INTERNATIONAL JOURNAL of PARTICLE THERAPY

Proton Beam Therapy in the Treatment of Periorbital Malignancies

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Abstract

Purpose: Periorbital tumor location presents a significant challenge with 3-dimensional conformal radiation therapy or intensity modulated radiation therapy due to high tumor dose needed in the setting of close proximity to orbital structures with lower tolerance. Proton beam therapy (PBT) is felt to be an effective modality in such cases due to its sharp dose gradient.

Materials and Methods: We reviewed our institutional PBT registry and identified 17 patients with tumor epicenters within 2 cm of the eye and optic apparatus treated with passive scatter PBT with comparison volumetric arc therapy plans available. Maximum and mean doses to organs at risk of interest, including optic nerves, optic chiasm, lens, eye ball, pituitary, cochlea, lacrimal gland, and surrounding brain, were compared using the paired Wilcoxon signed rank test. Overall survival was determined using the Kaplan-Meier method.

Results: Median age was 67. Median follow-up was 19.7 months. Fourteen patients underwent upfront resection and received postoperative radiation and 3 received definitive radiation. One patient received elective neck radiation, 2 underwent reirradiation, and 3 had concurrent chemotherapy. There was a statistically significant reduction in mean dose to the optic nerves and chiasm, brain, pituitary gland, lacrimal glands, and cochlea as well as in the maximum dose to the optic nerves and chiasm, pituitary gland, lacrimal glands, and cochlea with PBT. The 18-month cumulative incidence of local failure was 19.1% and 1-year overall survival was 80.9%.

Conclusion: Proton beam therapy resulted in significant dose reductions to several periorbital and optic structures compared with volumetric arc therapy. Proton beam therapy appears to be the optimal radiation modality in such cases to minimize risk of toxicity to periorbital organs at risk.

Keywords: periorbital; proton; optics; pituitary; cochlea

Submitted 28 Apr 2020
Accepted 05 Jan 2021
Published 26 Mar 2021

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Original Article

DOI
10.14338/IJPT-20-00025.1

http://theijpt.org

Introduction

Periorbital tumors refer to lesions arising in proximity to the optic structures, including the nasal cavity, nasopharynx, paranasal sinus, adjacent dura, and skin. These tumors can be of varying histologic types, including squamous cell, basal cell, melanoma, adenoid cystic, adenocarcinoma, lymphoma, or sarcoma. Surgery when possible is considered the standard of care treatment in this region, especially for cutaneous lesions [1].

Adjuvant radiation therapy (RT) is often indicated when there are other high-risk features for recurrence, such as close or positive margins, bone invasion, perineural invasion, or history of recurrence(s). Radiation therapy can also be delivered in the definitive setting as an alternative to surgical intervention. This is typically performed when surgical resection cannot be accomplished without significant morbidity or if the patient is felt to be medically unfit for surgery.

The role of photon or X-ray and electron radiation in the treatment of orbital and periorbital lesions is well established [2–4]. Unlike photons, protons are charged particles. While considered biologically similar to conventional, photon radiation, they differ physically with a defined range depending on energy. Specifically, protons deposit most of their energy toward the end of their path, as defined by the Bragg peak, which allows for sparing of distal structures. Consequently, the primary advantage of PBT is decreased collateral damage due to a lower integral dose to the surrounding normal tissues, reported to be as high as 60% [5]. In the orbital location protons have been used in the management of ocular melanomas [6, 7], choroidal metastases [8], and orbital rhabdomyosarcomas [9] with good results. The aim of our study was to further evaluate the outcomes and dosimetry of PBT in the management of periorbital tumors. To the best of our knowledge, clinical experience using proton therapy specifically for periorbital tumors has not been reported to date.

Materials and Methods

To compare dosimetry and outcomes in periorbital tumors a retrospective review was conducted of the institutional review board–approved proton registry at our institution. Patients treated with curative intent PBT for tumors that had an epicenter within 2 cm of the orbit and had an intensity modulated radiation therapy (volumetric arc therapy [VMAT]) plan available for comparison were included. Both patients who received adjuvant RT and those that received definitive RT, with or without chemotherapy were included. Patients who received reirradiation were eligible as long as the dose delivered was considered to be curative. Patients were included if they received elective radiation to the ipsilateral neck. Of note, patients that require treatment to the bilateral neck are not treated with proton therapy at our institution.

From 2016-2019, 17 patients were treated who met study criteria. Target volumes were delineated primarily using computed tomography (CT) with or without contrast. Positron emission tomography/CT and magnetic resonance imaging information were also used when available. Passive scatter PBT and VMAT plans were generated with Pinnacle planning software (Philips Radiation Oncology Systems, Fitchburg, WI). Photon bean therapy planning was based on the clinical target volume (CTV). The number of beam angles chosen varied across patients from 2 to 4. The distal and proximal margins on the CTV were generated using a 3.5% range and 3 mm. The compensator smearing is calculated for each beam angle based on a setup error of 5 mm. VMAT plans were optimized using the planning target volume. Robust VMAT plans were produced not only for direct comparison, but also for clinical use as a backup in the event of proton machine downtime.

Maximum and mean doses to organs at risk (OARs) of interest, including optic nerves, optic chiasm, lens, globe, pituitary gland, cochlea, lacrimal gland, and surrounding brain, were recorded for both proton therapy and comparison VMAT plans. All patients were treated primarily with PBT and were immobilized using a custom thermoplastic face mask, head pad, and mouth piece. Daily, pretreatment alignment, orthogonal kilovoltage radiographs were obtained and compared with CT-generated digital reconstructed radiographs to ensure accurate delivery. In the event of machine downtime patients were treated with photons using VMAT technique with cone beam CT for image guidance.

Maximum and mean doses were collected for OARs. Paired structures were denoted as left or right. Doses were subsequently compared for proton and VMAT plans using a paired Wilcoxon signed rank test with corrections to control the false-discovery rate. A corrected P value $\leq .05$ was determined to be statistically significant. Clinical follow-up data were retrospectively collected using chart review. Available information included clinical examinations, imaging, and toxicity assessments. Local control was recorded using pathologic information when obtained. However, local failure was recorded on the basis of clinical and/or radiographic findings when pathologic proof was not available. Overall survival was determined using available medical records and obituary reports and reported using the Kaplan-Meier method. All clinical outcomes are presented in an observational fashion. Acute and late toxicity are both reported using Common Terminology Criteria for Adverse Events, version 5 (US National Cancer Institute, Bethesda, MD).

Results

The median age of the 17 patients included was 67 (range, 38-91). Nine patients were male and 8 female. The most common histology was squamous cell carcinoma, which was present in 5 patients. The most common primary site was the nasal cavity. A full list of patient characteristics is given in **Table 1**. Fourteen of 17 patients underwent initial surgical resection and received

Table 1. Demographic and disease characteristics of patients with periorbital tumors treated with proton therapy.

Baseline characteristics	n
Sex	
Female	8
Male	9
Primary site	
Nasal cavity	7
Nasopharynx	1
Orbit	3
Paranasal sinus	4
Skin	2
Histology	
Adenocarcinoma	2
Esthesioneuroblastoma	2
Ewings	1
Melanoma	1
Meningioma	2
Mucosal Melanoma	2
Sarcoma	2
Squamous	5

postoperative radiation and 3 received definitive radiation. Concurrent chemotherapy was used in 1 patient who received definitive radiation and in 2 additional patients in the postoperative setting. One patient had elective neck radiation performed. Two patients received reirradiation to a median dose of 62 GyRBE.

All patients included had VMAT plans available for comparison. Results from comparative dosimetry are shown in **Table 2**. With respect to mean dose, there was a statistically significant reduction in dose to the optic nerves and chiasm, brain, pituitary gland, lacrimal glands, and cochlea with proton therapy. With respect to maximum dose, there was a statistically significant reduction in dose to the optic nerves and chiasm, pituitary gland, lacrimal glands, and cochlea with proton therapy. Coverage to the target structures was compared using the mean dose with the CTV as proton therapy plans were generated based on the CTV. The median mean dose to the CTV was 104.36% (102.10%-105.65%) of the prescribed dose with protons and 103.59% (100%-104.43%) with photons.

The median follow-up of all patients included was 19.7 months (range, 4.8-42.4 months). The median follow-up for patients who remain living was 22.0 months. Currently, there have been 3 incidences of local failure, 1 with concomitant distant failure. There has been 1 distant only failure and 0 isolated regional failures. There were no patients who experienced local failure and received salvage local therapy. The cumulative incidence of local failure at 18 months was 19.1%, illustrated in **Figure 1**.

Figure 1. Local control of patients with periorbital tumors treated with PBT. Abbreviation: PBT, proton beam therapy.

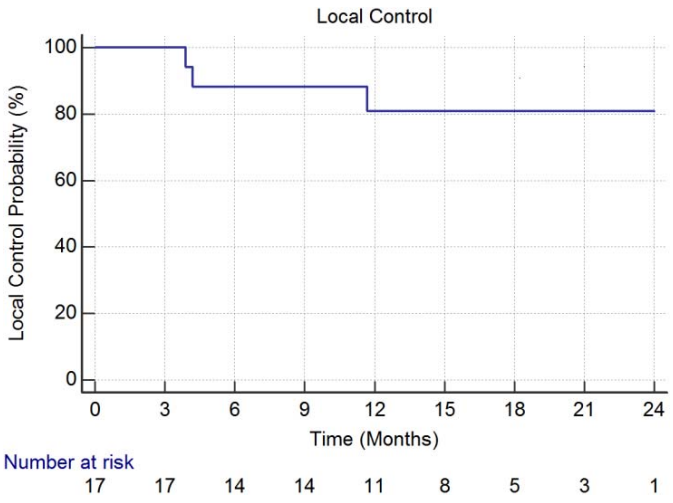

Table 2. Dosimetric comparison of maximum and mean doses to OARs between photon and proton therapy.

Organ	Mean proton	Mean VMAT	Mean difference	*P* value
Right eye				
Mean	12.65	12.43	0.23	.6
Maximum	36.37	33.36	3.01	.76
Left eye				
Mean	13.07	15.03	1.95	.12
Maximum	32.55	33.94	1.39	.23
Right lens				
Mean	7.37	7.18	0.18	.61
Maximum	12.25	9.11	3.14	.93
Left lens				
Mean	7.36	8.81	1.45	.24
Maximum	11.26	10.34	0.92	.61
Right optic nerve				
Mean	25.48	29.41	3.94	.04[a]
Maximum	35.89	39.66	3.77	.01[a]
Left optic nerve				
Mean	23.45	29.14	5.69	.003[a]
Maximum	35.9	38.65	2.75	.02[a]
Optic chiasm				
Mean	21.6	28.25	6.65	.005[a]
Maximum	34.33	39.04	4.71	.05[a]
Brain				
Mean	4.93	9.24	4.31	.001[a]
Maximum	59.87	59.4	0.47	.83
Pituitary				
Mean	35.44	38.98	3.54	.02[a]
Maximum	43.38	46.64	3.26	.02[a]
Right lacrimal				
Mean	7.83	13.2	5.37	.003[a]
Maximum	13.2	17.16	3.96	.02[a]
Left lacrimal				
Mean	8.85	15.64	6.79	.01[a]
Maximum	10.6	19.98	9.38	.001[a]
Right cochlea				
Mean	15.96	21.38	5.42	.01[a]
Maximum	19.82	25.56	5.74	.01[a]
Left cochlea				
Mean	8.11	19.41	11.31	.001[a]
Maximum	10.74	22.38	11.64	.001[a]

Abbreviations: OARs, organs at risk; VMAT, volumetric arc therapy.

[a]A significant *P* value at $\alpha = .05$; Benjamini–Hochberg correction applied to all tests.

There has been a total of 3 deaths to date, all in patients with recurrent/persistent disease. One patient died of distant disease without pathologic, radiographic, or clinical evidence of local failure. Overall survival at 12 months was determined to be 80.9% and is depicted in **Figure 2**.

Proton therapy was tolerated well overall. The most common acute toxicities to occur during or within 90 days of proton therapy were radiation dermatitis and mucositis. There were no acute toxicities related to the orbit, eye or visual apparatus, aside from dermatitis of the overlying or nearby skin. The overall incidence of acute grade III toxicity was low, occurring in only 2 patients (11.8%). There were 0 acute grade IV/V toxicities. A full list of acute toxicities is given in **Table 3**. At a median follow-up of 19.7 months, there have been a total of 7 late toxicities that occurred more than 90 days after completion of proton

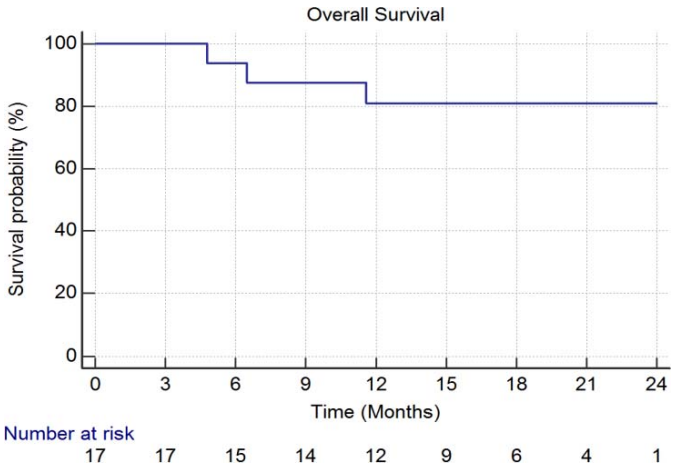

Figure 2. Overall survival of patients with periorbital tumors treated with PBT. Abbreviation: PBT, proton beam therapy.

therapy. Only 1 late grade III toxicity has been observed to date and no grade IV/V toxicities. A full list of late toxicities is given in **Table 4**. With respect to visual toxicity, there has been 1 patient who developed asymptomatic dry eye as a late effect. No instances of cataracts, vision loss, or other ocular toxicity have been reported.

Discussion

The treatment of periorbital tumors generally depends on the size, specific location, and extent of invasion. The development of an optimal treatment regimen for each patient usually involves close cooperation between the surgeon and radiation oncologist. Surgery is often the preferred initial local modality for malignancies in this location, except in cases of large tumors, recurrent disease, deeply invasive tumors, tumors with perineural invasion, and tumors with orbital invasion [10].

Use of radiation therapy in periorbital locations has been previously reported. Petsuksiri et al [11] reported a local control rate of 88% in 42 eyelid squamous cell carcinomas treated with kilovoltage X-rays and electrons to a median dose 50 to 55.25 Gy. In another large series of 850 patients with eyelid cancers treated with contact therapy or conventional RT or electrons (45-

Table 3. Acute toxicity in patients with periorbital tumors treated with PBT (within 90 days of PBT completion).

Acute toxicity	n
Dermatitis	
Grade I	1
Grade II	15
Grade III	1
Mucositis	
Grade I	2
Grade II	10
Grade III	0
Xerostomia	
Grade I	0
Grade II	3
Grade III	0
Dysphagia	
Grade I	0
Grade II	1
Grade III	1
Weight loss	
Grade I	0
Grade II	1
Grade III	0

Abbreviation: PBT, proton beam therapy.

Table 4. Late toxicity in patients with periorbital tumors treated with PBT (>90 days from date of PBT completion).

Late toxicity	n
Grade I xerostomia	1
Grade II xerostomia	2
Grade III hearing impairment	1
Grade I nasal congestion	1
Grade I dry eye	1
Grade II fatigue	1

Abbreviation: PBT, proton beam therapy.

70 Gy), Schlienger et al [2] reported a local control rate of 97.5%. Our local control rate with protons (80.9% at 18 months) was comparable to these reports of conventional RT. This was achieved with excellent sparing of the visual apparatus and other OARs.

The benefit of proton therapy has been well described for tumors that originate from the globe itself across several tumor types, such as rhabdomyosarcoma and uveal melanoma. Several series have reported low rates of toxicity when used in either the definitive [9], or postoperative setting [12]. In addition, definitive proton therapy has been shown to be a feasible strategy for organ preservation when the eye cannot be preserved with surgery [13, 14]. However, the benefit of proton therapy in periorbital tumors is not well described, despite the close proximity to similar OARs. This study has shown that there are numerous benefits to proton therapy in terms of dosimetry and patients experienced a low burden of both acute toxicity and late toxicity. Of note, these dosimetric benefits were observed without compromising coverage to the CTV. Unfortunately, there is no comparison group available to determine if side effects were reduced with the favorable dosimetric profile of protons. However, a prior study of patients with skin cancers in the same region treated with photons or electrons noted a 1.4% risk of

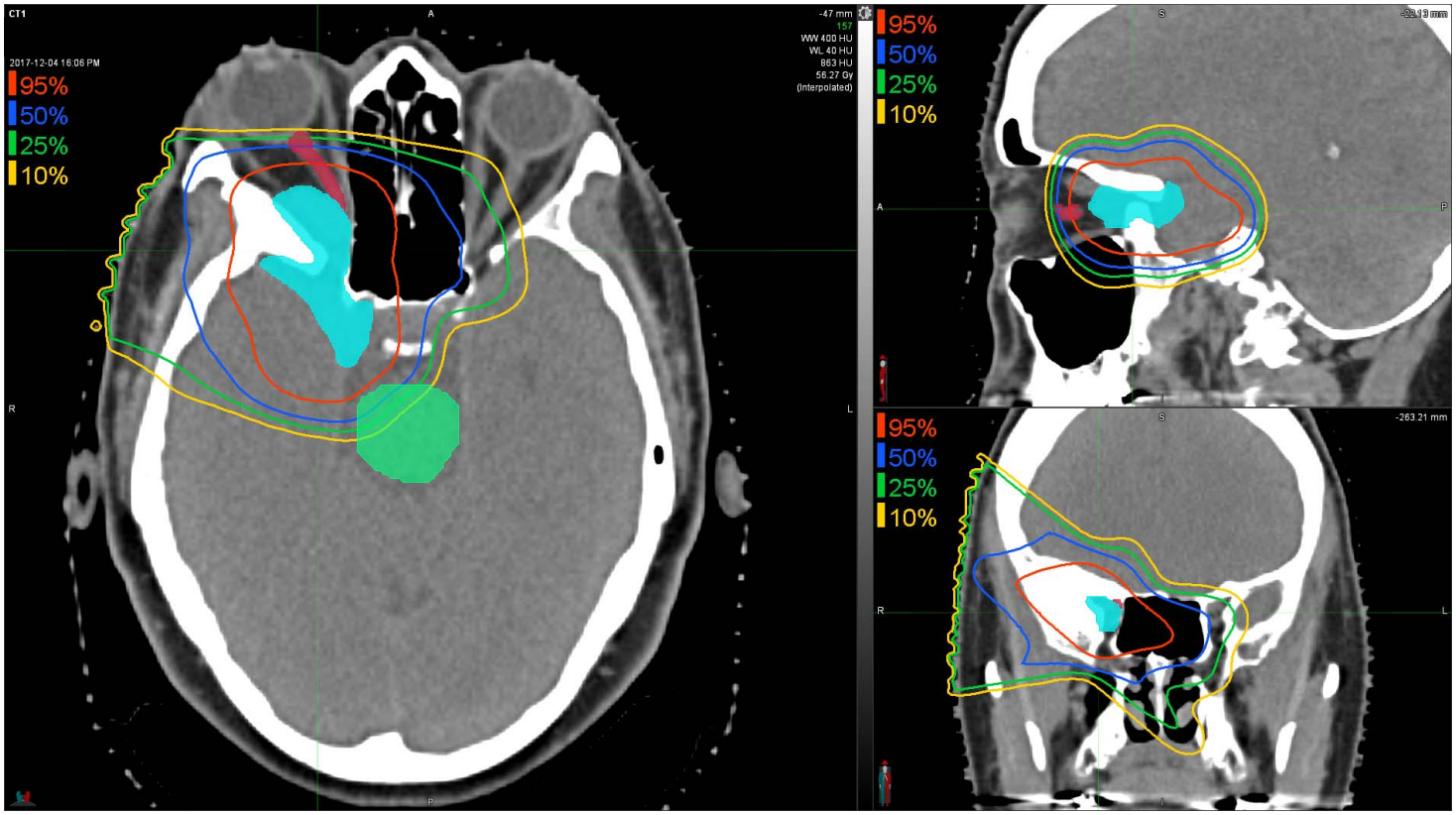

Figure 3. Axial, sagittal, and coronal cross-sections taken from the VMAT plan of a representative patient. The CTV is shaded in teal, the brainstem is shaded in light green, and ipsilateral optic nerve is shaded in red. The 95% isodose line is shown in red, 50% isodose line in blue, 25% isodose line in green, and 10% isodose line in orange. Abbreviations: CTV, clinical target volume; VMAT, volumetric arc therapy.

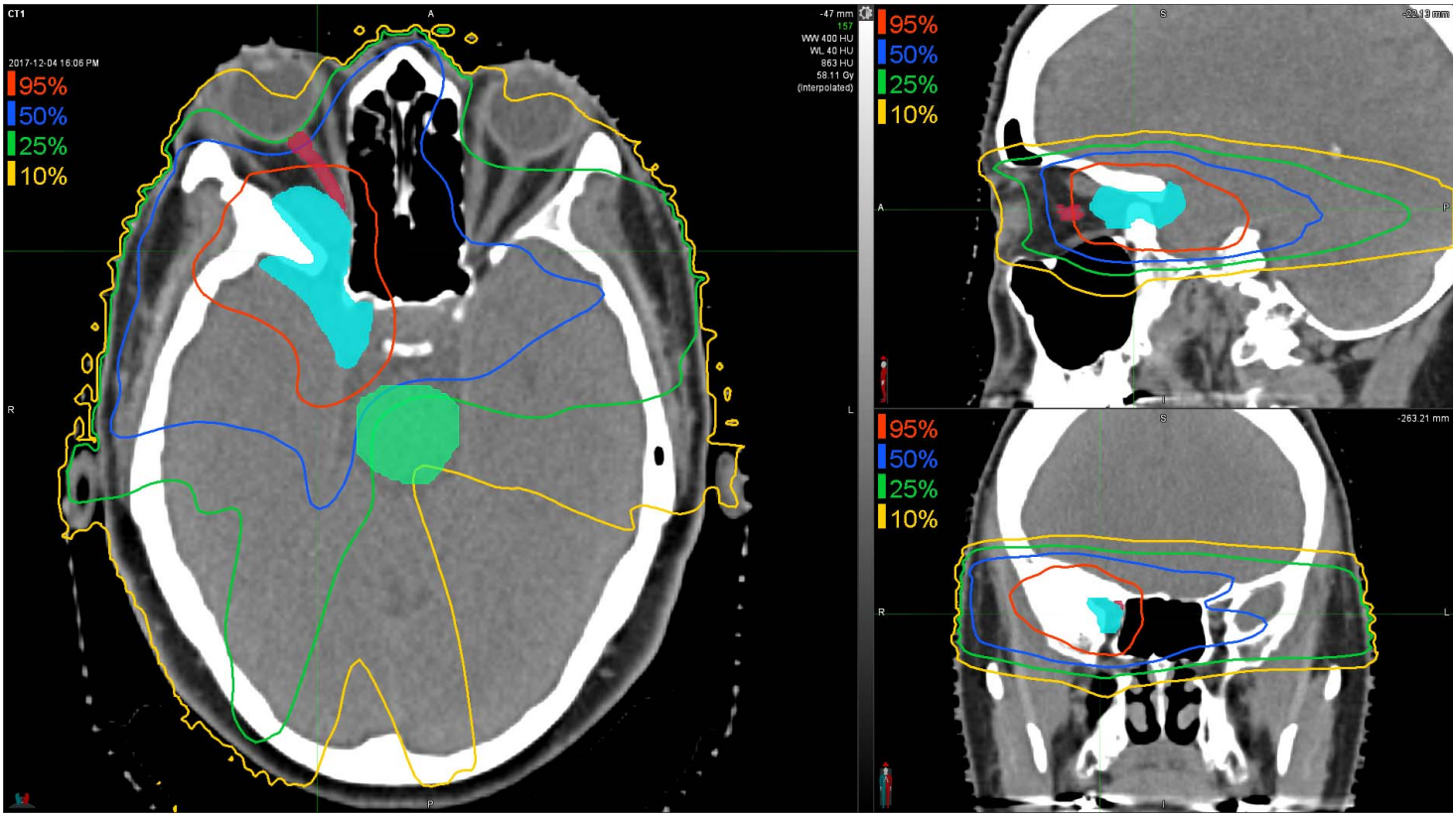

Figure 4. Axial, sagittal, and coronal cross-sections taken from the PBT plan of a representative patient. The CTV is shaded in teal, the brainstem is shaded in light green, and ipsilateral optic nerve is shaded in red. The 95% isodose line is shown in red, 50% isodose line in blue, 25% isodose line in green, and 10% isodose line in orange. Abbreviations: CTV, clinical target volume; PBT, proton beam therapy.

serious complications, such as vitreous hemorrhage, glaucoma, and loss of the eye [2]. In addition, in this series, 2.4% of patients developed keratitis, 4% xerosis, 4.5% ectropion, and 11.5% watering of the eye(s). Another study of patients with periorbital lymphoma found that 19.1% of patients develop corneal toxicity and 21.3% developed dry eye, although serious complications, such as glaucoma, were rare [3]. While long-term follow-up is currently premature, outcomes with proton therapy in the current study appear favorable because no patients have developed symptomatic late or persistent toxicity of the eye or orbit.

While the dosimetry for the nonproton plans would be considered acceptable per most standards, it is important to consider the benefit of reducing integral dose to OARs. Many potential toxicities that occur from radiation of structures near the orbit do not have well defined threshold values, such as the risk of brain atrophy and secondary malignancy. The median follow-up in this study remains relatively short and the lack of a comparative group treated with photons precludes a comparative analysis of late adverse events from radiation. However, prior studies suggest that reductions in mean dose to the brain lead to less brain atrophy [15]. In addition, the risk of secondary malignancy after radiation to the brain is apparent even at low mean brain doses, with the risk increasing as mean dose to the brain increases [16]. This suggests that the relative reduction in mean brain dose seen in this study could reduce the risk of secondary malignancy, despite the overall low mean dose given to the brain using photon therapy. To better illustrate the reduction in integral dose using proton therapy, **Figures 3** and **4** display the relative doses from corresponding proton and VMAT plans that were generated to treat 1 of the patients included in this study. The prescribed dose in this case was 50.4 GyRBE delivered in 1.8 GyRBE per fraction. A subtraction image is also included (**Figure 5**).

Another previously described risk of radiation to tumors in this region is late toxicity in the form of hypopituitarism [17]. The risk of hormone deficiencies as a result of radiation to tumors in the sella is high when the pituitary gland itself is often within the high-dose planning target volume. Hypopituitarism after radiation of nearby structures where the sella does not receive prescription dose is less well described. However, several series have shown that there is a linear dose response without a practical threshold, where increasing mean doses of radiation to the pituitary gland are more likely to cause hormone

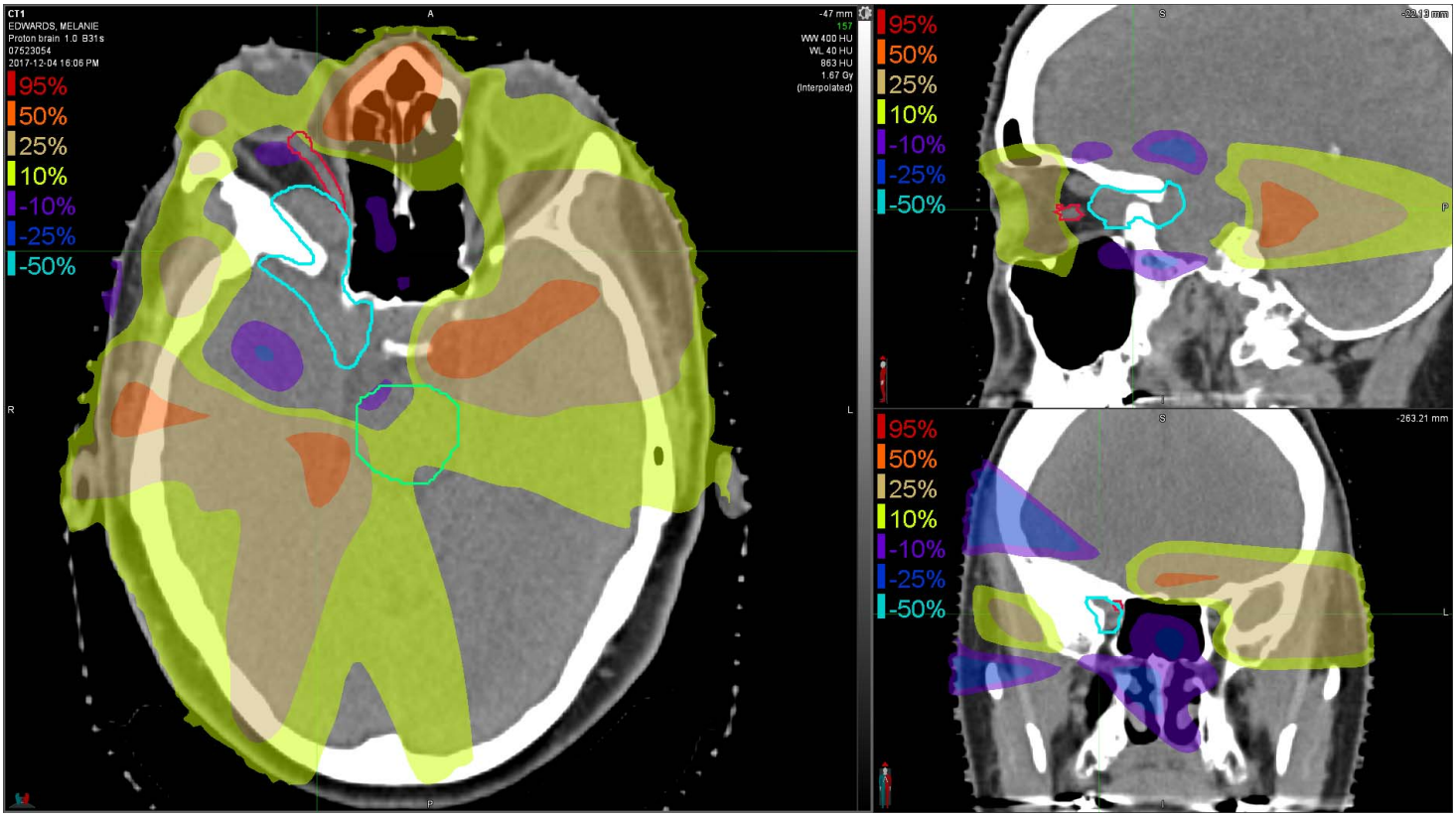

Figure 5. Digital subtraction images that were generated to show differences in integral dose. Positive percentages indicate areas where VMAT delivered higher dose while negative percentages indicate areas where PBT delivered higher dose. Abbreviations: PBT, proton beam therapy; VMAT, volumetric arc therapy.

deficiencies [18–20]. As a result, the reduction in dose with the use of proton therapy seen in this study could be hypothesized to reduce the risk of hypopituitarism.

A significant concern with PBT for periorbital tumors is uncertainty in dose delivery secondary to tissue changes during treatment. A large portion of patients included in this study had tumors located in the paranasal sinuses, nasal cavity, or nasopharynx. All of these locations are subject to changes in aeration of the sinuses. This has been previously shown to alter dose distributions in patients, which subsequently increased to dose to OARs [21]. Institutional strategies to reduce the risk of toxicity from such uncertainty include using multiple beams for treatment delivery as well as avoiding beam ranging into a common structure, particularly the optic apparatus or brainstem, which have well-established dose thresholds. A robustness analysis is also performed to account for range uncertainty. Patients who are at high risk for tissue changes, such as those with tumors arising in the paranasal sinuses or nasal cavity, are also scheduled to undergo repeat CT simulations during their treatment course. The dose distribution is then recomputed using the initial treatment plan to evaluate the maximum, minimum, and mean dose to the target area and organs at risk. Treatments for patients who exhibit significant changes are then replanned at the discretion of the treating physician.

We do acknowledge several limitations of our study. Being retrospective in nature, there may be an inherent selection bias to patients receiving PBT as only patients with insurance approval are treated with proton therapy. The comparison between proton and photon therapy is based on dosimetry and the lack of brain magnetic resonance imaging scans for most patients precludes analysis of dose to some OARs that cannot be defined using CT alone, such as the hippocampi. Although proton therapy was associated with reduced dose to several OARs, it can only be hypothesized that this differential reduces the burden of acute and/or late toxicity due to lower integral dose. In addition, clinical situations may arise where the lower integral dose associated with passive scatter PBT is not preferable to VMAT, which can generate sharper dose fall-off around irregularly shaped target volumes that are in close proximity to OARs. Despite this gradient consideration, it was encouraging

that we did not observe any significant visual toxicity with PBT and reduction in both mean and maximum doses were noted. It is also possible that the risk or severity of cutaneous toxicity is higher in this location with proton therapy due to reduced skin sparing. However, no late effects to the skin were observed to date. A larger study with longer follow-up would be needed to help establish if late toxicities are acceptable. Last, the patients treated with proton therapy in this study were treated with passive scatter, not intensity modulated proton therapy. The latter has been shown to further reduce dose to OARs in certain locations [22, 23]. Despite the above limitations, we do believe that our study contributes positively to existing literature. To the best of our knowledge, our series is the first to report clinical experience and advantages of proton therapy specifically for tumors in the periorbital location.

In conclusion, early results of proton therapy in the management of periorbital tumors show excellent tumor control with an acceptable toxicity profile. Proton therapy can be used in primary and recurrent periorbital tumors in either the definitive or postoperative setting. Longer follow-up is needed to further assess tumor control endpoints and late toxicities, but preliminary results are encouraging. This modality is safe and should be considered an effective management option as adjunct or alternative to surgery in this challenging tumor location.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: Mitchell X. Machtay, MD reports travel funding from Mevion Inc. and Varian Inc., and grants and travel funding from Elekta Inc., outside the submitted work. The authors have no other relevant conflicts of interest to disclose.
Ethical Approval: All patient data were collected under internal review board–approved protocol.

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