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# Definitive proton beam therapy for adenoid cystic carcinoma of the nasopharynx involving the base of skull

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ABSTRACT

*Objectives:* Management of unresectable adenocystic carcinoma (ACC) of the nasopharynx is challenging given the high dose required for tumor control while respecting dose constraints. We evaluated long-term outcomes and toxicity in patients with unresectable ACC of the nasopharynx treated with definitive proton beam therapy.

*Methods:* Between 2000 and 2013, 14 patients with ACC of the nasopharynx were treated. Ninety-three percent had T4 disease. All had involvement of the skull base. Seventy-nine percent and 21% of patients underwent biopsy and endoscopic debulking surgery, respectively. Median dose was 73.8 Gy (RBE). Fifty percent of patients received concurrent chemotherapy. Locoregional control and overall survival probabilities were estimated by the Kaplan-Meier method. Treatment toxicity was scored by the Common Terminology Criteria for Adverse Events version 4.0.

*Results:* Median follow-up of surviving patients was 69 months. There were 3 local, 1 regional, and 4 distant failures. Median time of local failures was 69 months (range: 63–161). All local recurrences were within previous high-dose regions. Four patients developed metastatic disease at a median of 30 months (range: 4–64). Five-year overall survival was 59%. The most common cause of death was due to metastatic disease. There was one acute grade 3 toxicity. No patient required gastrostomy tube or hospitalization. Three patients developed grade 3 or higher late toxicity. Two of these patients received combined modality treatment. With 176 months follow-up, no second cancer was observed.

*Conclusion:* Proton beam therapy results in promising local control with acceptable toxicity in patients with unresectable ACC of the nasopharynx. As late recurrence is common, longer follow-up is necessary to confirm our findings.



## Introduction

Adenoid cystic carcinoma (ACC) accounts for only 5–10% of salivary gland tumors and less than 1% of all head and neck malignancies. ACC is also an aggressive histology with a high metastatic potential. Nasopharyngeal ACC often presents at a locally advanced stage, precluding surgical resection. Thus, nasopharyngeal ACC can be challenging to treat, necessitating the high dose radiotherapy required for tumor control, while abiding by the dose tolerance of critical structures including the brainstem, optic structures, and cochlea.

ACC of the salivary glands in sites amenable to surgery is often treated with resection and post-operative radiotherapy. Previous published studies of outcomes for ACC of the nasopharynx treated with surgery and/or photon radiotherapy have been limited to small series and case reports. Lee et al., in a study of case reports and literature review, reported on 11 ACC patients, 55% with skull base involvement, treated mostly with photon radiotherapy alone at a median dose of 60 Gy. While median follow-up was not specified, the locoregional recurrence rate was 60% and overall survival was 40% [1]. Wang et al., in another study of case reports and literature review, reported on 20 patients, 65% with stage IV disease and 55% with skull base involvement, of which 70% were treated with photon radiotherapy alone to a median of 70.3 Gy. With a medium of 5 years of follow-up, the 5-year local recurrence rate was 56% and the 10-year overall survival was 50% [2].

Schramm et al., in a retrospective series of 23 patients with different minor salivary gland malignancies of the nasopharynx, reported a local control rate of 100% and an overall survival rate of 67% after surgical resection and postoperative radiation of 52–66 Gy in the 9 patients with newly diagnosed T4 ACC [3]. Liu et al. included a heterogeneous patient population of 26 patients,

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consisting of 46% T3-4, in which 39% received photon radiotherapy alone to a mean dose of 71.4 Gy. With a median follow-up of 4 years, the locoregional recurrence rate for the entire group was 65%. The 5-year survival rate was 28% in patients with T3-4 tumors. None of the patients with T4 tumors treated mainly with radiotherapy had survived more than 36 months [4]. Overall, the published data suggests that alternative treatment strategy is necessary, particularly for the treatment of unresectable T4 ACC of the nasopharynx.

Proton beam therapy offers a unique advantage in the treatment of nasopharyngeal ACC, allowing conformal high dose target coverage, while maximally sparing adjacent normal tissue. Give the unique dosimetry of the proton beam, most of its energy is delivered at the Bragg Peak, distributing low dose proximal to the target and no exit dose when compared with photons. In addition, proton beam therapy has approximately 60% less integral dose compared to photons [5].

We have previously shown that proton radiotherapy is an effective treatment for ACC of the skull base. Of 23 patients, 12 patients underwent a gross or subtotal resection with adjuvant radiotherapy, while 11 patients underwent definitive radiotherapy alone. With a median follow-up of 62 months, there was a 5-year local control rate of 93% and a 5-year freedom from distant metastasis rate of 62% [6]. A recent study evaluating definitive proton beam with concurrent cisplatin in 9 patients with unresectable ACC of the head and neck included 5 patients with tumor originating in the nasopharynx, and 67% of patients had radiographic evidence of base of skull involvement, showed a local control rate of 89% with a median follow-up of 27 months. There was an11% rate of late grade 3 or higher toxicity [7].

The purpose of this study was to determine the treatment outcomes for the use of proton beam therapy in the treatment of unresectable adenoid cystic carcinoma of the nasopharynx with skull base invasion, which comprises the most challenging group of ACC to manage definitively.

## Materials and methods

### *Patient population*

From 2000 to 2013, 14 consecutive patients with ACC of the nasopharynx were treated with proton beam at our institution. The study was approved by the Institutional Review Board. All available histopathologic slides were reviewed at our institution prior to treatment. All new patients were discussed at our weekly proton rounds attended by radiation oncologists, medical physicists, dosimetrists, and clinical research coordinators. Clinical history and imaging studies were reviewed, and only those cases for which protons could result in improved dosimetric and clinical outcomes when compared with photon therapy were approved for proton treatment. The median follow-up of all surviving patients in the study was 69 months (range, 34–175).

### *Patient and tumor characteristics*

#### *Patient characteristics*

The patient, tumor, and treatment characteristics of patients included in this study can be found in Table 1. The median age of the patient at diagnosis was 52 years (range, 26–71). The median Karnofsky Performance Scale score at the time of initial presentation was 90 (range, 80–100). The most common symptoms reported at presentation were facial numbness/pain (43%), epistaxis (36%), nasal obstruction/congestion (29%), ear fullness/decreased hearing (29%), headache (22%), and cranial nerve IX palsy including numbness of the posterior tongue (14%). None of the patients had received prior radiotherapy. All patients had localized disease except for one patient who had radiological evidence of bilateral small pulmonary nodules at presentation.

**Table 1**
Patient, tumor and treatment characteristics.

| Patient characteristics | Patients (%) |
|---|---|
| Male | 7 (50) |
| KPS ⩾ 90 | 11 (79) |
| Median age at diagnosis, years (range) | 52 (26–71) |
| *Tumor characteristics* | |
| Extension to: | |
| Meckel's cave | 8 (57) |
| Cavernous sinus | 8 (57) |
| Carotid canal in petrous bone | 8 (57) |
| Clivus | 6 (43) |
| Pterygopalatine fossa | 6 (43) |
| Middle cranial fossa | 6 (43) |
| Sphenoid sinus | 5 (36) |
| Orbital soft tissues | 4 (29) |
| Pterygoid musculature | 4 (29) |
| Infratemporal fossa | 3 (21) |
| Middle ear | 2 (14) |
| Optic nerve | 1 (7) |
| *Stage* | |
| T3 | 1 (7) |
| T4 | 13 (93) |
| *Treatment characteristics* | |
| Surgery | |
| Extent of surgery | |
| Gross total resection | 0 (0) |
| Partial resection | 3 (21) |
| Biopsy only | 11 (79) |
| *Chemotherapy* | |
| Concurrent | |
| Cisplatin q week* | 2 (14) |
| Carboplatin/Paclitaxel q week** | 5 (36) |
| None | 7 (50) |
| *Radiation characteristics* | |
| Twice daily (BID) radiation, 1.6 Gy BID | 1 (7) |
| Elective nodal radiation | 0 (0) |
| Median RT dose delivered (range) | 73.8 GyRBE (68–76) |
| Median duration of RT (days, range) | 52.5 (35–61) |
| Median% protons (range) | 100 (61–100) |

Key: *40 mg/m$^2$ IV d1, **AUC 1.5 IV d1; 30 mg/m$^2$ IV d1; BID = twice daily; KPS: Karnofsky performance status; RT: radiation therapy.

#### *Tumor characteristics*

The tumors were all pathologically confirmed as ACC. The histological subtypes included 21% cribriform (n = 3), 7% tubular (n = 1), 21% mixed cribriform/tubular (n = 3), 7% mixed cribriform/solid (n = 1), and 43% for which the histologic subtypes were not specified (n = 6).

All patients in this study had tumors involving the skull base. Tumors were staged per the AJCC staging version 7 used for nasopharyneal carcinoma. Ninety-three percent of patients had T4 disease. All patients had gross tumor prior to initiation of radiation. Median gross tumor volume was 39.1 cc (range, 14.3–138.2 cc). The sites of disease extension include Meckel's cave (57%), cavernous sinus (57%), carotid canal in petrous bone (57%), clivus (43%), pterygopalatine fossa (43%), middle cranial fossa (43%), sphenoid sinus (36%), orbital soft tissues (29%), pterygoid musculatures (29%), infratemporal fossa (21%), middle ear (14%), and optic nerve (7%).