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Clinical Investigation: Central Nervous System Tumor

Projected Second Tumor Risk and Dose to Neurocognitive Structures After Proton Versus Photon Radiotherapy for Benign Meningioma

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Summary

In this dosimetric comparison of photon vs. proton radiotherapy (RT) for benign intracranial meningioma, proton RT reduced the projected risk of developing an RT-associated second tumor by half in comparison with photon RT, with greater benefit in patients with larger tumors and long posttreatment survival. Doses received by neurocognitive, visual, and auditory organs were significantly lower among proton plans, yet there was no significant difference in anticipated late toxicities using normal tissue complication probability models.

Purpose: To calculated projected second tumor rates and dose to organs at risk (OAR) in patients with benign intracranial meningioma (BM), according to dosimetric comparisons between proton radiotherapy (PRT) and photon radiotherapy (XRT) treatment plans.

Methods and Materials: Ten patients with BM treated at Massachusetts General Hospital during 2006–2010 with PRT were replanned with XRT (intensity-modulated or three-dimensional conformal radiotherapy), optimizing dose to the tumor while sparing OAR. Total dose was 54 Gy in 1.8 Gy per fraction for all plans. We calculated equivalent uniform doses, normal tissue complication probabilities, and whole brain–based estimates of excess risk of radiation-associated intracranial second tumors.

Results: Excess risk of second tumors was significantly lower among PRT compared with XRT plans (1.3 vs. 2.8 per 10,000 patients per year, $p < 0.002$). Mean equivalent uniform doses were lower among PRT plans for the whole brain (19.0 vs. 22.8 Gy, $p < 0.0001$), brainstem (23.8 vs. 35.2 Gy, $p = 0.004$), hippocampi (left, 13.5 vs. 25.6 Gy, $p < 0.0001$; right, 7.6 vs. 21.8 Gy, $p = 0.001$), temporal lobes (left, 25.8 vs. 34.6 Gy, $p = 0.007$; right, 25.8 vs. 32.9 Gy, $p = 0.008$), pituitary gland (29.2 vs. 37.0 Gy, $p = 0.047$), optic nerves (left, 28.5 vs. 33.8 Gy, $p = 0.04$; right, 25.1 vs. 31.1 Gy, $p = 0.07$), and cochleas (left, 12.2 vs. 15.8 Gy, $p = 0.39$; right,1.5 vs. 8.8 Gy, $p = 0.01$). Mean normal tissue complication probability was $<1\%$ for all structures and not significantly different between PRT and XRT plans.

Conclusions: Compared with XRT, PRT for BM decreases the risk of RT-associated second tumors by half and delivers significantly lower doses to neurocognitive and critical structures of vision and hearing.

Keywords: Second tumor risk, Proton radiotherapy, Photon radiotherapy, Benign meningioma, Neurocognitive

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Introduction

Benign meningioma (BM) represent approximately one-third of all primary brain tumors and 80% of meningiomas, with a current estimate of 170,000 people with meningioma in the United States (1). Despite their benign histology intracranial BM may lead to substantial morbidity, due to the tumors and/or from treatment. Complete surgical resection is considered optimal management, but definitive radiotherapy (RT) or postoperative RT for sub−totally resected tumors is often used (2).

With cause-specific survival of at least 85−90% at 10 to 15 years (2), patients with BM treated with RT are at risk for late effects. Although short-term toxicity of RT for BM appears infrequently (3), potential late RT effects include neurocognitive impairment, visual or hearing deficits, hypopituitarism, and RT-associated second tumors (4−7). Radiotherapy-related factors that may be associated with these late toxicities include total RT dose, fractionation schedule, and volume of organs at risk (OAR) irradiated.

Proton RT (PRT) offers a strategy that maintains optimal tumor coverage but reduces RT dose to normal tissues and thereby may reduce side effects. Proton RT delivers radiation with characteristic rapid dose fall-off plus dose weighting at end range within targets. However, there are limited data on dose to OAR when treating BM, and no prior study examining either projected or actual late effects after PRT vs. photon RT (XRT) for BM. Previous reports have compared tumor coverage between these RT modalities but have included a variety of brain tumor types and prescription doses, making comparisons challenging (8−10).

The present study compared PRT and XRT dosimetry on patients with BM receiving standard doses, with a focus on dose and its effects on OAR.

Methods and Materials

Study population

Ten patients with BM treated at the Massachusetts General Hospital with PRT between March 2006 and August 2010 were identified. Tumor sites represented multiple intracranial locations, including the sphenoid wing ($n = 2$), olfactory groove ($n = 2$), anterior falx ($n = 1$), posterior falx ($n = 1$), tuberculum sellae ($n = 1$), temporal convexity ($n = 1$), and cavernous sinus ($n = 2$) (Table 1). Laterality included left-sided ($n = 4$), right-sided ($n = 2$), and midline ($n = 4$) lesions. Median target volume was 16.3 cm^3 (range, 2.7−79.8 cm^3).

Simulation and treatment planning

Patients were immobilized using a modified Gill-Thomas-Cosman head frame (Integra-Radionics, Burlington, MA) including custom dental mold and occipital head rest. Computed tomographic (CT) simulation was performed with intravenous contrast, and images were acquired at 2.5-mm intervals through the cranium. Targets were defined on CT planning scan with the assistance of magnetic resonance image fusion.

Table 1 Tumor locations and volumes and number of RT fields

Patient no.	Intracranial site	Laterality	Target volume (cm^3)	No. of fields	
				Proton RT plan	Photon RT plan
1	Sphenoid wing	Left	26.0	3	7
2	Olfactory groove	Midline	2.7	3	5
3	Anterior falx	Right	66.1	3	5
4	Tuberculum sellae	Midline	2.7	3	5
5	Posterior falx	Left	43.2	3	3
6	Cavernous sinus	Bilateral	17.9	4	5
7	Sphenoid wing	Left	8.8	4	7
8	Olfactory groove	Midline	79.8	3	5
9	Temporal convexity	Right	14.7	2	2
10	Cavernous sinus	Left	5.8	3	5

Abbreviation: RT = radiotherapy.

The clinical target volume (CTV) was defined as the radiographically visible tumor and where applicable included the microscopically positive resection margin, contoured by a radiation oncologist specialized in central nervous system (CNS) disease. A planning target volume (PTV) construct does not apply in PRT planning, given that penetration of each beam is significantly altered by movement and setup uncertainty, unlike photon beams. To ensure CTV coverage in PRT plans, adjustments are made on a per-beam basis using an 8-mm lateral margin for penumbra and setup uncertainty, smearing distance of 3 mm for compensator misalignment, and a 3.5% CT density correction applied to the range plus 1 mm for range uncertainty. These modifications provide CTV coverage equivalent to that used in XRT planning through use of a PTV construct. A 3-mm PTV expansion is standardly applied in our XRT practice for treatment of BM and was used for XRT plans in this study. Normal tissues were contoured by a neuroanatomist and approved by a CNS radiation oncologist. The same GTV and normal tissue volumes were used for both PRT and XRT planning.

All patients had PRT plans generated with the XiO planning system (CMS, St. Louis, MO), and these were used as the basis for actual patient treatment. Comparison 6-MV photon treatment plans were generated using the same planning system, using three-dimensional conformal XRT ($n = 2$) or intensity-modulated XRT (IMRT; $n = 8$) techniques, whichever was superior for optimization of tumor coverage while sparing OAR; the number of fields used for PRT and XRT plans are shown in Table 1. Normal tissue constraints included brainstem $\leq$54 Gy, optic nerves and chiasm $\leq$54 Gy, lens $\leq$10 Gy, and globes $\leq$45 Gy. To avoid bias in comparisons with treated PRT plans that had clinically acceptable target volume coverage, photon target volume coverage was assigned the highest planning priority. Proton doses were corrected with the accepted relative biologic effectiveness (RBE) value of 1.1 (11). Total dose was 54 Gy(RBE) in 1.8 Gy(RBE) per fraction for all PRT and XRT plans. All plans were approved by a CNS radiation oncologist.