Clinical outcomes of head and neck adenoid cystic carcinoma patients treated with pencil beam-scanning proton therapy

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\textbf{ABSTRACT}

Objective: The aim of this study was to evaluate the outcome of patients with head and neck adenoid cystic carcinoma (ACC) treated using pencil beam scanning proton therapy (PBS PT) at our institution.

Materials and methods: Thirty-five patients who underwent treatment with PBS PT for ACC between 2001 and 2017 were included. Local control (LC), distant control (DC), progression-free survival (PFS), overall survival (OS) and their prognostic factors were evaluated. Adverse effects were prospectively assessed.

Results: The median patient follow-up was 30 months. Prior to PT, 26 patients (74.3\%) underwent surgery with R0/R1/R2 outcome in 5, 13 and 8 cases, respectively. Nine patients (25.7\%) presented with inoperable disease. The 2-year LC, DC, PFS and OS was 92.2\%, 77.8\%, 74.3\% and 88.8\%, respectively. LC was influenced by patient age (\(p = 0.002\)) with a significant difference between local and distant failure (median 61.3 vs. 42.3 years, \(p = 0.005\)). Tumor T stage was a significant risk factor for PFS (\(p = 0.045\)) and tumor prognostic group affected OS (\(p = 0.049\)). No significant survival advantage for operable vs. inoperable disease could be identified. The acute and late grade 3 toxicity rates were 14.3\% and 6.1\%, respectively. No acute or late grade 4/5 toxicities were observed.

Conclusions: PBS PT is an effective and safe treatment for patients with head & neck ACC in both definitive and adjuvant setting. Distant metastases are the main pattern of failure. Age, tumor stage and clinical stage had a significant negative impact on LC, OS and PFS.

\textbf{Introduction}

Adenoid cystic carcinoma (ACC) is a rare tumor of the minor and major salivary glands. It typically features extensive local infiltration into the adjacent tissues and, regionally, along the neural fibers rather than into the local lymph nodes \cite{1}. Its treatment traditionally involves – ideally – a complete surgical resection \cite{2} and in vast majority of cases an adjuvant irradiation \cite{3}. Effective radiation treatment of ACC is often challenging due to proximity to vital organs at risks (OARs) which can tolerate radiation doses significantly lower than the prescription doses required (typically for ACC $\geq 70$ Gy) to achieve satisfactory local control \cite{4}. Proton therapy (PT), in particular utilizing the advanced pencil-beam scanning (PBS) delivery technique has certain physical properties which increase the chance to fulfill this goal. It uses thousands of millimeter-thin single beams which deposit their peak energy at a precisely set depth in tissue. Dosimetrically, this results in significantly reduced relative entry dose and no exit dose of each whole beam \cite{5}, enabling an exceptionally conformal dose distribution. A high chance of achieving local tumor control while maintaining an acceptable toxicity profile can be therefore expected clinically. In the present study we report the outcome of patients treated with PBS PT for ACCs.

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Material and methods

Eligibility

Adult patients (>18 years) with newly diagnosed ACC of the head and neck treated at our institution with PBS PT between 1997 and 2017 were included in this analysis. Patients who were inoperable or with incomplete (R1 or R2) resection or those who underwent complete resection (R0) for stage UICC T1 with vascular or perineural invasion, or any tumors of stage ≥ T2 were included into the study cohort. Patients were excluded if they had metastatic disease, Karnofsky Performance status < 80% and if they underwent prior irradiation. A total of 35 patients met the inclusion criteria, the characteristics of tumors in the cohort are detailed in Table 1. All patients were consented allowing our institution to use their clinical data for research purposes. The Ethic’s commission/IRB approved this study (EKNZ 2018-00756).

Proton therapy protocol

The patients were immobilized in supine treatment position using custom-moldable cushions and thermoplastic masks. Planning CT images were acquired with a slice thickness of 2 mm. The planning CTs were fused with the pre- and postoperative MRI studies to help delineate, with the help of a diagnostic radiologist, the target volumes and organs at risk (OARs).

The Gross Tumor Volume (GTV) was defined as macroscopic tumor whenever identifiable on planning imaging studies. The high dose Clinical Target Volume (CTV2) included the GTV (or the tumor bed for patients without macroscopic tumor) plus a 5–10 mm anatomically adapted margin for areas at high risk of microscopic tumor spread. The CTV2 was further extended with a margin of 5–10 mm and additionally including potential perineural spread pathways to create the standard-risk CTV (CTV1). Based on individualized risk assessment, in a small subset of cases three CTV levels were used with the one of highest dose (CTV3) being equal to the GTV (Table 2). A symmetric margin of 4–5 mm was added to CTVs to create the planning target volumes (PTVs). The target volumes were approved on a weekly internal delineation review board. Four patients with pathologically confirmed nodal metastases underwent prophylactic ipsilateral neck irradiation.

The treatment planning was performed using an in-house developed planning software according to the ICRU 62 and 83 guidelines and also approved on an internal review board. The proton dose was expressed in Gy (RBE), which equals the physical dose multiplied by the RBE of protons, valued at 1.1. PBS PT was applied using either field uniform dose (more robust) or intensity-modulated beams (better dose gradient, yet more prone to be affected by anatomical changes) selected individually. The number of beams used ranged from 2 to 4, depending on the anatomical site; all beams were applied from one side in cases of clearly lateralized disease. Critical OARs not radiologically suspected of tumor infiltration were excluded from CTVs but not PTVs. The planning goal was to ensure that the mean dose to the PTVs was equal to prescription dose and that at least 95% of the PTVs was covered with the prescribed dose. The OARs were spared as much as possible without compromising target volume coverage. The planners could however waive the dose-constraints for planning purposes, with the following exceptions: brainstem and spinal cord (both constrained at Dmean < 63 Gy RBE to the surface and D2% < 54 Gy RBE to the center), optic nerves and chiasm (D2% < 60 Gy RBE) as well as cochleas (Dmean < 45 Gy RBE) – these organs were prioritized above the PTVs. Daily patient positioning was verified and adjusted by static kV 2D imaging and weekly low-dose helical CT was performed to detect anatomical changes within the irradiated area which could affect the dose distribution and require plan adaptation. All patients were irradiated with one fraction per day, five times per week. All patients received the whole dose prescribed, the median overall treatment time was 49 days (range: 41–67). Detailed characteristics of the PT are shown in Table 2.

In- and post-treatment evaluation

The treatment-related toxicity was classified according to the CTCAE v. 4.03. The acute toxicity was assessed weekly during the treatment and subsequently 1 and 3 months after the completion of PT. The follow-up involved site-specific clinical examination (also considering the OARs at biggest risk of developing toxicities according to symptoms and dose received, i.e. visual, hearing and other tests), head & neck MRI, chest X-
Ray or CT. This was performed in individualized intervals, typically every 6 months until 3 years post PT and thereafter annually or whenever new symptoms occurred. Follow-up imaging and clinical records are obtained from referring physicians. They are reviewed at PSI by the clinical team in weekly meetings with regard to tumor control status and late toxicities. The evaluation results from these review meetings, as well as internal and external progress reports were retrospectively reviewed for this analysis.

**Statistical analysis**

Local control (LC) was defined as a tumor volume equal to or less than the tumor volume at start of PT if a residual tumor was irradiated and no tumor recurrence if radiotherapy was delivered after a complete resection. Local failures are thus defined as lack of LC within the head and neck region. Distant Control (DC) is defined as lack of occurrence of any tumor sites outside of the head and neck area. Progression-free survival (PFS) was defined as no evidence of any recurrence or progression (local or distant) as well as death from any cause. Overall survival (OS), was defined as the time from the first day of treatment to death from any cause. All other corresponding endpoint times including the time to local and distant progression (TTLP and TTDP, respectively) were calculated also from the first day of PT until the day of the first report of a given event [6,7]. For the characterization of the type of local failures, they were categorized according to the previously used definitions [8] as either in-field (defined as the >50% of recurrent lesion located within the 95% isodose), marginal (<50% but >25% of recurrent tumor volume inside the 95% isodose) and out of field (<25% of recurrent lesion partially outside of the 25% isodose).

The OS, TTLP, TTDP, and PFS were plotted using the Kaplan-Meier method. The univariate Cox analysis to identify risk factors was performed. For the continuous variables identified significant in this analysis, receiver operating characteristics (ROC) curves were used to determine the relevant cutoff point and its discriminating power. Finally, after this stratification, the univariate analysis was performed as for non-continuous variables. All tests performed were two-tailed and the results with P-value < 0.05 were considered statistically significant.

For detecting differences not related to survival across groups, comparisons were made by non-parametric Kruskall-Wallis ANOVA test. All but one of the 9 distant failures (88.9%) occurred in patients below 55 years of age (Fig. 2B). The median age of the patients who experienced distant failure (42.3 years, 95%CI: 33.4–51.3) was significantly lower than the ones in whom local failure was observed (61.3 years, 95%CI: 48.5–74, p = 0.005).

Noteworthy, the operability was not a significant predictor for any of the analyzed outcomes, the following univariate hazard ratio values were calculated: 0.29, 95%CI: 0.05–1.65, p = 0.17 for LC; 2.61, 95%CI: 0.32–21.3, p = 0.37 for DC; 0.7, 95%CI: 0.11–4.35, p = 0.7 for OS and 0.94, 95%CI: 0.28–3.19, p = 0.92 for PFS.

**Prognostic factors**

In univariate analysis, the risk of local failure was affected by a patient with a cutoff of 63 years (risk > 63 vs. ≤ 63: 55.6% vs. 7.7%; HR = 13.5, 95%CI: 1.6–116.7; p = 0.002; Fig. 2A). All patients who experienced local recurrence but not DM (n = 4) were above this age. The only factor predicting the risk of progression was the tumor T clinical stage (risk stage T4a-c vs. stages T1-3 combined: 50% vs. 9.1%; HR = 2.1, 95%CI: 1.01–4.4, p = 0.045). Significant predictors of the risk of death were the tumor prognostic group (IVB-C: 50%, IV-A: 7.7%, other stages: 0%: HR = 9.3, 95%CI: 1.0–85.3; p = 0.049) and the tumor stage (T4a-c: 20.8%, all other stages: 0%, HR = 10.74, 95%CI: 1.12–94.72; p = 0.032). The risk of DM was influenced by the CTV1 volume (above vs below 224 cm³: 50% vs. 9.5%; HR = 10.5, 95%CI: 1.3–85.3, p = 0.03).

Due to lack of direct explanation and after post-hoc analysis this finding was however considered coincidental to the tumor stage; a significantly different distribution of these was observed above CTV cutoff points with an expected tendency of lower T stages to fall into the group of lower CTV volume with better prognosis ($\chi^2 = 10.1, p = 0.039$).

Although the age was not found to be a significant prognostic factor for DC in the univariate analysis as it was for LC, a clear difference between local and distant pattern of failure could be observed according to the patient age. All but one of the 9 distant failures (88.9%) occurred in patients below 55 years of age (Fig. 2B). The median age of the patients who experienced distant failure (42.3 years, 95%CI: 33.4–51.3) was significantly lower than the ones in whom local failure was observed (61.3 years, 95%CI: 48.5–74, p = 0.005).

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**Toxicity**

All patients started and finished the treatment on an outpatient basis except one patient who had to be admitted to hospital due to complications with the PEG probe (implanted before the proton therapy). As an in-patient he was, however, able to complete the treatment without major interruption. Overall the PT was well tolerated by the patients. Five patients (14.2%) experienced grade 3 acute adverse events (AEs). Thirty-three out of 35 patients were eligible for evaluation of late toxicity (the two others did not exceed three-month follow-up post treatment). No late adverse events were reported in 21 patients (63.6%). Late grade 1 and grade 2 AEs were observed 3–31 (median, 7.5) months after PT in 6 (18.1%) and 4 (12.1%) patients, respectively. Four of these 10 patients had their late AEs extended directly from unresolved acute toxicities. Two patients (6.1%) developed grade 3 late AEs observed at a median of 22.3 months. One patient presented with unilateral cataract 28.7 months after the treatment and another patient presented with unilateral grade 3 optic neuropathy 11.7 months and grade 3 cataract 22.3 months after the treatment. All grade 3 late toxicities were expected due to the anatomic site irradiated and the doses received by
OARs. No grade 4 or 5 AEs were reported, both acute and late. The use of SIB dose regimes did not result in an increase of toxicity ($\chi^2 = 0.9; p = 0.33$ and $\chi^2 = 1.3; p = 0.24$ for acute and late adverse events, respectively); neither were any significant differences observed between patients irradiated in the standalone and adjuvant setting ($\chi^2 = 0.07; p = 0.79$ and $\chi^2 = 2.2; p = 0.13$). Table 4 shows the detailed incidence of acute and late adverse events.

### Discussion

The management of ACC is challenging due to its localization in direct vicinity of OARs and due to its peri-neural invasion propensity. Particle therapy is being extensively used worldwide in the treatment of ACC to achieve an optimized local tumor control by delivering high-dose radiation whilst sparing the OARs. It is a viable option in particular for patients who feature skull base infiltration, which typically makes it impossible to effectively utilize photon techniques delivering high-radiation doses because of the expected severe toxicity. The present study reported a 2-year LC rate of 92.2% in a cohort including approximately 50% of inoperable or R2 resected tumors and more than two thirds of the patients (68.6%) featuring T4 tumor clinical stage. These results are in line with other available publications of ACC treatment using protons [9–12] which all reported 2-year LC exceeding 90%. Due to assumed further biological advantages that could be relevant in overcoming the ACC radioresistance (higher LET compared to photons and protons, insensitivity to hypoxia [13]) carbon ion irradiation also found its application in ACC treatment. The published studies of standalone carbon ion irradiation [14,15] report similar disease control rates as the proton irradiation, while the results of combined photon-carbon approach appear to be inferior to either of these modalities [16].

The surgical procedures required for ACC are frequently associated with permanent visual and/or functional deficits secondary to facial nerve resection, extensive skin and soft tissue reconstruction to name a few [17]. Due to very satisfactory local control rates reported with particle radiation as a standalone modality, a shift in surgical paradigm for these tumors can be observed [18]. The proton treatment is becoming the standalone modality of choice not only of an inoperable ACCs but also for ones that would require a functionally mutilating surgery, without a significant chance that it would lead to sparing the patient a high-dose adjuvant treatment. As in line with the literature, we have observed that the operability does not have a prognostic impact on the ACC patient’s outcome [9,12]. As the median prescribed dose was only 8% higher for the definite irradiation compared to adjuvant radiotherapy, no significantly increased toxicities were observed in the former group versus the latter. It is therefore expected that – when backed up by prospective data of adequate significance – surgery will be the upfront treatment only for earliest stages of ACC where it is associated with low morbidity, and for all other cases it will remain a salvage option in case of local failures after particle radiation. An analogous transition has already taken place in other indications within head & neck oncology [19].
A high proportion of the ACC patients do achieve long-term survival and therefore the use of a conservative radiation technique seems fully justified. PBS has the advantage of shaping the dose very precisely outside or even around critical OARs, especially so proximal to the target volume; while maintaining optimal target volume coverage, a low rate of radiation-induced complications can be expected. Other previously mentioned studies of particle therapy in ACC reported rates of 0–27% for late grade 3 toxicity and 5–8% for severe grade ≥4 late AEs. In this aspect, the hereby observed three grade 3 late events in 33 patients (with the two incidences of G3 cataract being expected) as well as no grade 4 or 5 late events are very encouraging results which are among the lowest reported in the literature for ACC [10,14]. It has to be noted that our results might be positively biased due to the inclusion of early stage tumors that certain previously mentioned studies reporting higher toxicity [11,12,16] omit.

The predominant pattern of failure in our study and in all others was distant metastasis, occurring in up to 38% of patients [10–12,14–16]. In case of a tumor which fails predominantly distantly, an improvement would be expected with the introduction of effective systemic therapy. Unfortunately, ACC has been shown to be chemo-resistant and the addition of concomitant chemotherapy to the irradiation has not so far improved the patients’ outcome [20]. Trials investigating the possible benefit of adding cisplatin or cetuximab to radiation are ongoing [21,22].

The only factor influencing the risk of a local failure identified in our study was the patient’s age. Our inability to perform a multivariate analysis prohibits definitive conclusions regarding the impact of age on LC. Detailed post-hoc tests (data not shown) were performed to identify whether this was biased by another variable with borderline insignificance, but no such factor could be identified. This is complemented by our observations regarding the distant metastasis in the course of ACC, which had a significant tendency to occur sooner and in younger patients than local failures. These findings altogether show possibly age-related differential failure pattern of ACC. Our data suggests that aggressive local therapies could be of value to elderly patients, whereas younger patients may benefit from more effective systemic treatment but this observation is only hypothesis-generating. Noteworthy, age has been identified to affect OS but not PFS or LC in the study administering carbon ions in ACC by Sulaiman et al. [15].

Stage IV and T4 tumors have already been reported to have worse prognosis than less advanced stages [23]. Our study is in line with this observation, further demonstrating differences in OS between clinical substages IV-IVA and IVB-C. This stage is often determined by the presence of the previously mentioned skull base infiltration and has
been also specifically reported to have worse treatment outcome [11,24]. Noteworthy is the fact that the presence of advanced tumor stages only influenced OS and PFS, and not the LC. This demonstrates that PBS PT is able to deliver curative radiation doses even to tumors surrounded by critical structures, helping a significant proportion of patients achieve a long progression-free and complication-free survival.

There were several limitations of our study. First, the study design was retrospective in nature and thus lacked complete data for certain variables such as performance status and the body-mass index. The small sample size of 35 patients limited the statistical power to detect associations between patient’s outcome and some of the clinical factors examined. Additionally, the limited follow-up time (median, 30 months) of this series may not have captured all the events, as ACC is known to feature late local recurrences >5 years post treatment. Finally, the 19-year study period may seem long, most patients were however treated in the 2015–2017 period. This being said, the patient cohort studied was selected to represent a modern ACC population, treated by a multidisciplinary team using PBT planning methods and field design relevant to current clinical practice.

Conclusions

PBS PT is a safe and effective way of delivering curative irradiation in high doses required for ACC patients. Our data suggests that age had a significant impact on LC and distant metastasis. T and clinical stage were significantly prognostic factors for OS and PFS. The operability was not significant impact on LC and distant metastasis. T and clinical stage were examined. Additionally, the limited follow-up time (median, 30 months) of this series may not have captured all the events, as ACC is known to feature late local recurrences >5 years post treatment. Finally, the 19-year study period may seem long, most patients were however treated in the 2015–2017 period. This being said, the patient cohort studied was selected to represent a modern ACC population, treated by a multidisciplinary team using PBT planning methods and field design relevant to current clinical practice.

Declarations 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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2020.104752.