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Quantifying Proton Fields for Midline Brain Tumors: A Benefit/Cost Analysis of Planning Objectives

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Abstract

Purpose: We sought to quantify the optimum number of beams by using a midline sagittal arrangement for midline brain tumors when considering the competing demands of a high degree of target conformation and maximizing reduction of nontarget brain dose. The volume of nontarget brain tissue receiving between 5 and 20 Gy (V5-V20) was selected to measure "low-dose bath" to normal brain.

Materials and Methods: An exploratory model was developed with 6 midline brain targets created by using spheres of 1-, 3-, and 5-cm diameters located in superficial and deep locations. For each, five 3-dimensional proton treatment plans with uniform beam scanning were generated by using 1 to 5 fields. Dose-volume histograms were analyzed to calculate conformation number and V5-V20. A benefit/cost analysis was performed to determine the marginal gain in conformation number and the marginal cost of V5-V20 for the addition of each field and hypothesize the optimum number of treatment fields. We tested our hypothesis by re-planning 10 actual patient tumors with the same technique to compare the averages of these 50 plans to our model.

Results: Our model and validation cohort demonstrated the largest marginal benefit in target conformation and the lowest marginal cost in normal brain V5-V20 with the addition of a second proton field. The addition of a third field resulted in a relative marginal benefit in target conformation of just 3.9% but a relative marginal cost in V5-V20 of 78.7%. Normal brain absolute V5-V20 increased in a nearly linear fashion with each additional field.

Conclusions: When treating midline brain lesions with 3-dimensional proton therapy in an array of midline sagittal beams, our model suggests the most appropriate number of fields is 2. There was little marginal benefit in target conformation and increasing cost of normal brain dose when increasing the number of fields beyond this.

Keywords: protons; central nervous system; brain; dosimetry

Introduction

Radiation therapy remains essential to treatment of many brain tumors, but in light of recognized risks of cranial radiation, advancements in radiation techniques have emphasized target conformation and minimization of dose to normal brain and other intracranial organs at risk (OARs).

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Proton therapy is a modality of radiation distinguished from photon therapy by a finite range and the physical property of the Bragg peak. Using proton therapy, each beam's maximal energy is deposited in the target, after which point energy deposition terminates, with essentially no exit dose radiation to normal tissue beyond the target [1]. We have previously described the application of proton therapy in midline central nervous system (CNS) tumors by using an array from 1 to 5 midline sagittal beams to target superficial or deep-seated brain tumors [2]. The midline sagittal beam arrangement facilitates avoidance of the temporal lobes and hippocampi, and when using proton therapy there is no exit dose through the body (**Figure 1**). In our previously reported cohort, the number of midline beams used was driven by individual physician judgment based on qualitative evaluation of the tradeoff between improved target dose conformation and an increased volume of normal brain exposed to dose with the addition of more beams.

In an effort to quantify the competing objectives of dose conformation and integral dose exposure in identifying an "optimal" or most appropriate number of proton fields in a midline sagittal beam arrangement, we developed a model by using hypothetical targets of varied size and then tested our hypothesis against a cohort of previously treated patients.

Materials and Methods

This research was performed within an institution-reviewed board-approved retrospective study. Eclipse treatment planning software, version 11 (Palo Alto, California), was used for treatment planning using institutionally commissioned proton beam data for delivery with uniform beam scanning. Details of our proton system have been previously published [3].

Using the CT planning simulation scan from a prior patient, we created 6 hypothetical planning target volumes (PTVs) as spheres of 1, 3, and 5 cm in diameter in both a superficial parasagittal and deep suprasellar locations (**Supplemental Figure 1**). For each of these 6 models, five 3-dimensional conformal proton treatment plans were generated by using between 1 and 5 fields. Fields were added sequentially by using angles that minimized both the volume of brain traversed to the target and overlap with other fields (**Figure 1**). An aperture margin of 6 to 8 mm was used depending on the treatment depth for a particular field. Proximal and distal range uncertainties of 2 mm beyond the PTV were used for each beam, per our institutional approach to range uncertainties in treatment of brain tumors. This varies from a more common practice of applying a percentage of the beam range plus a fixed distance (eg, 3.5% +1 mm) used at other centers [4]. Compensator smearing of 3 mm was applied. The prescription dose was 54 Gy (relative biological effectiveness [RBE]) in 30 fractions where proton dose is reported as the physical dose multiplied by a weighting factor of 1.1. Plans were normalized at the 100% isodose line. A structure of "nontarget normal brain" was created by subtracting the PTV from the brain contour, which included the brainstem.

For each of the 30 resultant model plans, dose-volume histograms were analyzed to calculate metrics. The conformation number (CN) for each PTV was calculated by using the methodology of van't Riet et al [5] and Feuvret et al [6] where CN equals the product of the conformity index (a measure of target coverage by the 95% isodose line) and the healthy tissues conformity index (a measure of adjacent nontarget tissue covered by the same isodose line) (see **Table 1** and equations 1, 2, and 3). The CN ranges from 0 to 1, with a value of 1 indicating perfect conformation. Because of the proximal and distal range uncertainties applied in proton therapy, the dose intentionally overshoots the PTV to account for uncertainties in the calculated proton range [4], precluding plans with a high CN. The absolute volume of nontarget brain tissue receiving between 5 and 20

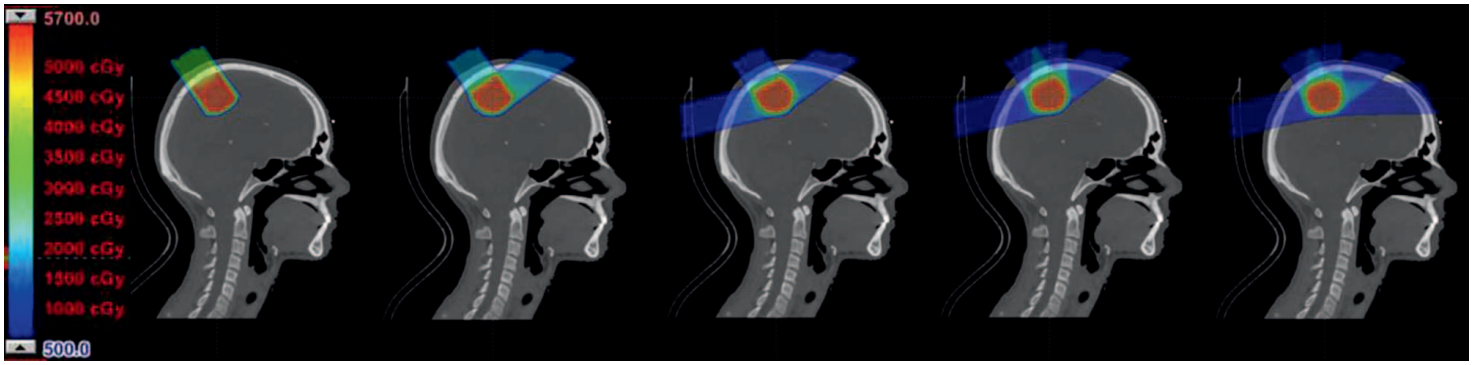

Figure 1. From 1 to 5 midline sagittal beams were applied to all 6 model targets to determine conformation number and V5-V20 for each, when V5-V20 is volume of nontarget normal brain receiving dose in the 5- to 20-Gy interval. This is the spherical 3-cm-diameter superficial target.

Table 1. Terms and definitions used for conformation number and homogeneity index calculations.

Abbreviation	Definition	Notes
CI	Conformity index	= (TVRI)/(TV) {equation 1}
HCTI	Healthy tissues conformity index	= (TVRI)/(VRI) {equation 2}
CN	Conformation number	= (CI) × (HTCI) {equation 3}
TVRI	Target volume covered by reference isodose line	95% isodose line was used
TV	Target volume	Spherical target volume in model or planned target volume in actual tumors
VRI	Volume of reference isodose	Volume of the 95% isodose line
HI	Homogeneity index	= $(D_{2\%} - D_{98\%})/D_{50\%}$[a]

[a]$D_{2\%}$ and $D_{98\%}$ are minimum doses to 2% and 98% of TV, respectively, while $D_{50\%}$ is mean TV dose.

Gy (RBE) (V5-V20) was calculated as a measure of the "low-dose bath," a dose range where neural stem cell toxicity may putatively occur [7–9]. A homogeneity index was calculated for each plan by using the ratio of the minimum dose to 2% of the PTV ($D_{2\%}$) minus the minimum dose to 98% of the PTV ($D_{98\%}$) divided by the mean dose ($D_{50\%}$), where a value of 0 indicates perfect homogeneity and an increasing value indicates less homogeneity [10].

To assess the most appropriate number of beams, we sought to quantify the added "benefit" from the addition of each subsequent beam in terms of additional CN gained compared to the added "cost" of increased dose exposure to nontarget normal brain in terms of V5-V20. In classical benefit/cost analysis both benefits and costs are in monetary units. One expands operations as long as the marginal benefit (added benefit) exceeds the marginal cost of doing so. Once that no longer holds, we stop expanding, as we have found the optimal level of operation. In the current consideration, we cannot monetize the benefits and costs; they are in physical units that are different. Hence, we use what we will call *relative benefit/cost analysis*.

To summarize the data from 30 individual model plans, an average model was created by calculating the mean values for each data point for a given number of fields. We defined benefit as the mean CN at each interval moving sequentially from 1 to 5 beams. The marginal benefit of moving from 1 to 2 beams, for example, is the increase in the mean CN.

In the same way, we defined cost as the mean V5-V20 at each interval from 1 to 5 beams. Similarly then the marginal cost of moving from 1 to 2 beams is the corresponding increase in the mean V5-V20.

In our relative benefit/cost analysis we do not consider how the marginal benefit compares to the marginal cost. Instead we look at the percentage increase in marginal benefit as the relative marginal benefit (RMB) and the percentage increase in marginal cost as the relative marginal cost (RMC) at each increment. The relative benefit/cost analysis suggests increasing the number of beams when RMB is high and RMC is low, but stopping if adding a beam has a low RMB or a high RMC.

Next we assessed the validity of our model by re-planning 10 previously treated patients with midline CNS tumors, 5 superficial and 5 deep in the brain. Mean dose delivered to these patients was 53.6 Gy (RBE). Using the same methodology and planning parameters as in our model, for each patient, we generated five 3-dimensional conformal proton treatment plans by using between 1 and 5 fields, with fields added sequentially by using angles that minimized both the volume of brain traversed to the target and overlap with other fields. The same data were collected for CN and V5-V20 dose to nontarget normal brain for these 50 plans, based on actual tumor volumes. Total and marginal benefit in terms of mean CN and total and marginal cost in terms of mean V5-V20 were then calculated for these plans. The mean data from these 50 plans were used for comparison to the model.

Results

Our spherical models of superficial and deep CNS targets of varied sizes found that CN reached a maximal value of 0.55 with 4 fields. The marginal benefit in CN was minimal after the second field, with an increase of just 0.01 in CN per field with the addition of a third and fourth field (RMB $\sim$ 1%-2%) and no increase in CN with the addition of a fifth field. The absolute V5-V20 to nontarget normal brain increased with the addition of each field. The marginal cost in V5-V20 increased sharply with the addition of a third field, with an RMC 109.2% greater than the marginal increase seen with adding a second field. The homogeneity index for all plans was near zero, with a value of 0.03 and no change with additional fields (**Table 2** and **Figure 2**).

We analyzed the 1-, 3-, and 5-cm-diameter superficial and deep volumes of the model individually to understand how the addition of a field from 1 to 5 affected the CN and V5-V20. For each of the 6 individual models, the largest increase in CN was found with the addition of the second field with smaller gains or even sometimes losses in CN with the addition of the third,

Table 2. Mean results from model of 30 total plans in 6 hypothetical targets.

	1 Field	2 Field	3 Field	4 Field	5 Field
Total benefit (mean CN)	0.43	0.53	0.54	0.55	0.55
Marginal benefit (marginal increase in CN)	-	0.10	0.01	0.01	0.00
Relative marginal benefit	-	21.9%	2.5%	1.4%	0.0%
Total cost (mean V5-V20[a])	25.7	73.5	153.8	172.0	264.0
Marginal cost (marginal increase in V5-V20)	-	47.8	80.3	18.2	92.0
Relative marginal cost	-	186.4%	109.2%	11.8%	53.5%
Mean homogeneity index	0.03	0.03	0.03	0.03	0.03

Abbreviation: CN, conformation number.

[a]Volume of nontarget normal brain (cm^3) receiving between 5 and 20 Gy.

fourth, and fifth fields. When evaluating each of the 6 models individually for the increase in V5-V20 with the addition of a field, a similar pattern to that seen in the previously described average of the models emerged. V5-V20 increased with the second field but then there is a substantial increase observed with the addition of the third. A difference was noted in that the increase in V5-V20 with the third field is more pronounced in the 3 superficial models than in the 3 deep-seated models, but the general pattern holds for all 6 hypothetical models (data not shown).

In validating our model with actual patient data, similar results were seen. Conformation number increased with each additional field to a maximal value of 0.68 with all 5 fields. The marginal benefit was minimal after the second field, increasing by 0.02 to 0.03 (RMB ~ 3%-4%) with the addition of each subsequent field. The absolute nontarget normal brain V5-V20 increased in a nearly linear fashion with the addition of the third, fourth, and fifth fields with an increase of approximately 82 cm^3 of normal brain V5-V20 per field. Although less pronounced than seen in the model, the marginal cost increase in nontarget brain V5-V20 again reached an inflection point with the addition of a third field, where the RMC was 78.7% greater than the increase seen with the addition of a second field. The marginal costs of adding a fourth and fifth field were similar to the cost of adding a third field. Again, the mean homogeneity index for these actual patient tumors was low for all plans and decreased minimally with each added treatment field (**Table 3** and **Figure 3**).

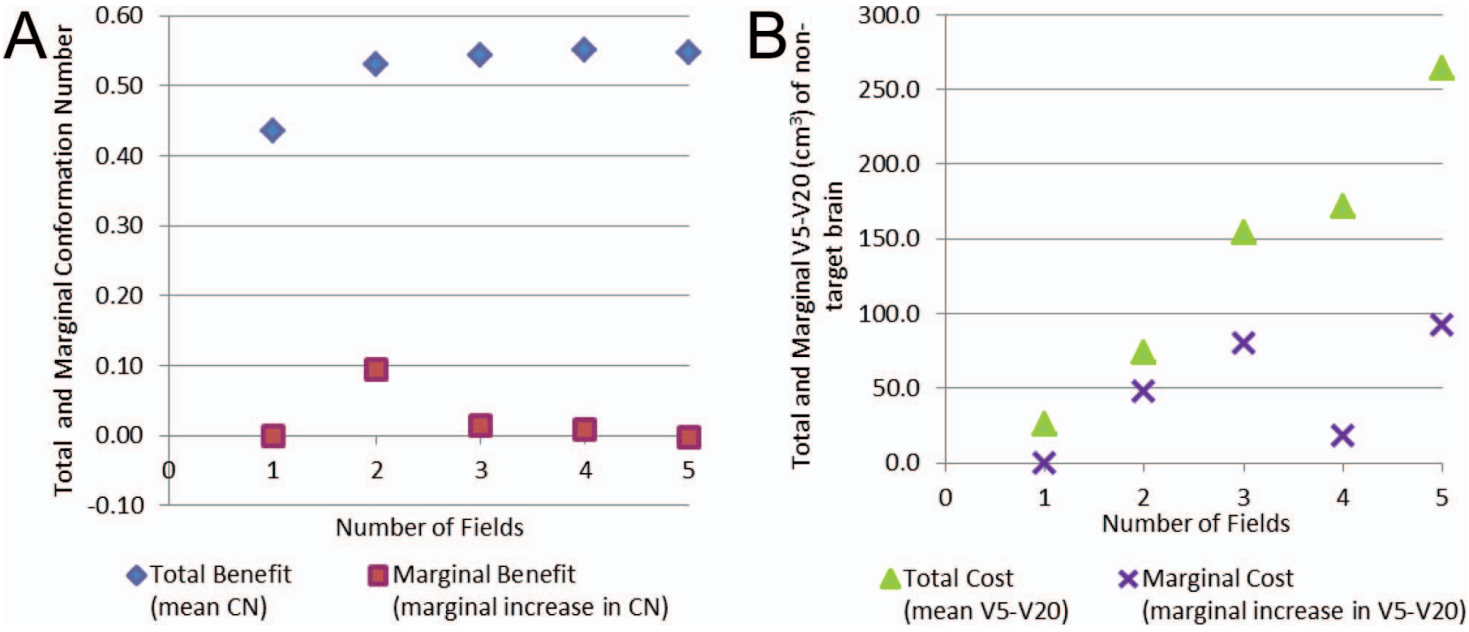

Figure 2. Mean data from the 6 model targets with 30 model plans. (A) The total and marginal benefit is reported as the total and marginal CN on the y-axis against the number of treatment fields on the x-axis. (B) The total and marginal cost is reported as the total and marginal volume of normal nontarget brain receiving between 5 and 20 Gy (V5-V20) on the y-axis against the number of treatment fields on the x-axis. Abbreviation: CN, conformation number.

Table 3. Mean results from 50 total plans in 10 previously treated patients.

	1 Field	2 Field	3 Field	4 Field	5 Field
Total benefit (mean CN)	0.48	0.61	0.64	0.66	0.68
Marginal benefit (marginal increase in CN)	-	0.14	0.02	0.02	0.02
Relative marginal benefit	-	28.4%	3.9%	3.1%	3.6%
Total cost (mean V5-V20[a])	41.9	106.8	190.8	269.0	353.2
Marginal cost (marginal increase in V5-V20)	-	64.9	84.0	78.2	84.3
Relative marginal cost	-	154.8%	78.7%	41.0%	31.3%
Mean homogeneity index	0.07	0.06	0.05	0.05	0.04

Abbreviation: CN, conformation number.

[a]Volume of nontarget normal brain (cm^3) receiving between 5 and 20 Gy.

Both the model and the patient data suggest that following the gains made from the addition of a single field, 2 fields achieve the largest sequential gain in target conformation with the smallest sequential cost in marginal V5-V20. The findings did not vary by superficial versus deep targets in either the model or the validation cohort (data not shown).

Discussion

As expected, our data showed that a single proton field provided the lowest absolute V5-V20 to nontarget brain. However, with uniform scanning, a single proton field did not provide optimal proximal target conformation, and it is seen from our data that the CN is improved with an additional field. A single field is often clinically unsatisfactory owing to a relatively high entrance dose, and the skin dose in treatment of CNS lesions with a single proton beam may be associated with a risk of permanent alopecia. There is also a measurable increase in RBE in the terminal few millimeters of a proton beam's spread-out Bragg peak [11]. The potential clinical consequences of this increase must be considered in single-field plans, which are generally not advised if the beam terminates in a critical structure. Single-field plans are more susceptible to the cumulative impact of potential random and systematic errors in patient positioning, treatment field setup, and variability in beam path heterogeneities. This leads us to conclude that 2 proton fields appear to be the most appropriate number in a midline sagittal array to balance target conformation and minimize the low-dose exposure of nontarget brain.

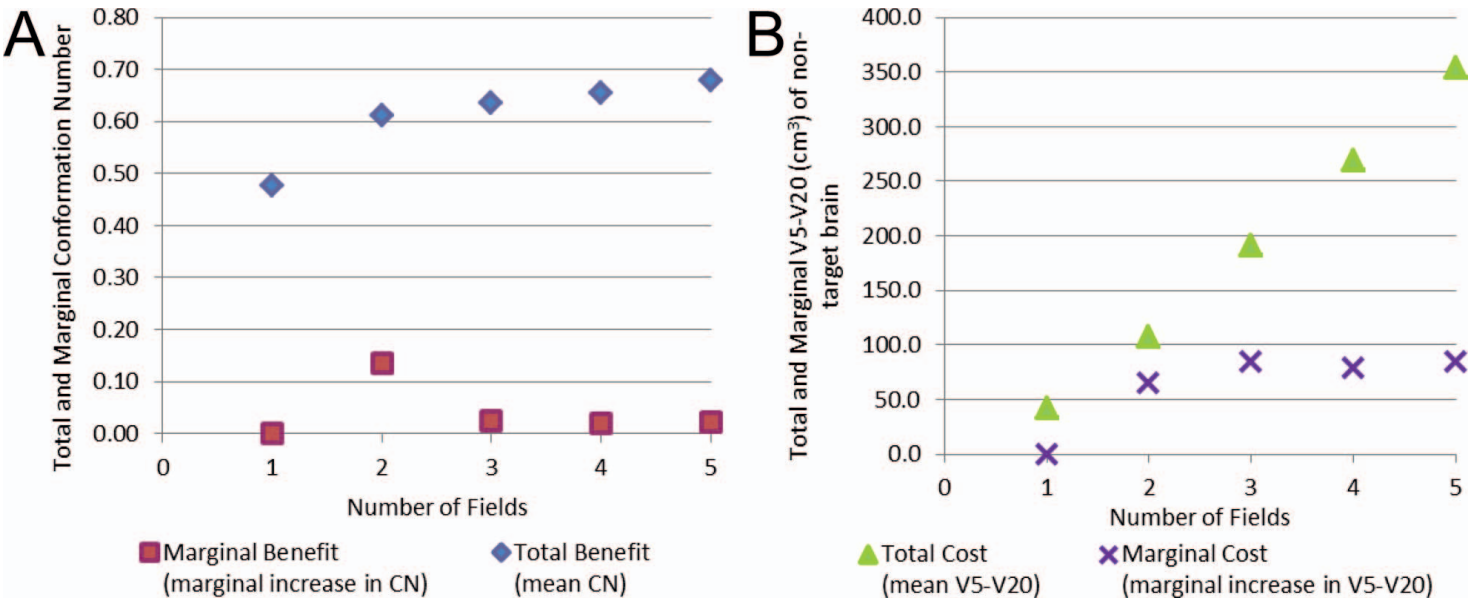

Figure 3. Mean data from the 10 actual patient targets with 50 plans. (A) The total and marginal benefit is reported as the total and marginal CN on the y-axis against the number of treatment fields on the x-axis. (B) The total and marginal cost is reported as the total and marginal volume of normal nontarget brain receiving between 5 and 20 Gy (V5-V20) on the y-axis against the number of treatment fields on the x-axis. Abbreviation: CN, conformation number.

The addition of a third field increased the CN minimally but at the cost of a large increase to the V5-20 of the nontarget brain. As seen in our validation cohort (**Table 3**), the addition of a third field resulted in an RMB of just 3.9% at a RMC of 78.7%. **Figures 2** and **3** graphically demonstrate the same data, showing small gains in CN and continually increasing V5-V20 costs when adding a third field. While incorporation of more than 2 fields may further minimize some sources of random and systematic errors that contribute to range uncertainties and dose degradation, there is no reason to believe that more than 2 fields is required for typical CNS cases when accepted range uncertainties are applied to each beam [4]. Of course there may be individual patient considerations that drive the addition of additional fields, but our quantified data analysis indicates that the costs outweigh the modest benefits.

In a plan with 2 nonoverlapping beams delivering commonly used doses of 45 to 54 Gy, the entrance dose to the skin would be associated with a low risk of permanent alopecia [12], but scalp dose should be monitored and may require an additional field to reduce the risk of permanent alopecia. Uncertainties in distal RBE enhancement may also be clinically relevant in 2-field plans, particularly if one of the fields terminates in a critical structure. In these cases, uncertainties of distal RBE enhancement could be mitigated by applying "range modulation" to the beam that terminates in a critical structure to vary the terminal range of the beam over 2 positions [13]. While each beam is preferentially selected to provide the shortest path to the target, in certain circumstances it may be preferable to orient a beam through a slightly longer path in order to terminate the beam in bone or other noncritical structures. With advances in proton delivery including pencil beam scanning, highly conformal plans can be achieved with single-field optimization and multiple-field optimization. This does not mitigate the issue of potential RBE enhancement in the terminal range, nor eliminate proximal entrance dose and the concerns of greater susceptibility to systematic and errors in patient positioning, treatment field setup, and variability in beam path heterogeneities.

Of course, any individual patient plan has additional considerations of specific patient anatomy and constraints to other critical OARs. However, a practical problem in the era of modern treatment planning and standard target dose prescriptions is in selecting among multiple acceptable plan options that do not violate any standard planning constraints but that offer different distributions of dose to nontarget normal brain. In our experience, this selection has been largely dependent on the qualitative preferences of the treatment planner and physician, and can vary significantly.

A similar phenomenon is suggested in a published series of proton therapy for pituitary adenomas in which the number of treatment fields ranged from 2 to 7 [14], presumably in excess of the range needed owing to differences in target volume and reflecting variation in clinician judgment about how to satisfactorily distribute entrance dose. While our focus has been on the optimal number of beams in proton therapy, one can imagine a similar conundrum in comparing a 7-field versus 9-field intensity-modulated radiation therapy plan versus volumetric-modulated arc therapy. While all plans may meet specified constraints to OARs, may be technically deliverable, and may be clinically reasonable, a similar evaluation of marginal improvement in conformation versus marginal increase in low-dose exposure could be made by using a marginal benefit/cost analysis.

Our mutual goals in this work were to maximize target conformity while minimizing dose to normal brain. The goal to minimize dose was driven by the understanding that cranial radiation has long been associated with neurocognitive sequelae [15]. Neurocognitive toxicities in survivors of pediatric brain tumors who had received radiation therapy have been associated with profound lifelong challenges in domains such as employment, interpersonal relationships, and susceptibility to criminal activity [16].

Pathogenesis of radiation-induced toxicity is multifactorial. It appears that depletion of relatively radiosensitive neural stem cells is an important mechanism in development of neurocognitive dysfunction [17]. Multiple brain regions have been linked to neurocognitive toxicities [18, 19]. Microvascular fibrosis and inflammation with resultant ischemia are additional factors that can also contribute to other complications seen in both adult and pediatric patients receiving cranial radiation, including increased risks of endocrine dysfunction, visual disturbances, stroke, and seizures [20].

Medical comorbidities including the index tumor and environmental and social factors contribute to the complexity of evaluating and measuring neurocognitive dysfunction. Despite the challenges of measuring this often delayed toxicity of treatment, radiation dose-response relationships have been elucidated correlating radiation exposure to clinical outcomes including decline in intelligence quotient score [18, 21]. Early results of RTOG 0933 found that hippocampal dose reduction during whole brain radiation was associated with less neurocognitive dysfunction than in historical controls [22]. These experiences and other research suggest that relatively low doses of radiation are correlated with measurable impact on neurologic function. Brain parenchymal stem cell death has been associated with doses as low as 5 Gy, endocrine dysfunction with doses as low as 10 Gy, and T1 changes on magnetic resonance imaging indicating loss of white matter (believed to be associated with neurocognitive dysfunction) at doses as low as 20 Gy [8, 9, 21, 23].

As with any retrospective treatment planning evaluation, our study has limitations. Dose-response relationships for neurotoxicity are an area of evolving knowledge, and while we elected to assess the V5-V20 on the basis of these aforementioned data, another dose range may prove to be a more appropriate measure. As more data emerge to guide dose constraints to specific brain structures, further analysis of treatment field design will be warranted. Regardless of the measure, a quantitative analysis of total and marginal benefits and costs would be instructive in evaluating the tradeoffs between tighter conformation to target volumes and the corresponding increase one can expect in dose exposure to nontarget normal brain with increasing fields. There is inherent subjectivity in the selection of beam angles during treatment planning as treatment planners balance the shortest path length to the target with minimization of beam overlap, feasibility of patient setup and efficiency of actual treatment delivery, consideration of individual patient anatomic details such as potential beam path heterogeneities and end-of-range critical structures, and clinical scenarios that may prioritize sparing of different subvolumes. However, we do not believe that reasonable variations in selection of beam angles would dramatically affect the overall results of this study in terms of the benefit/cost analysis of an increasing number of treatment fields, particularly because the optimum number of fields in our model and validation cohort was 2.

When treating midline brain lesions with 3-dimensional conformal proton therapy using uniform scanning in an array of midline sagittal beams, 2 fields appear to be the most appropriate number to balance target conformation and minimize the low-dose exposure of nontarget brain. There was little marginal benefit in dose conformation and increasing marginal cost in terms of low-dose exposure to normal brain when increasing the number of fields beyond 2. Nonuniform targets and specific constraints to OARs are additional considerations that are unique and need to be considered when creating individual patient plans. Clinicians and dosimetrists can use the findings of this model as a starting point for developing proton plans for similarly situated tumors.

ADDITIONAL INFORMATION AND DECLARATIONS

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

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