Comparison of Pencil Beam Scanning Proton- and Photon-Based Techniques for Carcinoma of the Parotid

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Abstract

Purpose: To report the dosimetric advantages of a comparison between pencil beam scanning (PBS) proton therapy versus intensity-modulated radiation therapy (IMRT) for parotid gland cancers.

Patients and Methods: This was a retrospective, dosimetric comparison of 8 patients who received external beam radiation therapy at our institution between 2009 and 2011. Two separate plans were generated for each patient: 1 IMRT and 1 PBS plan. The prescription dose for each plan was 60 Gy for IMRT and 60 Gy (RBE) for PBS. We measured dose-volume relationships for target volumes and organs at risk with each treatment technique. Dosimetric comparisons for each organ at risk were made by using the Wilcoxon signed rank test. All tests were 2-tailed, with \( P < .05 \) considered statistically significant.

Results: The mean patient planning target volume was 160.9 cm\(^3\) (SD 74.6). Pencil beam scanning, compared to IMRT, significantly reduced the mean dose to the following structures: ipsilateral temporal lobe (2.86 versus 9.59 Gy (RBE), \( P = .01 \)), oral cavity (0.58 versus 13.48 Gy (RBE), \( P = .01 \)), mandible (\( V_{50} \): 7.4% versus 12.8%, \( P = .01 \)), contralateral parotid gland (0.03 versus 4.64 Gy (RBE), \( P = .01 \)), ipsilateral submandibular gland (16.59 versus 38.94 Gy (RBE), \( P = .03 \)), and contralateral submandibular gland (0.02 versus 5.34 Gy (RBE), \( P = .01 \)). Pencil beam scanning also significantly reduced the maximum dose delivered to the brainstem (7.1 versus 30.9 Gy (RBE), \( P = .01 \)).

Conclusion: Pencil beam scanning allows for superior normal tissue sparing while still maintaining excellent target coverage in patients with resected parotid gland cancers. These findings suggest that PBS may allow for an improved therapeutic index for these patients. Clinical outcomes with PBS should be evaluated prospectively, with a focus on disease outcomes as well as treatment-related toxicities and patient quality of life.

Keywords: proton therapy; pencil beam scanning; head and neck cancer; parotid cancer

Introduction

Patients with a diagnosis of malignant major salivary gland carcinomas frequently receive radiation therapy (RT) as part of their treatment either following surgery or as definitive treatment for unresectable disease. In the postoperative setting, doses \( \geq 56 \) Gy have been associated with improvements in local control [1]; however, such treatment may also be associated with significant treatment-related toxicity including mucositis;
xerostomia; hearing loss; and rarely, temporal lobe necrosis. Proton therapy may offer an improved therapeutic index in this setting by reducing dose to adjacent organs at risk (OARs).

Proton therapy may be particularly advantageous in the treatment of parotid carcinomas, compared to other head and neck cancers, given that the treatment fields generally target the unilateral base of skull and upper neck. The sharp dose gradient, possible by virtue of the Bragg peak, may allow for improved avoidance of adjacent structures such as the cochlea, the temporal lobe of the brain, the mandible, or the oral cavity. In addition, reduced integral dose through proton therapy for structures such as the oral cavity, submandibular glands, and contralateral parotid glands may help to reduce or avoid long-term xerostomia for patients. Several studies [2–12] have suggested potential dosimetric advantages associated with the use of proton therapy for other head and neck cancers. However, relatively little has been published regarding the use of protons to treat carcinomas of the major salivary glands.

We therefore conducted a retrospective treatment planning study to compare intensity-modulated radiation therapy (IMRT) with pencil beam scanning (PBS) proton therapy in a series of patients receiving treatment for parotid gland carcinoma at our institution.

Methods and Materials

Study Design and Patient Population

This study retrospectively compared dosimetric endpoints by radiation treatment technique among patients receiving treatment for parotid carcinoma. We identified 8 patients receiving external beam radiation therapy (EBRT) for parotid carcinoma at our institution between December 2009 and July 2011. Most patients in our study had undergone resection of carcinoma involving the parotid and were recommended to receive adjuvant RT. In addition, we also included 3 patients with disease who received RT alone for disease that was deemed unresectable by our head and neck surgeons.

Simulation and Treatment Planning

All patients underwent computed tomography (CT) simulation with axial images acquired at 1.5- to 3.0-mm increments. Thermoplastic masks were used for immobilization of the head and neck. Computed tomography images were imported into a commercial treatment planning software (Eclipse, Varian Medical Systems, Palo Alto, California), which was used for both photon and proton treatment planning. Target volumes and normal OARs were contoured by 2 radiation oncologists with significant experience treating head and neck cancer. Gross tumor volumes in patients with unresected disease were based on clinical examination and imaging findings including CT, magnetic resonance imaging, or positron emission tomography/CT. Clinical target volumes (CTVs) were customized for each patient to account for microscopic or subclinical extension of disease. The CTV included the ipsilateral cervical lymph nodes in 3 patients and tracked the facial nerve to the base of skull in 5 patients. Consistent with our institutional policy, each CTV was expanded 3 mm to a planning target volume (PTV) to account for organ motion and setup variation. The PTV was then cropped from the skin by 3 mm for planning optimization purposes.

From methods established by Moyers et al [13], proton margins were calculated as 3.5% of the range with an additional 1 mm for beam delivery uncertainty. Owing to the shallow depth of the parotid targets, the largest calculated margin for range uncertainty was 4.5 mm. Since the PTV expansion was a uniform 5 mm from the CTV, which was larger than the calculated range uncertainty margins, the same PTV was used for PBS optimization to be conservative. The proton plans were therefore calculated with a 5-mm range uncertainty margin from the CTV, which is equivalent to the PTV margin for the photon plans. No modifications of OAR contours were made for planning between the 2 modalities.

The OARs evaluated for each patient included ipsilateral cochlea, ipsilateral temporal lobe, brainstem, oral cavity, mandible, contralateral parotid gland, and bilateral submandibular glands. The same target and OAR structures in each patient were used for all EBRT treatment plans generated.

We developed separate treatment plans for each study patient by using the following techniques: (1) 5-field IMRT and (2) PBS proton beam therapy using a single field. The PBS treatment plans were optimized by using customized bolus to reduce spot size and resultant penumbra [14]. Single-field PBS plans have been used to treat shallow targets with reliable bony alignment such as with the spine field of a craniospinal treatment. For the purposes of the study, a worst-case scenario robustness analysis was performed by forward calculating the nominal plans by using 3-mm isocenter shifts in 6 directions ($\pm x$, $\pm y$, $\pm z$) and $\pm 3.5$% shifts in the Hounsfield unit. The minimum CTV $D_{95}$ among all parameters of all cases was 95%, and the mean CTV $D_{95}$ worst-case scenario from each of the patients was 97% $\pm$ 1%. All treatment plans evaluated for the
purposes of the study were developed by a single physicist with experience in both head and neck cancer and proton treatment planning (B.-K.K.T.). The prescription dose for each plan was 60 Gy for photon plans or 60 Gy (RBE) for proton plans, using a conversion factor of 1.1 relative biological effectiveness (RBE) [15]. This uniform dose was selected for the sake of simplicity in the study, with the understanding that patients with positive surgical margins or unresectable disease will typically receive EBRT doses $\geq 60$ Gy. In all cases, plans provided dose coverage such that $\geq 95\%$ of the planning target volume received at least 95\% of the prescription dose.

### Analysis

We measured dose-volume relationships for target volumes, and OAR (ipsilateral cochlea, ipsilateral temporal lobe, brainstem, mandible, oral cavity, contralateral parotid gland, bilateral submandibular glands) with each treatment technique. Using Wilcoxon signed rank test, we performed pair-wise comparisons of dose parameters with PBS versus IMRT for each OAR. All tests were 2-tailed and $P$ values $< .05$ were considered statistically significant. Statistical analyses were conducted by using Stata version 12 (College Station, Texas).

### Results

#### Characteristics of the Study Population

The characteristics of the study population are displayed in Table 1. Five patients (63\%) were treated for a primary parotid carcinoma, while 3 patients (37\%) received treatment for cutaneous malignancies involving the parotid gland. Three patients received RT for disease that was unresectable owing to base of skull involvement. The facial nerve was specifically targeted to the base of skull (stylomastoid foramen) in 6 patients (75\%). The mean patient PTV volume was 160.9 cm$^3$ (SD 74.6).

#### Comparison of Dose to Normal Structures Using IMRT versus PBS

The comparative distribution of dose to normal structures for all study patients, using IMRT and PBS, is shown in Figure 1. A representative comparison of dose distribution and dose-volume histograms between IMRT and PBS treatment plans for a single study patient can be seen in Figure 2. Descriptive statistics and the results of univariate statistical comparisons are shown in Table 2.

### Ipsilateral Cochlea

Pencil beam scanning did not result in a statistically significant reduction in the mean dose to the ipsilateral cochlea when compared to IMRT ($P = .16$). The average mean cochlear dose was 1.49 Gy (RBE) with IMRT and 1.10 Gy (RBE) with PBS.

### Ipsilateral Temporal Lobe

The PBS technique resulted in a statistically significant reduction in the mean dose to the ipsilateral temporal lobe when compared to IMRT ($P = .012$). The average mean temporal lobe dose was 9.59 Gy (RBE) with IMRT versus 2.86 Gy (RBE).
with PBS. The average maximum temporal lobe dose was also reduced with PBS compared to IMRT (25.0 Gy (RBE) versus 19.62 Gy (RBE), respectively). However, this reduction was not statistically significant ($P = .09$).

**Oral Cavity**

Dose to the oral cavity was nearly eliminated when using PBS (Figure 1). The average mean oral cavity dose with PBS was 0.58 Gy (RBE), compared to 13.48 Gy (RBE) with IMRT. Pencil beam scanning resulted in a statistically significant reduction in the mean oral cavity dose when compared to IMRT ($P = .01$).

**Brainstem**

Similarly, dose to the brainstem was minimal when using PBS. The average maximum brainstem dose was 7.1 Gy (RBE) with PBS, compared to 30.9 Gy (RBE) when using IMRT. Pencil beam scanning resulted in a statistically significant reduction in the maximum brainstem dose when compared to IMRT ($P = .01$).

**Mandible**

The maximum point doses to the mandible for each patient, using IMRT and PBS, were similar. The average maximum dose to 0.03 cm$^3$ of the mandible was 64.15 Gy (RBE) with IMRT and 62.59 Gy (RBE) with PBS. There was no statistically significant difference in the maximum mandibular dose between IMRT and PBS ($P = .67$). The mandibular $V_{50}$ (volume of the organ...
receiving ≥ 50 Gy (RBE) was 12.8% with IMRT, compared to 7.4% when using PBS. Pencil beam scanning resulted in a statistically significant reduction in the mandibular V50 when compared to IMRT (P = .01).

**Contralateral Parotid Gland**

Contralateral parotid dose was nearly eliminated when using PBS. The average mean dose to the contralateral parotid gland was 4.64 Gy (RBE) with IMRT and 0.003 Gy (RBE) with PBS. The PBS technique resulted in a statistically significant reduction in the mean dose to the contralateral parotid gland when compared to IMRT (P = .01).

**Ipsilateral Submandibular Gland**

In 2 patients, the ipsilateral submandibular glands were located entirely within the treatment target volume. Therefore, doses were only compared for the remaining 6 patients in whom at least a portion of the submandibular gland was located outside the treatment target volume. Pencil beam scanning resulted in a statistically significant reduction in the mean dose to the ipsilateral submandibular gland when compared to IMRT (P = .03). The average mean dose to the ipsilateral submandibular gland was 38.94 Gy (RBE) with IMRT, compared to 16.59 Gy (RBE) when using PBS.

**Contralateral Submandibular Gland**

Pencil beam scanning again nearly eliminated dose to the contralateral submandibular gland. The average mean dose to the contralateral submandibular gland was 5.34 cGy with IMRT versus 0.02 Gy (RBE) with PBS. Pencil beam scanning resulted in a statistically significant reduction in the mean dose to the contralateral submandibular gland when compared to IMRT (P = .01).

**Discussion**

Our study demonstrates that in patients receiving radiation therapy for cancers of the parotid, treatment with a PBS proton-based approach delivers significantly less radiation exposure to adjacent normal OARs than an IMRT photon-based approach. This study is the first of its kind to compare the most advanced technique of both proton and photon therapy for the treatment of parotid malignancies.
Unlike more common malignancies of the head and neck, salivary gland cancers are relatively rare, with an overall incidence in the population of 0.9 to 4.0 cases per 100,000 persons per year [16]. Therefore, the ability to perform large-scale, comparative randomized trials in this population is limited, and dosimetric comparisons such as this may be helpful in determining the optimal radiation approach for treating these patients. The treatment of other types of head and neck cancer with external-beam photon-based RT can cause severe late effects [17–23] and impact posttreatment quality of life [19]. A pencil-beam proton-based approach for parotid cancers, we believe, is currently the optimal approach to minimize potential acute and long-term side effects for those requiring RT.

There are several limitations to our study that warrant mention. This study describes a PBS-based approach and compares its dosimetric results to an IMRT plan. However, the safe clinical implementation of PBS requires stringent technical and quality assurance, with issues such as daily variation in patient positioning [24], anatomic changes that occur during the course of treatment [25], and the inherent uncertainties associated with proton beam delivery. The intensity-modulated proton therapy technique was not used for this planning study owing to its sensitivity to treatment uncertainties [26–28], and a more robust uniform dose technique was used. Additionally, the question of whether significant decreases in doses to OARs with proton
therapy leads to improvement in patient outcomes remains unanswered and requires clinical follow-up. However, given that previous level 1 evidence demonstrated that improved salivary gland sparing with IMRT (versus conventional RT) reduced the severity of xerostomia and consequently improved quality of life [29], we would expect that the improved normal tissue sparing seen with PBS should produce similar benefits.

In summary, given the demonstrated dosimetric advantages achievable with PBS proton therapy, we would advocate for the clinical implementation of such a technique in the treatment of patients with parotid malignancies. Careful attention needs to be made to ensure treatment quality assurance, as well as reporting of long-term clinical outcomes.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no conflicts to disclose.

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