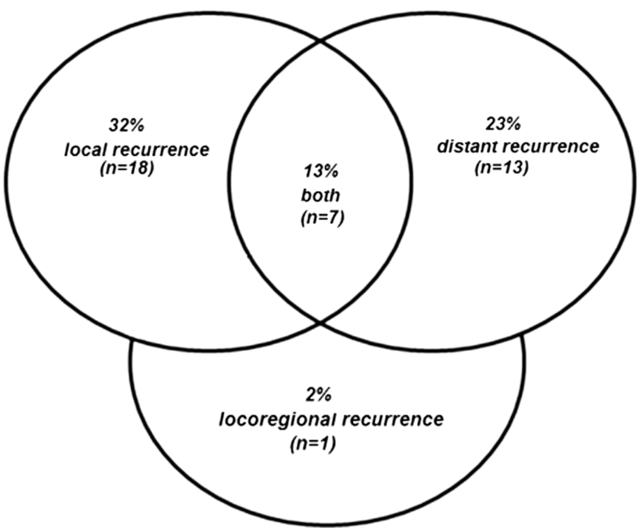

Fig. 2. Venn-diagram illustrating the distribution of local recurrence (32%), distant recurrence (23%) and locoregional recurrence (2%) for patients with nasopharyngeal ACC irradiated with bimodal RT.

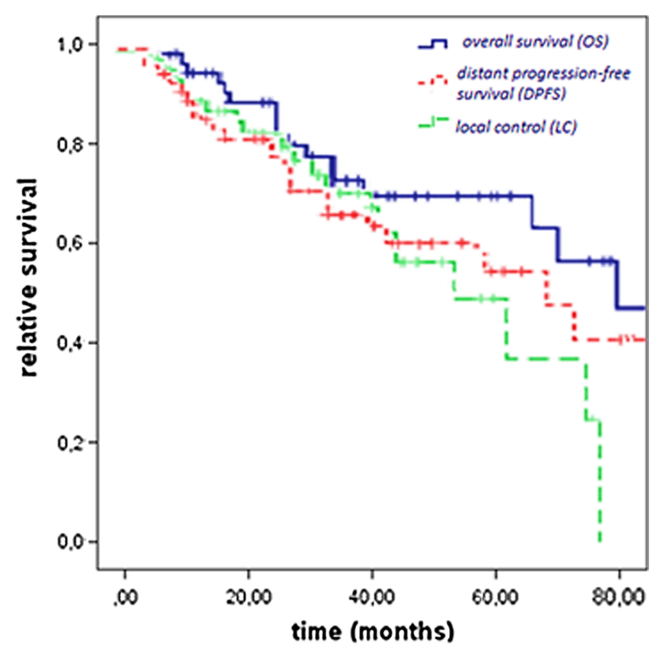

Fig. 3. Kaplan-Meier estimates for LC, DPFS and OS for patients with nasopharyngeal ACC with a median LC of 28 months (range 7–76 months), a median DPFS of 34 months (range 8–106) and a median OS of 34 months (8–106) months).

(GTV > 100c, *p = 0.020*) to be a significant prognostic factor for LC, while recurrences predominantly occurred at the margin, where critical structures were spared (n = 11, 58%). As known, ACCs are relatively radio resistant tumors and typically show high local relapse rates, especially due to perineural spread. Overall, toxicity was moderate with 12% acute and 8% late grade 3 side effects.

Several dosimetric comparisons between IMRT and alternative RT techniques, i.e. proton beam RT, applied in nasopharyngeal tumors have shown promising results, but clinical results on CIRT are lacking [26,27]. Especially for nasopharyngeal ACC, no clinical data are available. Recent experiences from the Gesellschaft für Schwerionenforschung (GSI), Helmholtz Center for Heavy Ion Research (Darmstadt, Germany) proved feasibility and safety of CIRT, especially in the treatment of skull base tumors [32,33]. Further treatment results at the Heidelberg Ion-Beam Therapy Center (HIT) showed adequate local control and moderate toxicity using the physiological and biological advantages of CIRT in hypoxic radio resistant tumors of the head and neck region [9,34–36]. For malignant salivary gland tumors, Jensen et al. found a superior 3-year local control rate of 82% and OS rate of 78% with less toxicity in a prospective phase II trial (COSMIC trial) compared to photon RT (overall 9% of the patients had an ACC of the nasopharynx) [7,34,37,38]. Additionally, in accordance with our results, they were able to show that ACC histology was associated with a high local relapse rate and that local relapses occurred generally within several years after treatment, while late recurrences were possible [34,39]. While 5-year LC and OS rates after photon RT alone for head and neck ACC ranges from 25% to 56% and 25% to 78%, superior

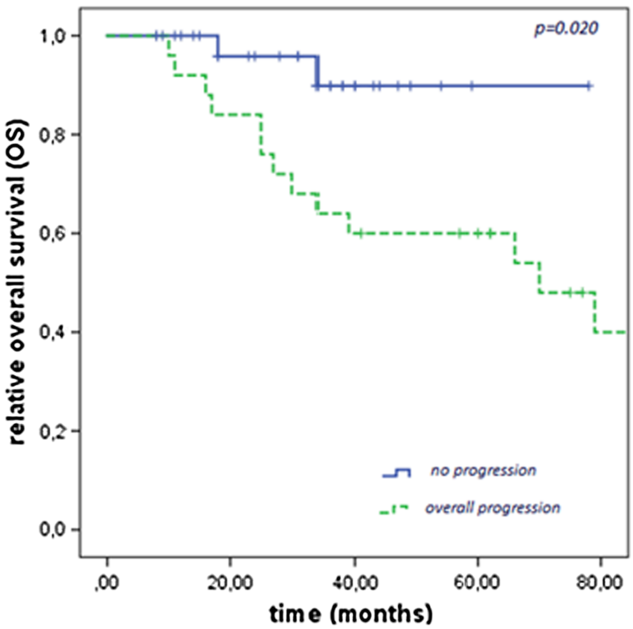

Fig. 4. OS depends significantly on the overall disease progression (including local and distant relapse) ($p = 0.02$). 5-Year OS amounts 60% vs. 91% for patients with progressive disease vs. no progressive disease after RT.

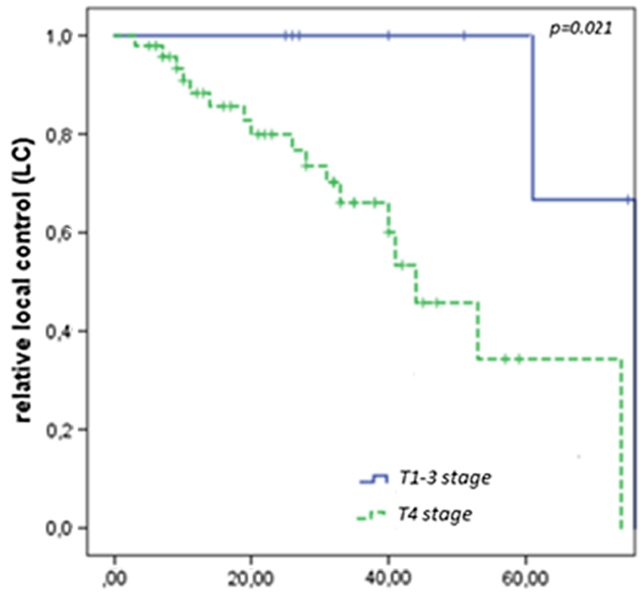

Fig. 6. LC depends significantly on the T stage of the primary tumor with survival benefit for patients, who had tumors with T1-3 stage $p = 0.021$). 5-year LC amounts 65% vs. 34% for these patients in contrast to patients with T4 stage tumors.

5-year LC and OS rates for bimodal treatment with IMRT and CIRT boost, as used in the current study, have been described in the literature [7,40,41]. Jensen et al. showed in a prospective carbon ion pilot project superior outcome for bimodal treatment including IMRT and CIRT vs. IMRT alone for head and neck ACC with a 5-year LC, PFS and OS of 60%, 48%, 77% vs. 40%, 27%, 59% [35]. These findings were strengthened by Japanese data on CIRT alone [42–44]. RT with CIRT alone for head and neck ACC treated at the National Institute of Radiological Sciences (NIRS) achieved a 5-year LC and OS rate of 74% and 72% with a superior 5-year LC and OS of 96% and 92% for T1 to T3 tumors and adequate 5-year LC and OS rates of 71% and 69% for T4 tumors. In accordance to these findings, a retrospective multicenter subanalysis of 289 patients with ACC of the head and neck by the Japan Carbon-Ion Radiation Oncology Study Group (J-CROS, Study 1402 HN) showed a 5-year OS and LC rate of 74% and 68% [45]. In the current analysis as well, we could identify a significant decreased LC for T4 tumors compared to T1 to T3 tumors with a 5-year LC rate of 35% vs. 68%. In comparison to the Japanese data, our patients showed regardless of the T stage a considerably lower LC, possibly due to differing tumor locations. Although some clinical data on the application of CIRT in the head and neck region are available, data of randomized controlled phase-III trials are missing to date. Nevertheless, the current study showed significant higher local relapses, when compared with recent data for ACC of the head and neck treated with the same method in our center as well [9,34,36,42,46,47]. An analysis of the recurrence patterns showed, that the most local relapses occurred at the margin to critical structures, where the treatment dose was spared according to the applied QUANTEC dose constraints, possibly due to the dose compromise in critical organs. These findings could be strengthened by the fact, that skull base infiltration seems to affect local failure significantly with decreased local control rates due to the proximity of these tumors to critical structures, i.e. optic system, orbit, brain stem [48–50]. In accordance to our results, Pommier et al. as well described decreased 5-year disease-free and OS rates of 56% and 77% for skull base ACCs compared to ACC of other locations in the head and neck region [51]. Therefore, treatment decision (dose-escalation for tumor control vs. preservation of organs at risk) remains a therapeutic challenge in these tumors and should be individually discussed with the patients. Nevertheless, 73% of the recurrences were successfully salvaged with re-RT of

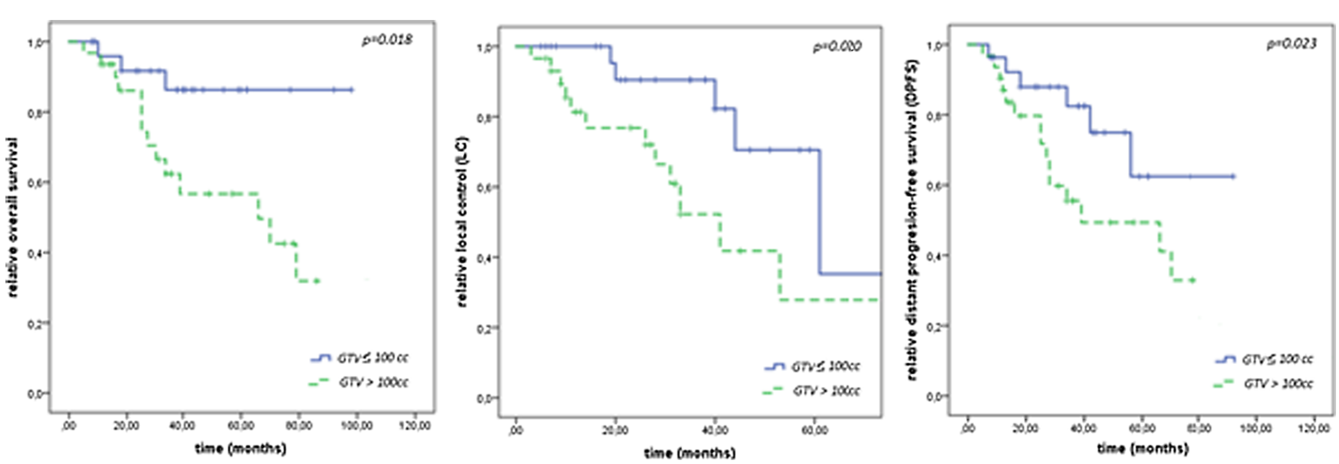

Fig. 5. Kaplan-Meier curves for OS, DPFS and LC in dependence of the gross tumor volume (GTV) showing a significant disadvantage for patient with tumors > 100 cc according LC ($p = 0.020$), DPFS ($p = 0.023$) and OS ($p = 0.018$).

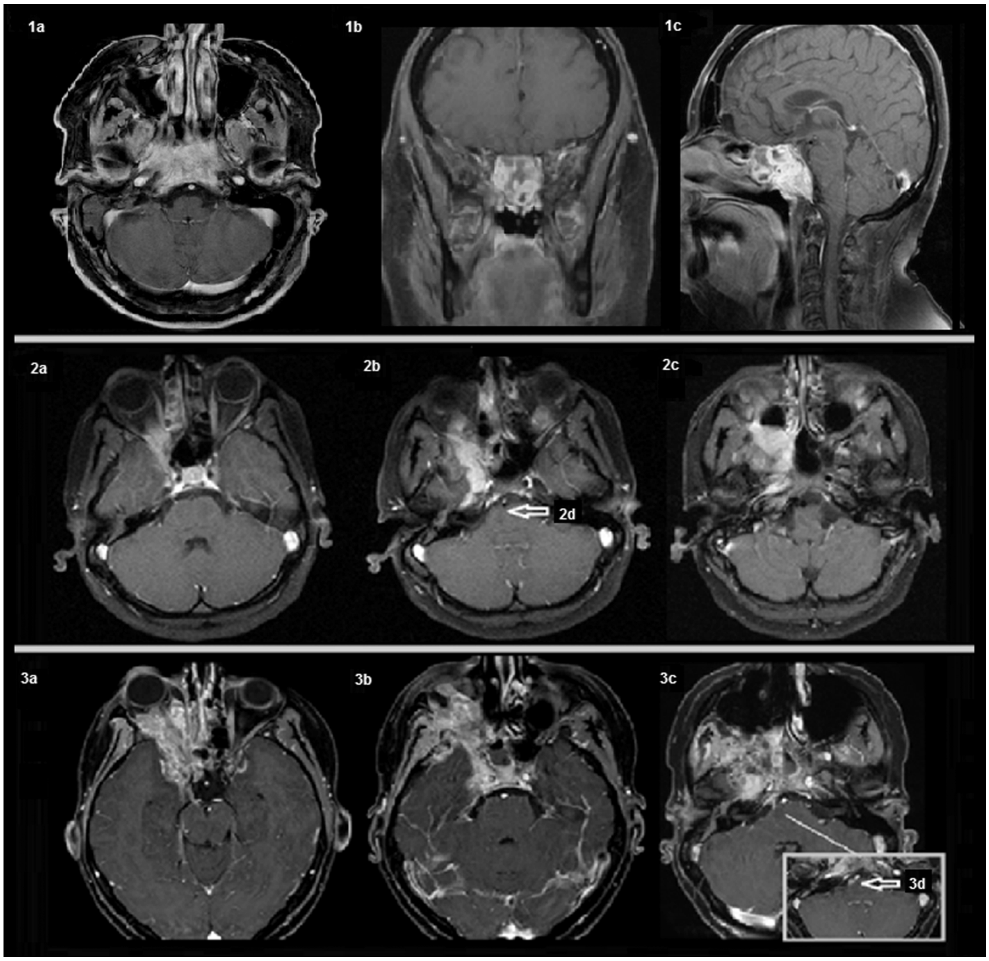

Fig. 7. Initial MRI scan at the first diagnosis (1a–c), MRI scan before RT for treatment planning (2a–d) and MRI scan at recurrence (3a–d) of a patient with a T4 nasopharyngeal ACC, which initially infiltrated the right parapharyngeal space and the right infratemporal fossa. Figs. 2a–d and 3a–d show the MRI slices of the recurrence localization after RT. In the MRI scan at recurrence (3a–d), the recurrent tumor shows intra orbital growth (3a–b) and perineural spread over the right facial nerve towards brain stem (3c/d vs. 2b/d).

51 Gy (RBE) in 3 Gy (RBE) fractions corresponding an EQD2 of 64 Gy (8/11), while dose-escalation remained limited by the organs at risk. Based on these results, we are planning a prospective dose-escalation study for these tumors with CIRT alone (ACCO trial).

As operational approaches are limited in these tumors, alternative neoadjuvant treatment options should be developed to downstage the tumors for better prognosis. All in all, the retrospective character should be taken into account, when interpreting the current results. Additionally, the sample size of the current study, identified within 9 years of experience, was rather small because of the rareness of ACC, especially in the area of the nasopharynx.

Bimodal treatment including CIRT was tolerated well with low acute and late toxicity due to the biological and physical advantages of carbon ions, comparable to prior experiences in skull base infiltrating tumors treated with heavy ions [52]. All late severe side effects occurred in patients with large treatment volumes > 250 cc. Chew et al. showed for tumors close to the skull base, that severe late side effects may occur up to 20 years after RT and, therefore, a longer follow-up time than 32 months in the current study would be necessary to assess late toxicities more clearly [21].

Temporal lobe necrosis, osteoradionecrosis and cranial nerve palsy can be considered as the most serious chronic side effects after RT for skull base infiltrating tumors. Only one patient (2%) developed osteoradionecrosis of the maxillary bone without any severe consequences for the patient. In contrast, skull base osteoradionecrosis, which is already described in a few cases in the literature for CIRT in radio resistant tumors, can be a lethal side effect of RT [23,53]. Thus, Sulaiman et al. reported 15% grade ≥3 late toxicity; osteoradionecrosis of the jaw bone as the most common [45]. Temporal lobe necrosis is predominantly diagnosed within a few years after RT and several authors found a dose-dependence, while irradiated treatment volume additionally seemed to affect the incidence of brain necrosis [54,55]. Schlampp et al. e.g. illustrated, that patients with tumors close to the skull, are more likely to develop temporal lobe necrosis (5% vs. 50%), when higher RT doses were applied on the skull base (68.8 Gy (RBE) vs. 87.3 Gy (RBE)) [54]. In the current analysis, 5 of 56 patients (9%), who received RT up to doses of 80 Gy (EQD2, corresponding 74 Gy (RBE)), developed a blood-brain barrier damage with a T2/flair hyper intensity in the follow-up MRI without any symptoms in three patients (5%) and mild symptoms in two patients (4%). Regarding cranial nerve palsy, we observed a slight affection of the cranial nerves in 8 patients within a median follow-up time of 32 months (14%). Chew et al. reported bulbar palsy with functional loss to occur up to 18 years after photon beam RT in nearly 20% of patients with nasopharyngeal tumors [21]. Kong et al. identified a cranial nerve palsy in 45% of the patients within 20 years after photon RT [56]. Taking these data into account, the rate of cranial nerve palsy identified in the current study may substantially increase with longer follow-up. However, more than 50% of the diagnosed cranial nerve palsies are assessed within the first 24 months after RT [57].

Table 2
Overview of acute and chronic toxicity.

Characteristic	Acute toxicity, *n = 59* No. (%)	Chronic toxicity, *n = 56* No. (%)		
Toxicity overall				
< Grade 3	52 (88)	27 (48)		
= Grade 3	7 (12)	4 (8)		
		3–6 months post RT, *n = 56*	12 months post RT, *n = 48*	> 12 months post RT, *n = 39*
Mucositis				
Grade 1	7 (12)	2 (4)	0	0
Grade 2	23 (39)	0	0	0
Grade 3	4 (7)	0	0	0
Dermatitis				
Grade 1	36 (61)	7 (13)	1 (2)	0
Grade 2	5 (8)	1 (2)	0	0
Grade 3	1 (2)	0	0	0
Dysphagia				
Grade 1	8 (14)	2 (3)	1 (2)	1 (3)
Grade 2	10 (17)	1 (2)	0	0
Grade 3	4 (7)	0	0	0
Odynophagia				
Grade 1	5 (8)	3 (5)	0	0
Grade 2	13 (22)	0	0	0
Grade 3	2 (3)	0	0	0
Hyposmia				
Grade 1	5 (8)	1 (2)	2 (4)	1 (3)
Grade 2	9 (15)	3 (5)	2 (4)	0
Xerostomia				
Grade 1	13 (22)	16 (29)	18 (38)	9 (24)
Grade 2	16 (27)	12 (21)	6 (13)	0
Lockjaw				
Grade 1	13 (22)	3 (5)	7 (15)	4 (10)
Grade 2	0	2 (4)	2 (4)	1 (3)
Grade 3	1 (2)	1 (2)	2 (4)	1 (3)
Fatigue	5 (8)	5 (9)	2 (4)	1 (3)
Grade 1	6 (11)	2 (5)	4 (8)	1 (3)
Grade 2				
Gastric tube dependence	9 (15)	0	0	0
Keratoconjunctivitis sicca				
Grade 1	8 (14)	3 (5)	3 (6)	2 (5)
Grade 2	4 (7)	2 (4)	0	0
Tympanic effusion				
Grade 1	11 (19)	10 (18)	7 (15)	6 (11)
Grade 2	6 (10)	5 (9)	4 (2)	2 (5)
Grade 3	0	1 (2)	1 (2)	0
Neuropathic pain				
Grade 1	4 (7)	3 (5)	3 (6)	3 (8)
Grade 2	3 (5)	1 (2)	1 (2)	1 (2)
Cranial nerves affection				
Grade 1	0	3 (5)	3 (6)	2 (5)
Hypopituitarism				
Grade 1	0	0	0	0
Grade 2	0	0	0	0
Grade 3				1 (3)
Osteoradionecrosis				
Grade 1	0	0	0	0
Grade 2	0	0	0	0
Grade 3	0	1 (2)	0	0
Temporal lobe reaction				
Grade 1	0	0	0	3 (5)
Grade 2	0	0	0	2 (5)

Abbreviation: RT = radiotherapy.

In conclusion, RT with IMRT and CIRT appear to be a feasible treatment method for nasopharyngeal ACC with adequate survival results and moderate toxicity, despite a negative patient selection, high RT doses and large RT volumes. Although we could identify excellent LC in T1 to T3 ACCs, LC for gross T4 tumors remains challenging as a consequence of dose limitations next to adjacent critical structures. Nevertheless, due to limitations of the current study, i.e. its retrospective character and the small patient number, the current results should be considered critically.

Conclusion

Bimodal RT with IMRT and raster-scanning CIRT is a feasible treatment method for nasopharyngeal ACC with excellent survival results for T1 to T3 tumors and moderate toxicity despite the negative patient selection, high RT doses and large RT volumes applied in the current study. Nevertheless, local control in T4 stage tumors remains challenging due to the proximity of spared critical structures.

Ethics approval and consent to participate

The final protocol was approved by the ethics committee of the University of Heidelberg, Germany (S-421/2015).

Consent for publication

Not applicable.

Availability of data and material

All data generated or analysed during the current study are included in this published article. The dataset is available from the corresponding author on reasonable request.

Conflict of interests

The authors declare that they have no competing interests.

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CRediT authorship contribution statement

Sati Akbaba: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Dina Ahmed:** Writing - review & editing. **Kristin Lang:** Writing - review & editing. **Thomas Held:** Writing - review & editing. **Matthias Mattke:** Writing - review & editing. **Juliane Hoerner-Rieber:** Writing - review & editing. **Klaus Herfarth:** Writing - review & editing, Supervision. **Stefan Rieken:** Writing - review & editing, Supervision. **Peter Plinkert:** Writing - review & editing. **Juergen Debus:** Writing - review & editing, Supervision. **Sebastian Adeberg:** Conceptualization, Methodology, Writing - review & editing, Supervision.

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