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Monte Carlo evaluation of magnetically focused proton beams for radiosurgery

Running title: Magnetically focused proton radiosurgery

Grant A McAuley, ^{1*} Sarah Heczko, ² Theodore Nyguen, ² James M Slater, ¹ Jerry D Slater, ¹ Andrew J Wroe ¹

¹ Department of Radiation Medicine, Loma Linda University, Loma Linda, CA, USA

² School of Medicine, Loma Linda University, Loma Linda, CA, USA

*Email: gmcauley@llu.edu

Abstract

The purpose of this project is to investigate the advantages in dose distribution and delivery of proton beams focused by a triplet of quadrupole magnets in the context of potential radiosurgery treatments. Monte Carlo simulations were performed using various configurations of three quadrupole magnets located immediately upstream of a water phantom. Magnet parameters were selected to match what can be commercially manufactured as assemblies of rare-earth permanent magnetic materials. Focused unmodulated proton beams with a range of ~10 cm in water were target matched with passive collimated beams (the current beam delivery method for proton radiosurgery) and properties of transverse dose, depth dose and volumetric dose distributions were compared. Magnetically focused beams delivered beam spots of low eccentricity to Bragg peak depth with full widths at the 90% reference dose contour from ~ 2.5 to 5 mm. When focused initial beam diameters were larger than matching unfocused beams (10 of 11 cases) the focused beams showed 16% to 83% larger peak-to-entrance dose ratios and 1.3 to 3.4-fold increases in dose delivery efficiency. Peak-to-entrance and efficiency benefits tended to increase with larger magnet gradients and larger initial diameter focused beams. Finally, it was observed that focusing tended to shift dose in the water phantom volume from the 80%-20% dose range to below 20% of reference dose, compared to unfocused beams. We conclude that focusing proton beams immediately upstream from tissue entry using permanent magnet assemblies can produce beams with larger peak-to-entrance dose ratios and increased dose delivery efficiencies. Such beams could potentially be used in the clinic to irradiate small-field radiosurgical targets with fewer beams, lower entrance dose and shorter treatment times.

Introduction

The use of protons in the treatment of cancer provides a modality of external-beam radiation that can treat targets with fewer treatment beams and thus reduce integral dose delivered to the patient (Slater et al 2007). In addition, improvements in imaging technologies including CT, MRI and PET are allowing earlier detection of cancerous lesions, and the prospect of earlier stage treatments is fueling a trend in radiation medicine towards the irradiation of increasingly smaller targets. However, as field size decreases below 1.0 cm diameter, the peak-to-entrance dose performance of proton beams is degraded by beam broadening due to multiple Coulomb scattering (MCS). This beam degradation is typically overcome through the use of additional treatment beams, at the expense of increased integral dose and longer treatment times. Magnetic focusing of protons immediately before entrance into tissue could be used to counteract MCS, potentially leading to improved therapeutic ratios, fewer treatment beams, reduced entrance dose, reduced integral dose and decreased treatment times in clinical radiosurgery.

Since a magnetic field exerts a force on moving charged particles, the trajectory of protons can be altered using a single or series of magnets. Magnetic focusing is typically achieved in particle accelerators using quadrupole magnets, which consist of two pairs of alternating north and south magnetic poles. Because of this arrangement, a single quadrupole magnet focuses a chargedparticle beam in one plane longitudinal to the beam and defocuses in the other plane (Banford 1966). However, net focusing in both planes can be achieved by using a combination of two or more quadrupoles in series. Therefore, doublet or triplet sets of quadrupole electromagnets are used to focus charged particles in accelerators and particle transport systems.

In previous work we performed Monte Carlo simulations (McAuley et al 2013) and experiments with a single quadrupole focusing magnet (McAuley et al 2015) placed immediately upstream of a water phantom. This created a flattened beam with a narrow elliptical cross section at target depth. This work utilized (quadrupole) Halbach cylinders which consist of sections of directionally magnetized permanent-magnet material arranged to produce a high magnetic field inside a cylindrical cavity but with low field outside (Halbach 1980). Thus, in contrast to the electromagnets typically used in accelerator and beam transport systems, the low external magnetic fields produced by these magnet assemblies allow placement in close proximity (eg, a few cm) to patients. In addition, since the assemblies use permanent magnet material, electrical power and cryogenic cooling is not required. The experimental part of this previous work used Halbach cylinders made with of 24 segments of samarium-cobalt (Sm₂Co₁₇) permanent magnetic material (McAuley et al 2015, Choi et al 2016) chosen for its radiation hardness (Danly et al 2014, Chen et al 2005, Chen et al 2000, Barlow et al 1997). The results of these two studies demonstrated that, compared to passively scattered collimated beams (the standard delivery modality in proton radiosurgery (Wroe et al 2014)), the focused beams produced dose distributions with higher peak-to-entrance dose ratios (P/E) and showed improved efficiency in dose delivery (McAuley et al 2013, McAuley et al 2015).

However, beyond this specialized application of narrow elongated beams, most small radiosurgical targets such as brain metastases are nominally spherical and would require a combination of quadrupoles to produce beams with suitable low-eccentricity cross sections. Therefore, the purpose of the present study is to investigate the clinical potential of using a triplet of focusing magnets to target small spherical radiosurgical targets. To this end we performed

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Monte Carlo simulations involving various configurations of commercially available magnets,

and compared the resulting dose distributions with those of passively scattered collimated beams.

Methods and Materials

Monte Carlo Simulation Geometry

Monte Carlo simulations were performed using in house software that incorporates the Geant4.9.6 toolkit (Agostinelli et al 2003, Allison et al 2006). Similar to (McAuley et al 2013), monoenergetic unmodulated protons were tracked through a model of a research beam line at the James M. Slater, MD, Proton Treatment and Research Center at the Loma Linda University Medical Center and delivered to a water phantom (Fig 1). A proton energy of 118 MeV was chosen to match the range (~10 cm) in water commonly used for radiosurgery, and is relevant to treatments of small intracranial lesions. The water phantom was placed 25 mm downstream of the final beamline component (a clinically relevant air gap).



Figure 1: Simulated beam line consisting of secondary emission monitor (burgundy), transmission ionization chamber detectors (pink), collimators (orange), quadrupole focusing magnets (green), and water phantom (cyan). The geometry used for unfocused simulations was identical except it contained no magnets. (Inset) Close-up of collimators and water phantom for

unfocused configuration. Also, shown is a phase space detector (green disk) located at Bragg peak depth (R100).

An essential goal for the focusing system under study is to produce millimeter-sized dose distributions of low eccentricity at target depth (ie, Bragg peak depth). While a doublet of magnets may be preferred under certain system requirements, using a symmetric triplet of magnets has several advantages including it being generally easier to produce round beams (Banford 1966, Wollnik 1987). To compare unfocused passively scattered collimated beams (UNF) and passively scattered beams magnetically focused using such a symmetric triplet of quadrupoles (MF3), terminal components upstream from the phantom were either a two-stage collimator system of circular cross section (for UNF beams), or a similar collimator system followed by three focusing quadrupole magnets (for MF3 beams) (see Fig 1). In each triplet, the 1^{st} and 3^{rd} magnets were identical in dimensions and magnetic field gradient. The 2^{nd} (middle) magnet also had the same field gradient and differed only in length and that it was axially rotated 90 degrees with respect to the former two. For all triplet sets, the magnet length for the 1st and 3rd magnets was 40 mm, and was 68 mm for the 2nd magnet. These lengths, as well as bore diameters, were chosen to match focusing magnets being tested in our lab. Finally, the intermagnet separation distances between the 1^{st} and 2^{nd} , and 2^{nd} and 3^{rd} magnets were always equal.

Dose Scoring and Analysis

Dose from primary and secondary particles was scored in the water phantom using 0.25 mm x 0.25 mm x 0.25 mm voxels with range cuts of 100 μ m and 6.144 x 10⁹ particle histories (beams with diameter \geq 7 mm) or 9.126 x 10⁹ particle histories (beams with diameter < 7 mm). Transverse dose profiles were determined and normalized by maximum dose. From these

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profiles, the full width of the 90% of maximum dose contour was measured for both the vertical and horizontal directions (vFW90M, hFW90M) at the Bragg peak depth. Full width at half maxima (vFWHM, hFWHM), beamspot eccentricities (eFW90M, eFWHM), and 80/20 transverse penumbra (vPenumbra, hPenumbra) were also determined at this depth. Depth dose profiles were calculated using dose deposited in the central voxel at each depth. To compare P/E dose ratios between simulation cases, depth dose profiles were also normalized by maximum dose. However, to estimate the efficiency of dose delivery, simulation cases were compared by absolute dose.

In addition to depth and transverse dose profiles, volumetric dose analysis was also performed similar to (McAuley et al 2013). The reference dose (RD) (ICRU 1999) was determined as the average dose of a central 8 x 8 x 1 voxel array (dimensions of 2 mm x 2 mm x 0.25 mm) at the depth of the Bragg peak, and dose in all phantom voxels were normalized relative to the RD. Volumetric target dose was determined by dividing the total energy deposited in all voxels with a dose of \geq 90% RD by the total mass of all voxels in this volume. Likewise, integral dose was determined by dividing the total energy deposited in all phantom voxels with a dose < 90% RD (i.e. outside the target) by the total mass of the phantom minus the target mass. Volumetric 80/20 dose and < 20% dose were similarly defined using voxels with dose between the 80% and 20% contours, and below the 20% contour, respectively (McAuley et al 2013).

Phase Space Ellipses

As particles move through the focusing system, harmonic focusing and hyperbolic defocusing of charged particles in a quadrupole magnet field leads to somewhat complicated beam dynamics. It is convenient and instructive to describe the state of the beam as a whole using the beam phase

space data (i.e., the aggregate state of displacement *x* and angular divergence θ with respect to the beam axis of each particle). In particular, the statistical phase space ellipse associated with the rms beam emittance can be used to visualize the shape and distribution of phase space points as well as the overall convergent or divergent action of the beam. In addition, useful properties of this ellipse can be related mathematically to the elements of a 2 x 2 symmetric matrix (the socalled sigma matrix σ) whose elements are second statistical moments of particle displacement and divergence (ie, $\langle x^2 \rangle$, $\langle \theta^2 \rangle$, $\langle x \theta \rangle$) (Banford 1966, Wollnik 1987, Lee 2012) (see Appendix). Statistical phase space ellipses were determined from particle displacement and divergence measured by sensitive elements consisting of very thin circular disks (18 mm in radius and 2 µm thick). These phase space detectors were placed 1 mm up- and downstream from each focusing magnet, water phantom surface, and Bragg peak depth (ie, R100). 256M histories were used to determine the second moments of beam displacement and divergence in the vertical and horizontal planes at each detector position. From these moments the elements of associated σ matrices were determined.

Matching MF3 and UNF Beams

Baseline simulations were performed with 5, 6, 7, 8, 9, 10, and 11 mm diameter UNF beams. MF3 beams were matched with baseline UNF beams by varying the magnetic field gradient of the triplet (100, 150 or 200 T/m), inter-magnet separation distance, and the initial beam diameter. MF3 beams were considered to match a particular UNF beam if:

- The average of vFW90M and hFW90M values (aveFW90M) fell within 0.25 mm of the closest matching UNF aveFW90M
- ii) The eccentricity of the MF3 beam spot 90% contour was 0.25 or less

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- iii) The total volumetric dose, volumetric maximum dose, and volumetric reference dose were within 1.0 %
- iv) The 90% contour volume was within 2.5 mm^3 of the UNF beams.

The properties of 11 different MF3 beams configured using various combinations of magnet field gradient, magnet bore diameter, magnet separation and initial beam diameter that were matched with the UNF beams are listed in Table 1. For brevity, we introduce the nomenclature used throughout this manuscript as follows: UNF-Xmm will refer to an unfocused beam of diameter X mm (e.g., UNF-5mm is used for a 5 mm unfocused beam). MF3-Xmm-Y beam will refer to a beam with initial diameter of X mm that is focused by magnets with a Y T/m gradient (e.g., MF3-5mm-200 refers to a beam of initial diameter 5 mm that is focused by a triplet of magnets with 200 T/m gradients). Finally, MF3-Y is used to refer to all the MF3 beams focused by magnets with a gradient of Y T/m (e.g., MF3-100 refers to the group consisting of the MF3-12mm-100, MF3-13mm-100, MF3-15mm-100 and MF3-20mm-100 beams).

UNF Beams	MF3 Beams	Magnet Field Gradient (T/m)	Magnet Bore Diameter (mm)	Magnet Separation (mm)
UNF-5mm	MF3-5mm-200	200	10	39
UNF-5mm	MF3-9mm-200	200	10	42
UNF-6mm	MF3-8mm-150	150	20	74
UNF-7mm	MF3-12mm-150	150	20	85
UNF-8mm	MF3-15mm-150	150	20	87

Table 1 – Triplet magnet set parameters of matching MF3 beams

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UNF-8mm	MF3-18mm-150	150	20	84
UNF-8mm	MF3-20mm-150	150	20	82
UNF-9mm	MF3-12mm-100	100	20	133
UNF-9mm	MF3-13mm-100	100	20	135
UNF-10mm	MF3-15mm-100	100	20	136
UNF-11mm	MF3-20mm-100	100	20	120

UNF – unfocused beams

MF3 - triplet focused beams

UNF-Xmm - unfocused beam of diameter X mm

MF3-Xmm-Y - beam with initial diameter of X mm focused by magnets with Y T/m gradient

Results

Properties of transverse dose distributions at Bragg peak depth of matched MF3 and UNF beams are listed in Table 2. The table reveals MF3 beams delivered beam spots of low eccentricity to Bragg peak depth (eFW90M) with FW90M from ~2.5 to 5 mm. Figure 2 shows vertical and horizontal transverse dose profiles as well as normalized and un-normalized longitudinal dose profiles for MF3 beams compared with corresponding UNF beams for three target beam spot sizes. Each column of the figure shows a pair of matching MF3 and UNF beams with FW90M target sizes corresponding to prescribed isodose levels relevant to functional radiosurgery (ie, \sim 2.5, 3.5 and 5 mm respectively). Finally, Fig 3 shows three different MF3 beams matched to the 3.5 mm target: in addition to the MF3-20mm-150 beam shown in Fig 2E – H, MF3-18mm-150 and MF3-15mm-150 beams are also matched with the UNF-5mm beam.

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Table 2 – Transverse dose property comparisons

	vFW90M	hFW90M	aveFW90M	eFW90M	vFWHM	hFWHM	aveFWHM	eFWHM	vPenumbra	hPenumbra
	(mm)	(mm)	(mm)		(mm)	(mm)	(mm)		(mm)	(mm)
MF3-5mm-200	2.37	2.44	2.40	0.25	6.30	6.39	6.34	0.17	3.11	3.17
MF3-9mm-200	2.52	2.57	2.54	0.20	6.50	6.67	6.58	0.23	3.10	3.20
UNF-5mm	2.38	2.45	2.41	-	6.18	6.21	6.20	-	2.97	2.94
MF3-8mm-150	2.70	2.78	2.74	0.24	7.08	7.42	7.25	0.30	3.41	3.67
UNF-6mm	2.64	2.72	2.68	-	6.70	6.73	6.71	-	2.97	2.94
MF3-12mm-150	3.00	3.01	3.01	0.04	7.62	7.88	7.75	0.25	3.57	3.83
UNF-7mm	3.04	2.98	3.01	-	7.29	7.29	7.29	-	3.28	3.31
MF3-15mm-150	3.14	3.20	3.17	0.19	7.87	8.18	8.02	0.27	3.59	3.95
MF3-18mm-150	3.39	3.42	3.41	0.14	8.28	8.60	8.44	0.27	3.67	4.09
MF3-20mm-150	3.49	3.51	3.50	0.10	8.50	8.93	8.71	0.31	3.70	4.23
UNF-8mm	3.28	3.33	3.31	-	8.03	8.04	8.04	-	3.47	3.46

MF3-12mm-100	3.68	3.75	3.72	0.19	9.19	9.76	9.47	0.34	4.17	4.69
MF3-13mm-100	3.79	3.90	3.85	0.24	9.47	9.99	9.73	0.32	4.22	4.78
UNF-9mm	3.76	3.67	3.72	-	8.85	8.84	8.85	-	3.63	3.62
MF3-15mm-100	4.09	4.03	4.06	0.18	9.85	10.42	10.13	0.33	4.15	4.93
UNF-10mm	4.35	4.24	4.29	-	9.74	9.70	9.72	-	3.73	3.77
MF3-20mm-100	5.15	5.05	5.10	0.19	11.21	12.25	11.73	0.40	4.20	5.12
UNF-11mm	5.15	5.13	5.14	-	10.72	10.71	10.71	-	3.81	3.83

MF3 beams are grouped with matching UNF beams

UNF-Xmm - unfocused beam of diameter X mm

MF3-Xmm-Y - beam with initial diameter of X mm focused by magnets with Y T/m gradient

vFW90M, hFW90M, aveFW90M - vertical, horizontal, and average full widths of transverse dose profiles at 90% of maximum dose, and vFWHM, hFWHM and aveFWHM are vertical, horizontal and average full widths of transverse dose profiles at half

maximum dose at Bragg peak depth (R100), respectively

eFW90M and eFWHM - eccentricities of the ellipses defined by vertical and horizontal FW90M and FWHM, respectively

vPenumbra and hPenumbra - vertical and horizontal penumbra (80% - 20% dose) at Bragg peak depth, respectively.

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Figure 2: MF3 vs. UNF Beams. Each column shows a comparison of matching MF3 and UNF beams with FW90M target sizes of ~ 2.5 , 3.5 and 5 mm, respectively. Panels in first two rows display transverse profiles at entrance and Bragg peak depth (R100), in the vertical and horizontal planes, respectively. Panels in last two rows show normalized and un-normalized depth dose profiles, respectively (Legend: 'Xmm UNF' - unfocused beam of diameter X mm; 'Xmm Y' – focused beam with initial diameter of X mm focused by a triplet of magnets with Y T/m gradient).



Figure 3: Multiple MF3 Beams Compared with a Single UNF Beam. Panels A) and B) show transverse profiles at entrance and Bragg peak depth (R100), in the vertical and horizontal planes, respectively. Panels C) and D) show normalized and un-normalized depth dose profiles, respectively (Legend: '8mm UNF' - unfocused beam of diameter 8 mm; 'Xmm 150' – focused beam with initial diameter of X mm focused by a triplet of magnets with 150 T/m gradient).

By design (ie, according to matching criteria) the aveFW90M of the MF3 and UNF transverse profiles all match within 0.25 mm (Table 2). AveFWHM for all MF3 beams match UNF counterparts within 0.7 mm, except for the MF3-13mm-100 and MF3-20mm-100 beams, which

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match within ~1 mm. Table 2 also shows that all MF3 aveFWHMs are larger than matching UNF beams. Average transverse profile penumbras (ave80/20) match within 0.3 mm for 200 T/m beams, within 0.6 mm for 150 beams, and within 0.9 mm for 100 T/m beams, respectively; and all MF3 avePen values are larger compared to UNF beams. These trends are qualitatively apparent in Fig 2A, B, E, F, I, J and Fig 3A, B, where MF3 Bragg peak depth profiles that match UNF profiles at 90% maximum gradually widen at lower doses and to a greater extent as magnet gradients decrease and initial beam diameters increase.

Table 3 reveals that in all cases where focused initial beam diameters were larger than matching unfocused beams (10 of 11 cases), MF3 P/E ratios were 16 to 83% larger and relative efficiencies increased by 1.3 to 3.4x compared to associated UNF beams (see also Fig 2C, D, G, H, K and L). However, for the MF3-5mm-200 beam, P/E ratios were 3% smaller and efficiency was 0.9x that of the UNF-5mm beam. In addition, all UNF beams could be matched with MF3 beams with a larger initial diameter than their UNF counterparts. The transverse profiles of Figs 3A, B illustrate that more than one MF3 configuration could be used to match a particular UNF beam. However, certain configurations had superior P/E and dose delivery efficiencies compared to other matching configurations. For example, P/E ratios increased with initial MF3 beam diameter within the matching magnet configurations of Fig 3, as did relative dose delivery efficiency (Fig 3C and D; Table 3). In particular, P/E ratio gains were 49%, 72% and 83%, and efficiency gains were 2.8x, 3.3x and 3.4x, for the MF3-15mm-150, MF3-18mm-150 and MF3-20mm-150 beams, respectively (Table 3). Fig 4A and B summarize the P/E ratio and dose delivery efficiency for all simulation cases. Finally, the Bragg peak depth for all UNF beams was 97.375 mm (voxel midpoint), and was always larger than MF3 beams. For the MF3-5mm-

200, MF3-9mm-200 and MF3-8mm-150 beams it was 97.125 mm, and was 96.875 mm for all other MF3 beams. The average difference between the UNF and MF3 Bragg depths was 0.43 mm (95% confidence interval 0.34 to 0.53), which is larger than the 0.25 mm voxel dimension, and as an unpaired *t* test reveals, is statistically significant (p < 0.0001).

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	P/E	P/E %	Relative	Integral	80/20 Dose*	< 20% Dose	(80/20)/(<20)
	Ratio	Difference	Efficiency	Dose (a.u.)	(a.u.)	(a.u.)	Ratio**
MF3-5mm-200	1.91	-2.9	0.89	0.336	11.8	0.128	92.4
MF3-9mm-200	3.00	52.2	2.3	0.354	10.8	0.139	77.8
UNF-5mm	1.97	0.0	1.0	0.339	12.9	0.108	118.9
MF3-8mm-150	2.99	17.9	1.5	0.556	13.4	0.253	53.2
UNF-6mm	2.54	0.0	1.0	0.497	15.2	0.159	95.7
MF3-12mm-150	4.20	40.2	2.5	0.741	15.2	0.373	40.8
UNF-7mm	3.00	0.0	1.0	0.684	17.1	0.220	77.4
MF3-15mm-150	5.08	49.3	2.8	0.898	17.0	0.481	35.3
MF3-18mm-150	5.84	71.7	3.3	0.968	16.9	0.555	30.5
MF3-20mm-150	6.2	83.1	3.4	1.03	16.9	0.608	27.9
UNF-8mm	3.403	0.0	1.0	0.899	18.4	0.284	64.8
MF3-12mm-100	4.20	15.5	1.3	1.32	18.6	0.695	26.7
MF3-13mm-100	4.46	22.5	1.5	1.37	18.5	0.732	25.2
UNF-9mm	3.64	0.0	1.0	1.14	19.4	0.353	55.1
MF3-15mm-100	4.89	28.3	1.7	1.55	19.5	0.841	23.2
UNF-10mm	3.81	0.0	1.0	1.41	20.2	0.422	47.9
MF3-20mm-g100	5.63	43.5	1.5	2.03	20.4	1.12	18.2
UNF-11mm	3.93	0.0	1.0	1.71	20.8	0.491	42.3

Table 3 – Longitudinal and volumetric dose property comparisons

MF3 beams are grouped with matching UNF beams

UNF-Xmm - unfocused beam of diameter X mm

MF3-Xmm-Y - beam with initial diameter of X mm focused by magnets with Y T/m gradient P/E - Peak to entrance dose ratio

80/20 Dose - Dose in phantom volume in the range of the 80% to 20% contour

< 20% Dose - Dose in phantom volume below the 20% contour

(80/20)/(<20) Ratio - (80/20 Dose)/(< 20% Dose)

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Figure 4: Summary of MF3 vs. UNF Beam Properties. A) Peak-to-entrance dose ratio, B) dose delivery efficiency, C) integral dose, and D) the ratio of volumetric 80/20 dose to volumetric <20% dose, are compared for all cases ('Xmm UNF' - unfocused beam of diameter X mm; 'Xmm Y' – focused beam with initial diameter of X mm focused by a triplet of magnets with Y T/m gradient).

The volumetric dose data of Table 3 and Fig 4 C and D reveal that, compared to associated UNF beams, integral dose was 1% smaller for the MF3-5mm-200 beam but 4% larger for the MF3-9mm-200 beam. Integral dose was equal or 8 to 14% larger for MF3-150 beams, and 10 to 20% larger for MF3-100 beams. For cases where multiple MF3 were matched with a UNF beam, integral dose tended to increase with initial beam diameter. While the lateral penumbra at Bragg peak depth was always slightly larger for MF3 beams compared to UNF beams (see above), volumetric 80/20 dose was 2 to 16% smaller for MF3 beams. Dose below the 20% contour was 18% to 28% larger for MF3-200 beams and 59% to 129% larger for MF3-150 and MF3-100 beams. Finally, the ratio of (volumetric 80/20 dose) to (volumetric < 20% dose) was 22% to 35% smaller for MF3-200 beams, and 44% to 57% smaller for MF3-150 and MF3-100 beams compared to UNF beams (Table 3). The apparent shift in dose below the 20% contour is best explained by increased energy deposits and not by changes in volume size since all MF3 < 20 % volumes are larger or essentially the same compared to their UNF counterparts (data not shown).

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Figure 5: Phase Space Evolution Along Beam Axis. Panels A - E and F - J show the evolution of the MF3-9mm-200 beam through the focusing system in the vertical and horizontal planes, respectively. Phase space contours are shown ~ 1 mm before each magnet, at the water

phantom surface, and at 97.13 mm WED (Bragg peak depth \pm 0.3 mm). Panels K – M show contours at corresponding depths for the UNF-5mm beam. Statistical phase space ellipses are super imposed in red on each contour. Panels N – P show these ellipses plotted on the same axis (UNF-5mm - unfocused beam of diameter 5 mm, MF3-9mm-200 - beam with initial diameter of 9 mm focused by triplet of magnets with 200 T/m gradient).

Figure 5 shows vertical- and horizontal-plane phase space plots for the MF3-9mm-200 beam at five positions along the beam axis (before each of the three magnets, before the water phantom surface and at Bragg peak depth (Fig 5A - J). The UNF-5mm beam is also compared at corresponding depths (Fig 5K - M). Statistical phase space ellipses are shown superimposed on the contour plots in red and plotted together on the same axis (Fig 5N - P). A negative slope of the ellipse indicates that particles tend to have velocities directed toward the beam axis and thus imply converging behavior. In contrast, a positive slope indicates diverging activity. Thus, Fig 5 shows the focusing effect each individual magnet exerts as well as the final effect of the focusing system. Note that panels D, I and O imply a converging action of the focusing system at the water phantom surface, whereas panels L and O imply diverging action of unfocused beams. Phase space ellipses have negative slopes at the water phantom surface in both planes for 9 of the 11 simulation cases. The two exceptions are the ellipses of the MF3-5mm-200 beams, which have positive slopes in both planes, and the MF3-8mm-150 ellipses, which have a negative slope in the vertical plane but a positive slope in the horizontal plane. The effect of MCS is also apparent in Fig 5E, J, M and P where the displacement and the divergence of the beam in the water tank grow significantly (note scale of axes) and the beam displays diverging behavior at Bragg peak depth. Finally, note that while generally different along the beam axis, the phase space ellipses in each plane of the focused beams closely match both at the water phantom surface and at Bragg peak depth. This is expected for beams with low eccentricity beam spots at target depth.

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Discussion

The purpose of this work was to investigate the clinical potential of using a triplet of focusing magnets to irradiate the small targets commonly associated with radiosurgery. We performed Monte Carlo simulations involving proton beams focused by 11 configurations of quadrupole magnet triplets and compared the resulting dose distributions with those of target-matched collimated beams. All MF3 beams produced beam spots at the Bragg peak depth with low eccentricity and aveFW90M of ~2.5 to 5 mm. When MF3 initial beam diameters were larger than matching UNF beams (10 of 11 cases), the focused beams had 16% to 83% larger peak-to-entrance dose ratios and 1.3 to 3.4-fold increases in dose delivery efficiency compared to unfocused collimated beams. Peak-to-entrance and efficiency performance tended to increase with larger magnet gradients and larger initial diameter focused beams.

For a given reference dose delivered to target, increased P/E ratios imply a reduced entrance dose. In the case of head lesions, this implies lower dose delivered to the cortex and subcortical regions as well as to the scalp. In addition, larger P/E ratios could result in radiosurgery treatment plans using fewer beams and support escalated dose treatment protocols. Increases in dose delivery efficiency suggest that treatment times could be shortened, resulting in improved patient experience, reduction of complications in dose delivery due to patient alignment and motion effects, as well as greater patient throughput and cost savings related to staffing and facility operation.

The advantages of the MF3 dose distributions can be attributed to the acceleration of protons toward the beam axis by the magnetic triplet. That is, the focusing system behaves as a

converging magnetic lens. This is illustrated in Fig 5 where the MF3 beam is seen converging at the phantom surface whereas the UNF beam is already diverging away from the target. Thus, the phase space plots concisely show the essential advantage of the MF3 beams is due to this convergent action of the beam, which, at least initially, opposes the Coulomb scattering of protons away from smaller targets. Interestingly, the MF3-5mm-200 beam is the only beam that does not display convergent behavior in both planes at the water phantom surface and is also the only MF3 beam that shows a decrease in both P/E ratios and efficiency compared to UNF beams. On the other hand, the focusing effect displayed in the MF3-8mm-150 beam showing partial convergence (ie, displayed only in one plane) is apparently strong enough to produce a benefit as shown by increases in P/E ratios and efficiency. This suggests that the presence of at least partial convergence at phantom entrance and/or other quantitative measures of focusing strength should be considered when matching MF3 and UNF beams and warrants further study.

The convergent nature of the MF3 beams also explains the 0.4 mm overall average reduction in the Bragg peak depth compared to UNF beams: Assuming an identical effective average particle path length, if the rms divergence ($\langle \theta^2 \rangle^{1/2} = \sigma_{22}^{1/2}$, (see Eqs A3 and A9)) of a converging MF3 beam is greater than that of a diverging UNF beam, then the average particle range would be expected to be shorter. For example, the MF3-12mm-150 beam has a 0.5 mm shorter Bragg peak depth than the matching UNF-7mm beam and has larger σ_{22} values at the water phantom surface associated with vertical and horizontal planes (1.98 x 10⁻⁴ and 1.35 x 10⁻⁴ respectively) compared to the UNF-7mm beam (σ_{22} = 1.02 x 10⁻⁴). It is possible that the difference in Bragg peak depth of the three smaller diameter MF3 beams that showed a 0.25 mm (ie, a single voxel depth) reduction could largely disappear with a shift in voxel boundaries. However, the data as a

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whole suggests a trend toward marginally shorter depths. First of all, the 8 large diameter MF3 beams show a 0.5 mm (ie, two voxel lengths) depth decrease. Secondly, 7 of the 11 MF3 beams show larger σ_{22} values in both planes, and all MF3 beams except the divergent MF3-5mm-200 beam have a larger σ_{22} value in at least one plane than matching UNF beams. Third, the 0.4 mm average difference of all MF3 beams is statistically significant and larger than 0.25 mm. Finally, a similar pattern regarding the shift in Bragg peak depth has also been observed in ongoing triplet magnet focusing experiments in our laboratory.

Our results showed that increases in P/E performance and efficiency tended to be greater for larger initial diameter MF3 beams and larger magnetic gradients (eg, compare MF3-20mm-100 and MF3-20mm-150 in Fig 2, and MF3-150 beams in Fig 3 and Table 3). This is expected because particles distributed in both stronger gradients and larger beam cross sections experience greater average magnetic forces and thus greater focusing. Further, since larger diameter beams exhibit greater lateral particle equilibrium compared to smaller diameter beams they are less susceptible to MCS degradation even apart from focusing effects. However, larger beam diameters (whether focused or unfocused) also tend to increase integral dose because, for a given fluence and target size a larger initial beam diameter implies that a larger volume of tissue will receive a non-zero dose compared to a small diameter beam. While focusing works against this tendency, integral dose for MF3-150 and MF3-100 beams were 0% to 14% larger, and 10% to 20% larger, respectively, compared to UNF counterparts (Table 3). On the other hand, these lower gradient beams show large increases in dose below the 20% contour (18% to 129% larger compared to UNF) as well as larger (volumetric 80/20 dose) to (volumetric < 20% dose) ratio decreases (22 to 57%) (Table 3). Thus, compared to UNF, more integral dose appears to be

shifted below the 20% contour. In addition, for a given magnet gradient, it is possible that integral dose could be reduced by use of a smaller initial beam diameter without the loss of significant P/E and efficiency gains. For example, note that the MF3-15mm-150 beam matches the UNF-8mm with an equal integral dose and - while less than e.g. the MF3-18mm-150 beam - it still has a 49% P/E increase and 2.8x efficiency gain (Table 3). Finally, it is worth emphasizing that the relative increase in integral dose for the larger diameter MF3 beams is based on a single-beam comparison. However, due to larger P/E gains, it is likely that beam number can be reduced by the removal of at least one treatment beam which implies a large reduction in the overall integral dose. In any case, the cost vs. benefit of larger diameter beams, increased Bragg peak performance, single beam integral dose, and dose shift below the 20% contour will have to be weighed on a case by case basis in the context of a radiosurgery treatment plan.

Commercial manufacture of focusing magnets consisting of assemblies of rare-earth permanent magnetic material fashioned as Halbach cylinders (Halbach 1980) is currently feasible. Ten magnets with parameters corresponding to the simulated magnets used in the present research were recently manufactured and are being tested at our institution. The capability of the magnets to produce beam spots of high symmetry indicate that the assemblies can be practically manufactured at a sufficient level of quality at costs on the order of thousands of dollars (McAuley et al 2015, Choi et al 2016). In contrast to electromagnets, neither power nor cryogens for cooling are required and, because of the Halbach design, magnetic fields external to the cylinder bore are relatively low. Therefore, a triplet of magnets could be easily integrated into a treatment cone and used as a drop in replacement for our existing stereotactic radiosurgery

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cone (Wroe et al 2014), or in place of the aperture commonly employed in passive proton radiotherapy. A group of preconfigured cones in combination with a set of range shifters could provide a robust focusing system to deliver radiosurgery treatments to the clinical range of target sizes and lesion depths. A focusing system could also be used within a proton scanning nozzle in at least two ways. It could be rotated inline for static (i.e., unscanned) beam delivery treatments and thus provide radiosurgery capability. Secondly, it could also be used to pre-focus pencil beams before scanning and potentially improve the properties of the dose distribution. Finally, while discussed in the context of proton radiosurgery, applications of a similar focusing system could extend to standard fractionation regimens and other treatment sites, or other treatment particles.

For clinical deployment of the magnetic focusing system, treatment planning is an important consideration. All magnetic focusing data presented in this paper was generated in liquid water similar to commissioning data. For clinical deployment of this system, it is expected that full beam sets (including depth dose and cross profile data) for multiple energy, beam diameter and magnetic cone configurations would be collected during the commissioning process. These data sets would provide the basis for the treatment planning algorithm with sufficient data collected to allow for interpolation where necessary. As the initial clinical deployment of magnetic focusing is expected to be for intracranial targets, material inhomogeneity is not expected to be a significant issue. However, the impact of different tissues and tissue boundaries on converging beams will need to be accounted for correctly in order to appropriately optimize the beam delivery. While this could pose a challenge for existing analytical proton transport algorithms, the movement towards integrated Monte Carlo algorithms in commercial treatment planning

systems is expected to allow support for the integration of a magnetic focusing system into the clinical workflow.

Conclusions

Our results suggest that a triplet of Halbach cylinders constructed from rare-earth magnetic materials could be used to reduce entrance dose and beam number while delivering dose to millimeter-sized nominally spherical targets over a shorter time compared to unfocused beams. Such focusing magnets can be practically manufactured, are inexpensive, do not require electric power or cryogens for cooling, and could be easily incorporated into existing treatment nozzles. Potential clinical applications include those associated with proton radiosurgery and functional radiosurgery of the brain.

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Appendix

Phase Space and the Sigma Matrix

The aggregate state of the position and momentum of all particles makes up the six-dimensional phase space of the beam that passes through the focusing system. If we assume constant momentum along the beam axis and independent motion in the spatial coordinates, the phase space description can be simplified and consists of separate motion in each longitudinal plane. The state of each particle can then be described by points in each plane consisting of its displacement and angular divergence with respect to the beam axis (Banford 1966).



Figure A1: Schematic of phase space ellipse.

Consider a symmetric 2x2 matrix σ defined by Eq A1 where x is a 2 x 1 column vector:

$$\boldsymbol{x}^T \boldsymbol{\sigma}^{-1} \boldsymbol{x} = 1$$
 [A1]

With this definition σ is a positive definite matrix and thus has positive diagonal elements and a positive determinant (Kwak & Hong 2004). In addition, Eq A1 describes an ellipse with its centroid at the origin. In particular, if the displacement and divergence of a particle make up the components of the column vector, Eq A1 describes a phase space ellipse in each longitudinal plane. Furthermore, the elements of σ completely characterize the essential properties of the

ellipse. For example, Eqs A2 to A4 (where a, b, φ , x_{max} and θ_{max} are defined in Fig A1) show that $\sigma_{11}^{1/2}$ and $\sigma_{22}^{1/2}$ are equal to the maximum displacement and divergence, respectively, and σ_{21} is related to the 'tilt' and shape (ie, eccentricity) (Wollnik 1987, Lee 2012).

$$x_{max} = \sqrt{\sigma_{11}}$$
 [A2]

$$\theta_{max} = \sqrt{\sigma_{22}}$$
[A3]

$$ab = |\boldsymbol{\sigma}|^{1/2} \tag{A4}$$

Finally, because the area of the ellipse is proportional to $det(\sigma)^{1/2}$ (Eq A5), the elements of σ may be associated with the r.m.s. emittance (A6) (Lapostolle 1971)

$$\tan(2\varphi) = \frac{2\sigma_{12}}{\sigma_{22} - \sigma_{11}}$$
[A5]

$$\epsilon_{rms} = \sqrt{\langle x^2 \rangle \langle \theta^2 \rangle - \langle x \theta \rangle^2}$$
 [A6]

and the second order statistical moments of the phase space distribution (Eqs A7 to A9) and thus provides a means to calculate the statistical phase space ellipse used in this paper (Lee 2012).

$$\sigma_{11} = \langle x^2 \rangle \tag{A7}$$

$$\sigma_{21} = \langle x\theta \rangle \tag{A8}$$

$$\sigma_{22} = \langle \theta^2 \rangle \tag{A9}$$

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