Proton therapy for atypical meningiomas

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Abstract

We report clinical outcomes of proton therapy in patients with World Health Organization grade 2 (atypical) meningiomas. Between 2005 and 2013, 22 patients with atypical meningiomas were treated to a median dose of 63 Gy (RBE) using proton therapy, as an adjuvant therapy after surgery (n=12) or for recurrence or progression of residual tumor (n=10). Six patients had presumed radiation-induced meningiomas, but none had received prior radiotherapy for their meningioma. The median follow-up time after radiation was 39 months (range 7–104) and all patients remain alive at last follow-up. The 5-year estimate of local control was 71.1% (95% CI 49.3–92.9%). The 5-year estimate of local control was 87.5% following a radiation dose > 60 Gy (RBE), compared to 50.0% for ≤ 60 Gy (RBE) (p=0.038). The 5-year estimate of neuraxis dissemination was 5% (95% CI 0–14.6%) and 6.2% (95% CI 0–18.2%) for metastases outside of the central nervous system. Radiation necrosis was observed in one patient with a history of prior cranial irradiation. Fractionated proton therapy was associated with favorable tumor control rates for grade 2 meningiomas. Prospective studies are needed to define the optimal radiation dose for high-grade meningiomas.

Introduction

Meningiomas represent approximately 25% of primary brain tumors diagnosed in adults [1]. The great majority are benign World Health Organization (WHO) grade 1 tumors and long term disease control is typically achieved with surgery, radiation, or combination therapy [2-4]. WHO grade 2 (atypical) and 3 (anaplastic) meningiomas are uncommon subtypes of meningioma which are associated with a higher risk of local recurrence after surgery and radiation [5, 6], and a probability of neuraxis dissemination and distant metastases beyond the central nervous system (extra-CNS) [7]. While a recent retrospective series suggests that adjuvant radiotherapy is associated with improved local control even after gross total resection of atypical meningiomas [8], a systematic review of the literature highlights the uncertainties regarding the role of radiotherapy in this disease [9].

The optimal radiation dose for high-grade meningiomas remains unclear [10]. Local control with fractionated external beam radiation in conventional doses used for benign meningiomas, on the order of 50-54 Gy, is poor [11, 12], and the pattern of failure appears to be primarily in-field [13], suggesting a rationale for dose escalation or intensification. However, doses greater than 60 Gy have infrequently been used with fractionated X-ray techniques due an increasing risk of brain radiation necrosis. Results of stereotactic radiosurgery for high-grade meningiomas have been disappointing [14] and there appears to be a higher risk of marginal tumor failure [15, 16], although many of these patients receive radiosurgery for salvage after prior fractionated external beam radiation.

Proton therapy is a modality of radiation therapy distinguished from X-ray radiation by the physical property of energy deposition within the target at the Bragg peak. Proton dosimetry exhibits dose deposition to the depth of the target, after which the dose rapidly terminates, delivering essentially no radiation beyond the depth of the target. The absence of exit dose minimizes radiation exposure to non-target tissues and can allow for radiation dose escalation when indicated [17, 18]. Two prior retrospective reports on combined photon-proton therapy for grade 2 and 3 meningiomas suggested a benefit to radiation dose escalation beyond 60 Gy for both local tumor control and overall survival [19, 20]. We report our experience using proton therapy for atypical WHO grade 2 meningiomas.

Materials and Methods

Institutional review board approval was obtained for this retrospective review. Inclusion criteria were patients with grade 2 meningiomas who were receiving their initial meningioma-directed radiotherapy. Details of the proton beam delivery system have been previously published [21]. Orthogonal kilovoltage X-ray images were used for daily patient alignment prior to treatment of each field, using a robotic patient position with 6 degrees of freedom [22]. Radiotherapy was administered exclusively with protons. Patients were treated with once daily fractionation of 1.8–2 Gy (RBE). Proton dose is expressed in Gy (RBE) with a relative biologic effectiveness of 1.1 compared to megavoltage X-ray therapy.

Treatment planning involved an alpha cradle and thermoplastic mask for immobilization and acquisition of a computed tomography (CT) scan with 1 mm slice thickness. Preoperative and postoperative magnetic resonance imaging (MRI) scans were coregistered to delineate the

original extent of the tumor, the tumor bed, and any macroscopic residual disease. The clinical target volume was defined as the original tumor bed with an expansion for potential microscopic tumor extension, including intraparenchymal brain extension, that varied with anatomic location, was anatomically constrained to natural boundaries of spread and typically ranged from 0.5–1 cm. Most commonly, a 1 cm expansion was used to treat to 54 Gy (RBE) and then a field reduction was made to treat the tumor bed and residual tumor with a 0.5 cm margin. A 2 mm uniform expansion was added for a planning target volume (PTV). For patients with delayed recurrence of tumor after prior surgery, after delivery of an intial 54 Gy (RBE) that encompassed the original tumor bed, a field reduction was typically made to encompass the area of recurrent disease with similar margins for a boost to the total dose.

Total dose selection was variable over the time period of this study based on the preference of different treating physicians. Eight patients received a dose of 60 Gy (RBE) or less. Two patients with radiation-induced meningiomas received 54 Gy (RBE) due to concern for cumulative dose to the optic apparatus and risk for visual loss. Five received 59.4 Gy (RBE) and one 60 Gy (RBE) because the treating physician preferred this dose for atypical meningiomas. Fourteen patients received a dose greater than 60 Gy (RBE). Nine patients received 63 Gy (RBE), one 66 Gy (RBE), and four 68.4 Gy (RBE).

Follow-up time was calculated from the completion date of radiotherapy. Information on acute and late toxicity was retrospectively gathered from weekly treatment status notes, the treatment completion summary, follow-up notes, and correspondence with other physicians. After radiation therapy, patients typically underwent magnetic resonance imaging at 2 months and then

every 6 months for tumor surveillance. Endpoints analyzed were local tumor control, neuraxis spread, metastases outside the central nervous system (extra-CNS), and overall survival. Local tumor progression was defined as radiographic enlargement of the residual tumor or development of adjacent new areas of tumor, as determined by neuroradiology interpretation of follow-up imaging. Neuraxis spread was diffuse and distant leptomeningeal spread including spinal drop metastases. Five year event estimates were calculated using the Kaplan Meier method and 95% confidence intervals (CI) are presented. The log-rank test was used to perform univariate analysis of patient and disease characteristics. Univariate Cox regression analysis was used to assess continuous variables. Statistical analysis was performed with SPSS version 20.

Results

Between 2005 and 2013, 22 patients with WHO grade 2 meningiomas were treated at the now closed Indiana University Health Proton Therapy Center with fractionated proton therapy as their first course of meningioma-directed radiation. Table 1 lists patient and treatment characteristics. The median prescribed dose was 63 Gy (RBE) with a range of 54–68.4 Gy (RBE). The median follow-up time after radiation therapy was 39 months (range 7–104 months), and all patients remain alive at last follow-up. The 5-year estimate of local control was 71.1% (95% CI 49.6–92.9%). One patient developed evidence of neuraxis spread and later distant metastases, with a 5-year estimate of 5% (95% CI 0–14.6%) for neuraxis dissemination and 6.2% (95% CI 0–18.2%) for extra-CNS metastases.

In univariate analysis of this cohort, there was no statistically significant difference in local control by gender, age (continuous variable), use of radiation in the adjuvant setting or for

recurrent disease, number of prior surgeries, radiation induced tumors, or GTV at the time of radiation. Radiation dose was associated with local control. At five years, local control was maintained in 87.5% (95% CI 64.6–100%) who received doses greater than 60 Gy (RBE), compared to 50.0% (95% CI 15.3–84.7%) for those who received 60 Gy (RBE) or less (p=0.038) (Figure 1).

Patterns of Failure, Salvage, Toxicity Analysis

Five patients developed local tumor progression. The median time to local tumor progression was 20 months from the completion of radiotherapy (range 13–39 months). Four were isolated local failures, and all were within the radiation treatment field. In the remaining patient, local tumor progression was accompanied by development of other foci of meningioma remote from the original site concerning for neuraxis spread and 10 months later by distant extra-CNS metastases. All patients with local tumor progression have received salvage therapy of radiosurgery (n=3), surgery alone (n=1), and surgery followed by fractionated reirradiation (n=1).

Acute toxicities related to radiation therapy were minimal, with grade 1-2 fatigue, and for patients with convexity and parasagittal meningiomas, temporary alopecia and mild radiation dermatitis. One patient with a history of prior pituitary radiation was treated for a radiation-induced sphenoid wing meningioma and developed grade 3 temporal lobe radiation necrosis that improved after treatment using pentoxifylline with vitamin E and hyperbaric oxygen.

Discussion

Clinical outcomes for patients with grade 2 and 3 meningiomas are inferior to those with grade 1 histology [12]. Table 2 summarizes results of radiotherapy from several studies. No randomized clinical data are presently available to guide clinical management of these relatively uncommon histologies, although an open randomized trial seeks to establish whether there is a benefit to adjuvant radiotherapy after gross total resection of grade 2 meningiomas [23].

Results from a small phase I/II dose escalation trial for high-grade meningiomas were reported by colleagues at the Massachusetts General Hospital, suggesting promising long-term local control with dose escalated proton therapy [18]. A larger retrospective series from the same institution found an association between improved local tumor control and overall survival in patients treated with doses greater than 60 Gy [19]. These results were echoed in a report by colleagues at the Institut Curie, who similarly noted an association between doses greater than 60 Gy and improved local control and overall survival [20]. Our own data also suggests a local control benefit for doses of greater than 60 Gy in patients with grade 2 meningioma receiving their initial meningioma-directed radiotherapy. Because no deaths have yet been observed in this cohort, we cannot assess potential factors associated with overall survival.

Not all series have seen an apparent benefit to treatment intensification for high-grade meningiomas [11]. A large multicenter retrospective review by the Rare Cancer Network on 119 patients with high-grade meningiomas did not identify a dose response within the ranges utilized [24]. However, a recent systematic review of the literature summarizes that the majority of published studies on grade 2 and 3 meningiomas support an association between higher dose and

improved clinical outcomes [9]. The Radiation Therapy Oncology Group has completed a phase II non-randomized trial that proposed a risk stratification based on grade, extent of resection, and recurrence after prior surgery, utilizing 54 Gy for those assigned to an intermediate risk group, and 60 Gy for those deemed high risk. The European Organisation for Research and Treatment of Cancer is also conducting a phase II non-randomized trial that utilizes 60 Gy for high-grade meningiomas after gross total resection and 70 Gy after subtotal resection. Results from these trials should provide prospective data on higher dose treatment strategies to better guide clinical decision-making but will not directly address the question of optimal radiation dose.

While our institutional approach has favored higher-dose radiotherapy for high-grade meningiomas, it was not always deemed appropriate, for example in two patients with radiation-induced grade 2 meningiomas who were treated to 54 Gy (RBE) due to concern about cumulative radiation dose and tolerance of the adjacent optic apparatus. Both of these patients fortunately maintain local control at last follow-up without visual complication.

Most studies of high-grade meningiomas, including our own, are limited by their retrospective nature and all the usual patient selection and treatment biases which confound retrospective analysis. Additionally, a limited number of patients precludes rigorous analysis of the many variables and confounding interactions of variables thought to be associated with outcomes. Longer-term follow-up is needed to capture late recurrences and toxicities after therapy. Our data does not directly address what potential benefit proton therapy may offer over X-ray based modalities of therapy. Others have demonstrated that proton therapy can achieve lower integral brain dose during treatment of intracranial targets [25]. These reductions may be meaningful in

patients with benign tumors at risk for late neurocognitive effects of brain radiation, but few clinical data are available. Given the increasing data to suggest a benefit to higher dose for high-grade meningiomas [9], it may be that proton therapy is preferential in targets where other treatment modalities are felt to have too great a risk in providing dose escalation[17].

Conclusions

Fractionated proton therapy was associated with favorable tumor control rates for grade 2 meningiomas. Doses greater than 60 Gy (RBE) were associated with improved local control. Prospective studies are needed to define the optimal radiation dose for high-grade meningiomas.

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Figure Legend

Figure 1: Local tumor control outcomes stratified by radiation dose for patients receiving their initial meningioma-directed radiotherapy for grade 2 meningiomas.

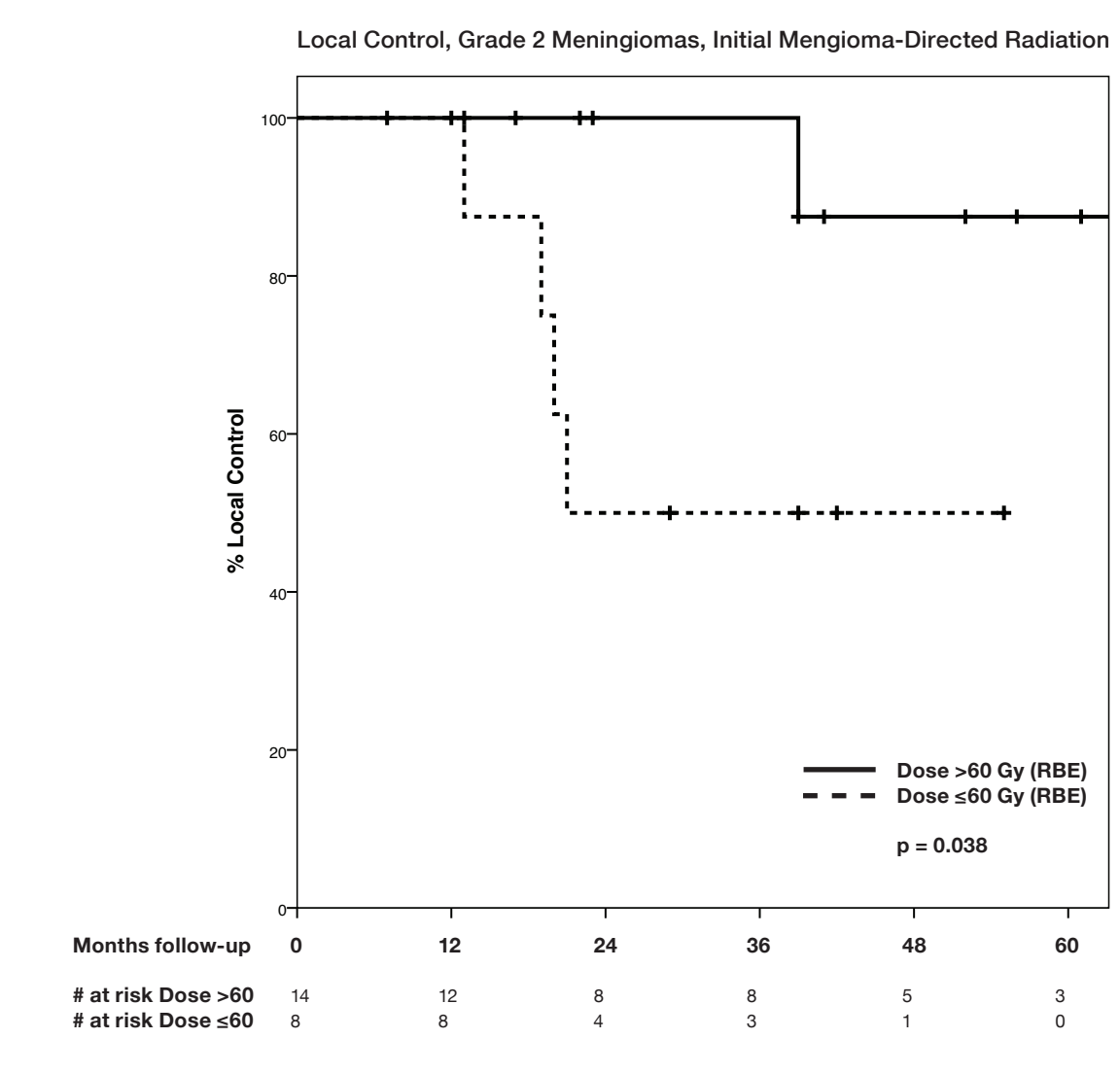
Local Control, Grade 2 Meningiomas, Initial Mengioma-Directed Radiation
% Local Control
100
80
60
40
20
0
Dose >60 Gy (RBE)
Dose ≤60 Gy (RBE)
p = 0.038
Months follow-up 0 12 24 36 48 60
at risk Dose >60 14 12 8 8 5 3
at risk Dose ≤60 8 8 4 3 1 0

Table 1: Patient and treatment characteristics

Number of patients	22
Age	
Median (range)	42 years (14 – 75)
Gender	
Male	10
Female	12
Tumor location	
Parasagittal	7
Skull base	6
Convexity	5
Posterior fossa	3
Orbit	1
Presumed radiation-induced	
No	16
Yes	6
Prior meningioma-directed radiation	0
Prior surgical interventions	
1 prior surgery	13
2 prior surgeries	7
3 prior surgeries	2
Result of surgery prior to proton therapy	
Gross total resection	11
Subtotal resection	11

Indication for proton therapy	
Planned adjuvant therapy	12
Treatment for recurrence or progression	10
Tumor identified at time of radiation planning	
Yes	18
No	4
GTV at time of proton therapy	
Median (range)	8.1 cm^3 (0–89.3)
Dose of proton therapy	
Median (range)	63 Gy (RBE) (54–68.4)
Dose ≤ 60 Gy (RBE)	8
Dose > 60 Gy (RBE)	14
Number of proton treatment fields	
Median (range)	5 (2 – 10)
Number of proton fields treated daily	
Median (range)	3 (1 – 4)

WHO = World Health Organization, GTV = gross tumor volume, RBE = relative biological effectiveness.

Table 2: Results of radiotherapy for grade 2 and 3 meningiomas

Institution	Ref	Years	# pts	Technique	Median Dose	Median f/u time	Grade 2 5yr LC	Grade 3 5yr LC
MGH	[19]	1973-1995	31	XRT or PBT	62.5 [a]	59 mo [a]	38%%	52%
RCN	[24]	1971-2005	119	XRT	54.6 [a]	49 mo	62% [b]	48% [b]
Institut Curie	[20]	1999-2006	25	XRT + PBT	64.2	48 mo	47% [c]	
U. Flor.	[11]	1984-1999	36	HART + SRS	60 [d] + 12.5	41 mo	45% [c]	
Heidelberg	[6]	1985-2004	45	XRT	59.4	43 mo	44.5% [e]	8.1% [e]
PMH	[12]	1966-1990	59	XRT	50	40 mo [f]	34%‡ [g]	
Wash. U.	[14]	2000-2011	35	SRS	18	34.5 mo	30% [e, h]	0%
Mayo	[15]	1990-2008	50	SRS	15	38 mo	45% [c]	
U. Tokyo	[16]	1991-2012	22	SRS	18	23.5 mo	16%	NA
Present series		2005-2013	22	PBT	63	39 mo	71%	NA

pts = number of patients, Dose expressed in Gy, f/u = follow-up, mo = months, 5yr = 5-year, LC = local control, XRT = fractionated external beam photon therapy, PBT = proton beam therapy; SRS = stereotactic radiosurgery, HART = hyperfractionated accelerated radiation therapy, NA = not applicable, MGH = Massachusetts General Hospital, RCN = Rare Cancer Network, U. Flor. = University of Florida; PMH = Princess Margaret Hospital, Wash. U. = Washington University; U. Tokyo = University of Tokyo

[a] mean value

[b] Disease free survival

[c] Results for grade 2 and 3 reported together

[d] Given in twice daily fractions of 1.5 Gy

[e] Progression free survival

[f] in patients remaining alive

[g] crude control results

[h] results at 3 years