Proton Beam Therapy for Bronchogenic Adenoid Cystic Carcinoma: Dosimetry, Toxicities, and Outcomes

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Abstract

Purpose: Bronchogenic adenoid cystic carcinoma (ACC) is a rare malignancy particularly challenging to irradiate, largely owing to anatomic location and associated toxicities. Proton beam therapy (PBT) can reduce doses to nearby organs at risk, but only one case report has been published detailing PBT for this neoplasm.

Patients and Methods: This study was an institutional review board–approved retrospective chart review of all patients at one institution with bronchogenic ACC treated with PBT. Toxicities were assessed per Common Toxicity Criteria for Adverse Events, version 4.0.

Results: Five patients, median age 67 years (range = 40-97 years), were all symptomatic before PBT. Two patients were debulked before PBT, which was delivered at a median 66.6 Gy (RBE) (range, 57.5-80 Gy (RBE)). Two patients received concurrent platinum-based chemotherapy. Symptoms improved in all patients. Acute toxicities included the following: grade 1 fatigue (n = 3), grade 1 dermatitis (n = 2), grade 1 esophagitis (n = 1), grade 2 fatigue (n = 1), grade 2 dermatitis (n = 1), grade 2 esophagitis (n = 2). There was one case of late radiation fibrosis causing bronchial stenosis and requiring a stent, and another of late grade 1 dysphagia. All grade 2 toxicities occurred in patients receiving concurrent chemoradiotherapy. At median follow-up of 10 months (range = 5-47 months), no patient experienced tumor recurrence and none had symptoms impairing daily functioning or quality of life. Although statistically nonsignificant owing to low sample sizes, dosimetric data revealed that PBT numerically reduced doses, most notably to the heart and to low-dose volumes of the lung.

Conclusions: This is the largest series to date evaluating PBT for bronchogenic ACC. PBT is associated with low rates of acute and late toxicities and excellent early local control.

Keywords: adenoid cystic carcinoma; trachea; proton beam therapy; toxicity; radiotherapy

Introduction

Although most commonly occurring in the salivary glands, adenoid cystic carcinoma (ACC) rarely arises in the thorax and accounts for approximately 0.2% of primary respiratory system neoplasms [1]. When in the thorax, these tumors are often tracheal or bronchial in origin. In fact, ACC and squamous cell carcinoma are the most common primary bronchial cancers [2]. Specifically, ACCs most commonly develop in the proximal portion of the tracheobronchial tree and histologically arise from submucosal...
glands, although ductal/myoepithelial origins have also been posited [3–5]. As such, glandular tissue is most commonly observed on pathological evaluation, although more aggressive ACCs may contain larger components of solid (nonadenoid) cells [6].

Despite the commonly indolent local growth and low risk for lymphovascular spread, these tumors can have associated perineural and hematogenous spread, most commonly to the lung parenchyma [7]. The most recognized first-line treatment for bronchogenic ACC is definitive surgical resection with a goal of complete tumor resection as well as relief of any potential obstruction and restoration of ventilation. However, complete resection is often not feasible, especially in cases with large tumor bulk, anatomically central disease, and/or extensive submucosal spread, or in patients who are medically inoperable due to advanced age or comorbidities [8].

Additionally, series have reported local recurrences well beyond one decade after curative resection, even with uninvolved surgical margins [9, 10]. As a result, despite a lack of prospective data owing to the uncommon incidence of bronchogenic ACC, adjuvant radiation therapy (RT) is often administered to improve local control. Small retrospective reports have observed high local control with postoperative RT [10–12]. Based on these reports and through extrapolation from head and neck ACC, adjuvant RT may be indicated for cases with surgical microscopically or gross positive margins, lymph nodal metastases, and/or perineural invasion [13, 14]. Furthermore, in cases of medical or surgical inoperability, definitive radiation therapy is the standard treatment approach and can achieve durable tumor control for primary bronchogenic ACC [15, 16].

However, adjuvant or definitive RT may incur substantial treatment toxicities, largely due to the close anatomic relationship of bronchogenic ACC with surrounding organs at risk (OARs), such as the pharynx, esophagus, lungs, heart, and uninvolved central airway. As is observed in thoracic and head/neck neoplasms, balancing the risks of RT-induced toxicities with the necessity to deliver doses adequate to control microscopic or gross disease is challenging.

The use of intensity-modulated radiation therapy (IMRT) for thoracic tumors can reduce doses received by centrally located OARs, which may help to reduce the risk of quality-of-life decline from thoracic RT compared with 3D conformal RT (3DCRT) [17]. In patients with ACC and other malignancies of the maxillary sinus, postoperative treatment with IMRT was demonstrated to improve target volume coverage and locoregional recurrence-free survival and distant metastasis-free survival compared with 3DCRT [18], with encouraging toxicity results [19, 20].

Spurred by its dosimetric benefits and the promise to clinically reduce toxicities over photon-based techniques, proton beam therapy (PBT) is increasingly being studied and used to treat a number of various malignancies [21–27]. Because there is maximal dose deposition (Bragg peak) in the target with virtually no exit dose [28], PBT offers considerable potential to reduce treatment-induced adverse effects in head and neck and thoracic neoplasms to reduce toxicities by means of reducing surrounding OAR doses [29–34].

Similarly, the anatomic locations of many bronchogenic ACCs offer substantial prospects for clinically evident toxicity reductions. Indeed, low toxicities have been reported when using PBT to treat other tumors in similar thoracic anatomic areas [35–37]. However, the use of PBT to treat bronchogenic ACC has been limited to just one case report to date [38]. Herein, we describe a series of five such patients treated with PBT, with particular emphasis on toxicity and early outcomes.

**Materials and Methods**

A single-institution retrospective chart review was conducted to identify patients with histologically proven ACC with an epicenter from the trachea on initial imaging. This study was approved by the institutional review board with informed consent obtained. Toxicities were evaluated at the time of treatment using the Common Toxicity Criteria for Adverse Events, version 4.0. Statistics were performed using SAS Version 9.4 (Cary, NC) software and utilized two-sided Wilcoxon rank-sum tests with \( P < 0.05 \) as statistical significance.

**Results**

**Case 1**

In October 2012, a 60-year-old man experienced progressive dyspnea. Workup demonstrated unresectable tracheal ACC with tumor impingement on the right mainstem bronchus (Figure 1A). He was treated with definitive double scattering proton therapy to 80 Gy (RBE) in 2 Gy (RBE) daily fractions and completed treatment 4 months after diagnosis (Figure 1B). Following treatment, he noticed a significant improvement in dyspnea. Acutely, he experienced grade 1 esophagitis along with grade 1
dermatitis. Late toxicities included narrowing of his right mainstem bronchus attributable to radiation fibrosis that required a Y stent (7 months after treatment completion). At last follow-up of 42 months, he no longer had any respiratory symptoms, and there was no evidence of disease (Figure 1C).

Case 2
In July 2015, a 67-year-old woman experienced cough, dyspnea, and wheezing. Thereafter, chest imaging revealed a 3 × 3 cm mass that was moderately fluorodeoxyglucose-avid (maximum standard uptake value of 4.7; Figure 2A) centered on the carina and involving the bilateral mainstem bronchi. Bronchoscopy demonstrated a friable submucosal lesion covering the main carina and extending to the proximal left and right mainstem bronchi; the distal left and right bronchial trees appeared normal. Although the lesion was inoperable, it was debulked and the bilateral mainstem bronchi were dilated; pathology showed an intermediate-grade ACC. She was treated with definitive concurrent chemoradiation with weekly cisplatin and double scattering proton therapy (66.6 Gy (RBE) in 1.8 Gy (RBE) daily fractions) and finished treatment 4 months after initial diagnosis (Figure 2B). She did, however, develop acute grade 2 fatigue, esophagitis, and dermatitis. After chemoradiation,
her coughing and wheezing resolved with minor residual dyspnea that did not interfere with her quality of life. At her 10-month follow-up, she was free of disease (Figure 2C) and has had no late toxicities.

**Case 3**
A 78-year-old man with multiple comorbidities began having hemoptysis in September 2015. Imaging demonstrated a mass centered at the carina extending into the left mainstem bronchus (Figure 3A). Due to medical comorbidities, he was neither a definitive surgical candidate nor a candidate for chemotherapy. He was treated with double scattering proton therapy in 2.5 Gy (RBE) daily fractions to a total dose of 60 Gy (RBE) and finished radiotherapy 3 months after diagnosis (Figure 3B). He experienced acute grade 1 fatigue but no skin or esophageal symptoms and late grade 1 dysphagia. He had no evidence of disease at last follow-up 9 months after completing radiotherapy (Figure 3C).

**Case 4**
A 97-year-old man presented in August 2012 with cough and dyspnea and was found on imaging to have a right mainstem bronchial mass causing postobstructive pneumonia (Figure 4A). Bronchoscopy was performed with biopsy, which revealed ACC. Subsequent positron emission tomography (PET) scan illustrated that the right brainstem bronchial mass was highly fluorodeoxyglucose-avid (maximum standard uptake value of 12.6). Due to his advanced age, he was not a candidate for definitive resection and instead underwent cautery debridement of the intraluminal tumor. After tumor debulking, he underwent 3 subsequent bronchoscopic procedures, each of which demonstrated histologically confirmed recurrent/progressive tumor and resulting progressive airway occlusion/stenosis.

He was treated with double scattering proton therapy in 2.5 Gy (RBE) daily fractions initially to the endobronchial regions at risk and hilum to 40 Gy (RBE), followed by a 17.5 Gy (RBE) conedown to gross disease with margin, for a total dose of 57.5 Gy (RBE) (Figure 4B). Treatment was completed 39 months after initial diagnosis. He experienced grade 1 fatigue but no other toxicities, including those of the skin or esophagus. At last follow-up 8 months after completing therapy, he had no evidence of disease and no respiratory or esophageal symptoms (Figure 4C).

**Case 5**
A 40-year-old woman presented with progressive dyspnea and wheezing in January 2016. Imaging revealed a 3.40-cm mass surrounding the trachea and extending into the right paratracheal soft tissue space (Figure 5A). Bronchoscopy showed
submucosal tracheal mass completely replacing the tracheal wall beginning 3 cm above the carina and extending down into bilateral mainstem bronchi; biopsy confirmed ACC. The treatment plan consisted of concurrent paclitaxel/carboplatin and modulated scanning proton therapy (65.25 Gy (RBE) in 2.25 Gy (RBE) daily fractions; Figure 5B). She experienced grade 1 fatigue, grade 2 esophagitis, and grade 1 dermatitis, and she completed treatment 4 months from diagnosis. She was oncologically free of disease or pertinent symptoms at 5 months after chemoradiation (Figure 5C).

**Dosimetry**

Clinical backup IMRT plans were generated for all patients and compared with the delivered PBT plans. Target coverage was comparable for both modalities. Table 1 displays dosimetric details for all patients, comparing doses to the target, spinal cord, heart, lungs, and esophagus. Although prescription doses varied among patients, these prescriptions were the same between each PBT and IMRT plan for a given patient. Although recognizing that no parameter was statistically significant between groups owing to the low sample size ($P > .05$ for all), PBT showed the greatest proportional numeric decrease in cardiac doses as well as low-dose areas of the lung (ie, V5).

**Discussion**

This series is the largest experience to date utilizing PBT for bronchogenic ACC and demonstrates low toxicities and high local control when used in both the adjuvant and definitive settings. These results call for other corroborative experiences in testing the safety and efficacy of PBT for this population that has historically been difficult to treat with definitive doses using photon-based approaches.

Our data illustrate that the potential to deliver high doses is indeed feasible for this condition. The median 67 Gy (RBE) utilized herein was associated with relatively few toxicities; those that were present were low-grade. The only grade 2 adverse effects noted were in patients who received concurrent chemotherapy, which is known to amplify radiotherapy toxicities with thoracic malignancies [39]. There were also just two late toxicities to date, one of which requiring a bronchial stent placement due to radiation-related fibrosis after 80 Gy (RBE). Lastly, in addition to no documented tumor recurrence thus far, each

| Parameter                              | Photons | Protons |
|----------------------------------------|---------|---------|
| PTV (%) receiving ≥95% of Rx dose      | 94.3 (80.0–99.7) | 98.0 (95.2–99.8) |
| Mean esophageal dose (Gy)              | 30.3 (12.5–44.2) | 33.5 (14.8–48.4) |
| Mean cardiac dose (Gy)                 | 8.8 (3.5–19.9) | 5.9 (1.1–16.9) |
| Heart V30 (%)                          | 11.1 (0.5–30.4) | 8.2 (0.6–24.4) |
| Heart V45 (%)                          | 7.1 (0–20.9) | 4.7 (0.1–13.4) |
| Spinal cord maximum dose (Gy)          | 47.5 (37.7–51.7) | 41.2 (36.7–51.0) |
| Mean lung dose (Gy)                    | 12.7 (9.0–19.2) | 11.1 (6.8–17.5) |
| Lung V20 (%)                           | 23.0 (14.6–33.7) | 22.7 (12.6–33.7) |
| Lung V5 (%)                            | 42.6 (28.6–58.1) | 32.3 (20.5–42.6) |

Abbreviations: PTV, planning target volume; Rx, prescription; Vn, volume of organ receiving at least n Gy

*Figures denote average (range) doses for a given parameter. All statistical comparisons (with Wilcoxon rank-sum test) insignificant ($P > .05$).
patient’s symptoms improved, and no patient experienced tumor-related or treatment-related symptoms that influenced quality of life.

Owing to the rarity of bronchogenic ACC, it is imperative to consider data in neoplasms of similar locations to assess the theoretical potential of PBT. If further proven, the impact of PBT-mediated toxicity reductions in any patient with thoracic cancers is not limited to the simple decrease in incidence/severity of toxicities. For instance, numeric reductions in OAR doses may be more correlated with clinically apparent benefits in populations with greater comorbidities. Second, the lower integral dose (overall radiation delivered to the patient) afforded by PBT over photon modalities may be of consequence. Whereas the most conformal photon techniques spare areas immediately around the tumor to high doses, they also result in higher volumes of tissue receiving low radiation doses, which is important in light of a study finding these low-dose volumes to correlate with clinical toxicities [40]. Moreover, in a patient population whose age is roughly 35 to 50 years (despite the older age of our patients), studies have supported the reduction of expected secondary malignancies with proton therapy compared with photon therapy [41–42].

Next, PBT may also benefit patients with disease at anatomically unfavorable areas to a greater extent; these relate to whether all disease is surgically accessible or to cases wherein there may be large differences between calculated doses to OARs between photon and proton plans. Moreover, a main objective of postoperative RT is to prevent the exacerbation of surgical complications, rehospitalization, and/or functional/quality-of-life decline caused by a surgical procedure. It is also theoretically true that PBT may provide advantages in these areas over photon-based RT and prove to be the more cost-effective RT modality [21, 43], although it is unlikely that comparative studies will be done for ACC. As part of ongoing proton versus photon trials of lung cancer, for instance, some of the aforementioned parameters are indeed being evaluated [44].

Given that treatment is often definitive or adjuvant with residual disease after surgery in ACC, high radiation therapy doses are often required. Because the ability to dose-escalate is very often related to dose limitations of surrounding OARs, the ability of PBT to dosimetrically limit these OAR doses may lend itself well to these circumstances. The heart, which is often anatomically posterior to the postoperative space, can be spared to a greater degree owing to the unique Bragg peak in anteriorly oriented beams. In a disease with good prognosis, reduction in heart doses could potentially result in late cardiac events, as observed in breast cancer [45–48]. PBT can also reduce the dose to the normal lungs, which may allow for lower rates of pneumonitis. Lastly, esophageal doses between modalities are often dependent on individual patient anatomy, but a reduction in high-dose areas could contribute to lesser morbidity as well.

In our study, however, there were no statistical differences between PBT and IMRT groups in terms of dosimetric parameters (Table 1). It is intuitive that the largest numeric difference between both techniques existed for low-dose parameters (eg, lung V5), with nearly all of the remaining parameters numerically favoring PBT. The lack of statistical significance between groups is likely due to a combination of low sample sizes, along with the fact that forward-planned passively scattered PBT is most appropriately compared with forward-planned 3DCRT and not inverse-planned IMRT [49].

This study has several limitations. This report is of a limited number of patients, is retrospective in nature, and has a relatively short follow-up. The case-by-case basis of chemotherapy delivery and tumor debulking before PBT may confound outcomes seen herein and may also limit generalizability. Also influencing the outcomes was the incomplete and nonstandardized nature of histopathological grading and subtyping. Furthermore, various PBT techniques were used in this study, also limiting generalizability. The dose distribution may have been further improved had pencil-beam scanning and/or intensity-modulated proton therapy been used in all cases [50, 51], particularly for lowering the dose received by the esophagus. Nevertheless, these discontinuities do not take away from the need to further test the safety and efficacy of PBT in this rare population.

**ADDITIONAL INFORMATION AND DECLARATIONS**

**Conflicts of Interest:** All authors declare that they have no conflicts of interest.

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