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SMALL ANIMAL IGRT SPECIAL FEATURE: FULL PAPER

Exploring the feasibility of a clinical proton beam with an adaptive aperture for pre-clinical research

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Objective: To investigate whether the Mevion S250i with HYPERSCAN clinical proton system could be used for pre-clinical research with millimetric beams.

Methods: The nozzle of the proton beam line, consisting of an energy modulation system (EMS) and an adaptive aperture (AA), was modelled with the TOPAS Monte Carlo Simulation Toolkit. With the EMS, the 230 MeV beam nominal range can be decreased in multiples of 2.1 mm. Monte Carlo dose calculations were performed in a mouse lung tumour CT image. The AA allows fields as small as $5 \times 1 \text{ mm}^2$ to be used for irradiation. The best plans to give 2 Gy to the tumour were derived from a set of discrete energies allowed by the EMS, different field sizes and beam directions. The final proton plans

were compared to a precision photon irradiation plan. Treatment times were also assessed.

Results: Seven different proton beam plans were investigated, with a good coverage to the tumour ($D_{95} > 1.95 \text{ Gy}$, $D_5 < 2.3 \text{ Gy}$) and with potentially less damage to the organs at risk than the photon plan. For very small fields and low energies, the number of protons arriving to the target drops to 1–3%, nevertheless the treatment times would be below 5 s.

Conclusion: The proton plans made in this study, collimated by an AA, could be used for animal irradiation.

Advances in knowledge: This is one of the first study to demonstrate the feasibility of pre-clinical research with a clinical proton beam with an adaptive aperture used to create small fields.

INTRODUCTION

The number of ion beam therapy centres has been growing rapidly in the last decade, making ion beam therapy a possible cancer treatment. To advance the understanding of ion beam therapy, pre-clinical research is needed combining different tumour models and ion beam irradiation.¹

Also in recent years, specialized image-guided irradiation platforms for conventional photon radiotherapy were installed in over 100 research departments worldwide, an order of magnitude more than in 2011.² Such platforms are radically changing the field of pre-clinical animal research in radiobiology by using image-guided irradiation with millimetric beams.³ Furthermore, specific treatment planning systems were developed, where the physics of low-energy X-ray beams was modelled to deliver accurately the prescribed dose to the target, while considering the constraints in dose to the organs at risk (OARs).^{4–6}

Integrating the existing state-of-the-art photon platforms with ion beams will initiate a completely new field in pre-clinical research. Greubel et al⁷ presented a study where 24 subcutaneous tumours in mice were irradiated with 20 Gy using 23 MeV proton beams and tumour growth was evaluated. Moreover, Constanzo et al⁸ published a radiobiological study, where a 4 MeV mini-proton beam was used to irradiate tumour cells and survival curves were comparable to the ones obtained with X-ray irradiation. In 2017, Ford et al⁹ demonstrated the feasibility of integrating a 50 MeV proton beam with a commercially available X-ray pre-clinical platform. The same group developed a Monte Carlo (MC) model for a small animal proton beamline and investigated the relative biological effectiveness (RBE) in tissues using fractionated proton minibeam.¹⁰

Since it is unlikely that dedicated small animal ion beam therapy facilities will be built due to cost, current clinical and non-clinical ion beam facilities look for solutions to adapt their beams for image guided pre-clinical

Figure 1. (a) Treatment room sketch with the synchrocyclotron mounted on the gantry, which rotates around the isocentre from -5 to 185° ; (b) close view of the AA module in the beam's-eye-view; (c) MC model of the module with the 16 plates of EMS in the beam path, indicating the range shifter plates, the AA and the exit window (the beam goes from right to left) with a representative slice of the micro cone beam CT of the mouse in front of the nozzle. The dotted box is zoomed-in on the right. AA, adaptive aperture; EMS, energy modulation system; MC, Monte Carlo.

research^{11–13}, while making use of platforms with existing X-ray beams for imaging and positioning.² For this reason, the work here presented investigates the possible use of a clinical proton beam, which has a unique adaptive aperture to create small fields with sharp beam penumbras and low proton energies, for small animal research. The study will focus on dose calculations with proton beam, and will not consider any effects of relative biological effectiveness at low proton energies. This would require extensive studies of the RBE in small proton beams in *in vivo* systems.

METHODS AND MATERIALS

Clinical system

The MEVION S250i with HYPERSCAN proton system (Mevion Medical Systems Inc., Littleton, MA) is a commercially available one-room compact system with a synchrocyclotron proton accelerator mounted on the gantry, which rotates in the treatment room around the patient (Figure 1a). The beam line consists of a dual axis scanning magnet, transmission ion chambers, a fast energy modulation system (EMS) and an Adaptive Aperture™ (AA) for beam collimation (Figure 1b). These components are mounted on the Nozzle, that can rotate between -5° and 185° in the gantry plane (Figure 1a). Furthermore, the module that contains the EMS and AA can be extended towards the isocentre, ranging from 3.6 to 33.6 cm.

The system produces a pencil beam with a fixed energy of 230 MeV and uses the EMS to decrease the pencil beam energy. This

device consists of 18 Lexan plates with specific thicknesses and air gaps that allow for a decrease of the pencil beam residual range in multiples of 0.21 cm in water, covering a depth from 32 cm (90% distal fall-off) to the surface. The AA is located at the end of the beam line and it consists of two opposing blocks of seven leaves made of Nickel¹⁴ moving in a 20×20 cm² treatment field enabling collimation of each pencil beam per energy layer. The AA moves as a block in the *y*-direction and each leaf can move in the *x*-axis direction (Figure 1b,c). Furthermore, the one nominal proton energy combined with the type of EMS, results in Bragg peaks with a constant range straggling [the full-width half maximum (FWHM) in the beam direction of approximately 27 ± 1 mm measured in integrated depth doses (IDDs)].

Beam model

The beam model of the S250i with HYPERSCAN system was created using the MC platform TOLKIT for Particle Simulation¹⁵ (Figure 1c). The model was validated with data provided by the manufacturer.

Simulation set-up

The submillimetric cone beam CT (μ CBCT) image of a mouse with an orthotopic lung tumour was acquired with the X-RAD 225Cx system (Precision X-ray, North Branford, CT) at a tube voltage of 80 kVp and with a $0.1 \times 0.1 \times 0.1$ mm³ voxel size. The main structures (tumour in the right lung, right and left lungs, spinal cord and heart) were delineated by a radiation oncologist. Using a dedicated small animal radiotherapy planning system SmART-Plan⁶

Figure 2. (a) Photon dose distribution, micro cone beam CT image and structure contours for the photon plan with two opposed 225 kVp photon beams using a 5 mm circular collimator to deliver a prescribed dose of 2 Gy to the tumour (statistical uncertainty of 0.1%, equivalent to approximately 10^8 histories per beam). The tumour is indicated in green in the right lung. (b) Illustration of the three proton treatment fields (and corresponding inner gantry rotation) used to create seven different proton plans.

(research v. 1.5, Precision X-ray), an optimal photon irradiation plan was designed to administer a prescribed dose of 2 Gy to the tumour (Figure 2a).

For the proton plans, simulations of a single spot proton pencil beam aimed at the tumour centre were performed combining two or three treatment fields (TF), using different energies and five field sizes (Table 1, Figure 2b). The choice of energy was limited by the EMS discrete steps. Treatment scenarios T1 to T6 use treatment fields with low energies (29.14, 32.97, 36.46 and 39.72 MeV), in which the Bragg peak stops inside the tumour, while T7 uses two opposed 158.87 MeV beams to “shoot-through” the tumour. The minimum field size in the y -direction (axis in Figure 1b) is limited by the leaf thickness of 5 mm, however in the x -direction, any

opening is possible with 0.5 mm resolution. The default physics list from TOPAS, validated for proton beams,^{15,16} was used and dose-to-water-in-medium (physical dose) was scored in a $0.2 \times 0.2 \times 0.2$ mm³ grid (double the original μ CBCT voxel size). A primary 230 MeV proton beam with an energy spread (standard deviation) of 0.2174 MeV and a virtual source-axis-distance (SAD) of 185 cm, was simulated with 1.75×10^9 protons per TE.

Each treatment scenario resulted in 64 (T1–T4) or 16 (T5–T7) dose distributions (Table 2), for each of these the dose volume histogram (DVH) metrics D95 and D5 (dose given to 95 and 5% of the tumour volume, respectively) were calculated to select the best plan for each treatment. Furthermore, the DVH metrics V90 and V10 were used to evaluate the volume of OARs that received 90 and 10% of the prescribed dose, respectively. Finally, the best dose distributions from the seven different scenarios were compared, arriving at the plan that best covers the tumour with the prescribed dose.

Table 1. Simulation set-up for seven different treatment scenarios (T), using two or three treatment fields (TF1–TF3) defined by the gantry rotation 0°, 90° and 180° (explicitly in Figure 1a), respectively

Treatment scenario #	Treatment fields (MeV)			Field size (mm ²)
	TF1	TF2	TF3	
T1	39.72	29.14	36.46	5 × 2.5 5 × 3 5 × 3.5 5 × 4
T2	39.72	32.97	39.72	
T3	39.72	29.14	36.46	
T4	39.72	32.97	39.72	
T5	39.72	–	36.46	
T6	39.72	–	39.72	
T7 shoot-through	158.87	–	158.87	

Clinical system output

System's delivery efficiency

The EMS can decrease the beam nominal range to 0. However, the use of almost all the 18 range shifter plates decreases the number of protons that exit the EMS. To quantify the protons lost due to the use of these plates, simulations with a single-beam aimed at the isocentre were performed with the system's nominal energy (230 MeV) and the energies chosen for treatments T1–T7. The AA was added to the simulations with the field sizes ranging from 5×1 mm² to 5×5 mm². The number of protons that arrived at the nozzle's exit window (Figure 1c) was scored and compared to the number of 10^7 primary protons generated.

Table 2. Field size for each TF corresponding to each combination number, e.g. the field size for combination 1 is (5×2.5 , 5×2.5 , 5×2.5); for combination 2 is (5×2.5 , 5×2.5 , 5×3). T1 to T4 yielded 64 combinations of field sizes, whereas T5 to T7, only 16 combinations, since only two TF were used (Table 1)

Combination	TF1 (mm ²)	TF2 (mm ²)	TF3 (mm ²)	Combination	TF1 (mm ²)	TF2 (mm ²)	TF3 (mm ²)
1	5 × 2.5	5 × 2.5	5 × 2.5	33	5 × 3.5	5 × 2.5	× 2.5
2			5 × 3	34			5 × 3
3			5 × 3.5	35			5 × 3.5
4			5 × 4	36			5 × 4
5		5 × 3	5 × 2.5	37		5 × 3	5 × 2.5
6			5 × 3	38			5 × 3
7			5 × 3.5	39			5 × 3.5
8			5 × 4	40			5 × 4
9		5 × 3.5	5 × 2.5	41		5 × 3.5	5 × 2.5
10			5 × 3	42			5 × 3
11			5 × 3.5	43			5 × 3.5
12			5 × 4	44			5 × 4
13		5 × 4	5 × 2.5	45		5 × 4	5 × 2.5
14			5 × 3	46			5 × 3
15			5 × 3.5	47			5 × 3.5
16			5 × 4	48			5 × 4
17	5 × 3	5 × 2.5	5 × 2.5	49	5 × 4	5 × 2.5	5 × 2.5
18			5 × 3	50			5 × 3
19			5 × 3.5	51			5 × 3.5
20			5 × 4	52			5 × 4
21		5 × 3	5 × 2.5	53		5 × 3	5 × 2.5
22			5 × 3	54			5 × 3
23			5 × 3.5	55			5 × 3.5
24			5 × 4	56			5 × 4
25		5 × 3.5	5 × 2.5	57		5 × 3.5	5 × 2.5
26			5 × 3	58			5 × 3
27			5 × 3.5	59			5 × 3.5
28			5 × 4	60			5 × 4
29		5 × 4	5 × 2.5	61		5 × 4	5 × 2.5
30			5 × 3	62			5 × 3
31			5 × 3.5	63			5 × 3.5
32			5 × 4	64			5 × 4

Calculation of the dose rate and treatment time

For practical reasons, it is important to assess whether the system would be able to deliver the prescribed dose of 2 Gy in an acceptable irradiation time,¹⁷ since the animal is under deep anaesthesia and the common workflow includes imaging, treatment planning and irradiation. With a maximum beam current of 10 nA, the Mevion S250i HYPERSCAN, can produce 6.24×10^{10} protons per second. From the simulations described in section *System's delivery*

efficiency, the time needed to deliver 2 Gy as function of energy and field size was estimated.

RESULTS

Proton plan that best covers the target

Simulations of the seven treatments described in Table 1 were performed. All DVHs were scaled to the prescribed physical dose $D_{90} = 2$ Gy (All doses reported in this work are physical

Figure 3. (a) D95 and D5 for all field combinations for T1, where the combination with the steepest slope between D95 and D5 is indicated with a black vertical line (combination 54). The x-axis shows the 64 combinations for T1: the first point on the x-axis has the field size (TF1 = $5 \times 2.5 \text{ mm}^2$, TF2 = $5 \times 2.5 \text{ mm}^2$, TF3 = $5 \times 2.5 \text{ mm}^2$) and the last (TF1 = $5 \times 4 \text{ mm}^2$, TF2 = $5 \times 4 \text{ mm}^2$, TF3 = $5 \times 4 \text{ mm}^2$). All the 64 field-size combinations are shown in Table 2. (b) representation of the ipsi-lateral right-lung V10 and the V90, and the heart V10. Horizontal lines show in both panels, as indicated, the D5, D95, V10 and V90 values extracted from the photon plan (Figure 2).

doses (Gy) and not RBE-weighted absorbed doses (GyE). Figure 3a presents the D95 and D5 extracted from each of 64 dose distributions from T1. The field size that produced the minimum difference between D95 and D5, *i.e.* the steepest slope of the tumour's DVH, is marked with a black line and hence chosen as the best combination for each treatment. Figure 3b shows the V10 and V90 for the right lung and heart for the 64 field size combinations (explicitly in Table 2), where the horizontal lines represent the V90 and V10 extracted from the photon plan. From the Supplementary Figure 1 gives the results for T3, T5 and T7.

The best case for each treatment scenario is described in Table 3 in terms of the AA opening and the DVH metrics: D95, D5 for the tumour, V10 and V90 for the ipsi-lateral right lung, and the V10 for the heart. Figure 4 shows the DVHs for the seven proton treatments, including the tumour, right lung and heart. The DVH extracted from the photon plan is shown in black.

Figure 5 shows the dose distributions for three different types of proton irradiation: using three fields and low energies, using two opposing fields and low energies, and using two opposing

Table 3. Combinations that best covered the tumour found for each treatment scenario, indicating the AA size for each TF and the dose volume histograms metrics D5, D95, V10 and V90

Treatment scenario #	AA size for each TF			D95	D5	V90 Lung (%)	V10 Lung (%)	V10 Heart (%)
	TF1	TF2	TF3					
T1	4	3	3	1.95	2.26	13	69	8
T2	4	3	3	1.95	2.27	13	69	8
T3	4	4	3	1.96	2.18	12	72	2
T4	4	4	3	1.96	2.21	12	72	19
T5	4	–	3	1.98	2.2	19	7	5
T6	4	–	3.5	1.96	2.18	19	69	5
T7	4	–	3	1.96	2.27	23	8	17
Photons	–	–	–	1.99	2.07	32	48	0

AA, adaptive aperture; TF, treatment field;

Figure 4. Dose volume histograms of the seven treatments for the tumour (solid line), ipsi-lateral right lung (dashed line) and heart (dotted line).

“shoot-through” fields with high energies. Dose differences between these three irradiations are shown in Figure 6.

Clinical system output

Figure 6a–f show the number of protons scored at the exit window of the nozzle for different field sizes, using a representative energy of 39.72 MeV. The fraction of protons for each energy that arrive to the exit window for an open field is shown in Figure 7a, while Figure 7b gives these values as function of the field size.

Considering the number of protons that the system produces per second at the exit of the cyclotron ($\sim 6.24 \times 10^{10}$ protons for 10 nA beam current), the efficiency of each beam with respect to its energy and field size (Figure 7b), the time to cover a 2 Gy target was determined and the results are shown in Figure 8.

Figure 5. Proton dose distributions in transverse, coronal and sagittal planes for the field size combinations depicted in Table 3 from irradiations T3, T5 and T7 (a, b and c panels, respectively). Dose differences between irradiation T7 and T3 (d), between T7 and T5 (e), and between T5 and T3 (f).

Figure 6. Number of protons scored at the exit window for a 39.72 MeV beam, with different collimations (b-f) and with no collimation (a).

DISCUSSION

This work presented a dosimetric study on the feasibility of pre-clinical irradiations with the compact proton system S250i with HYPERSCAN. Exploring the capabilities of the system EMS for range modulation, and AA for collimation, seven different proton irradiation scenarios were simulated in a MC platform to irradiate a mouse lung tumour. To perform the experiments simulated here, a high precision positioning platform with a coupled high-resolution CBCT imager would be necessary to assure a submillimetric uncertainty of the mouse positioning, while keeping the gantry at a fixed angle (Figure 1a). This has already been achieved by coupling commercially available small animal X-ray imaging platforms to a fixed proton beam line.⁹ On a gantry-based system, extra care has to be taken to position the beam nozzle in a reproducible fixed position.

The AA allows the creation of very small fields, limited to a minimum of 5 mm in the y -direction (axis in Figure 1b), but down to 0.5 mm in the x -direction. Considering the size of the tumour and without explicitly adding any margin, a range of five AA openings were simulated, resulting in 16 or 64 different field size combinations. In the field of pre-clinical radiotherapy research, no guidelines are given for margins, which is an important study point recommended by the ESTRO ACROP report from Verhaegen et al.³ In this respect, Vaniqui et al.¹⁸

published a method of calculating the optimal collimator diameter from a set of fixed diameters depending on the parameters of a cost function, especially relevant for tumours affected by the breathing motion. Such an approach could be implemented in a follow-up study to this work, adapting the recipe proposed to the constraints of the AA of this system.

Figure 3a plots the DVH metrics D5 and D95 for one scenario (T1), where the worst tumour coverage is seen for the smallest field (5×2.5 , 5×2.5 , 5×2.5 mm²) while generally improving for the largest fields. The best-case tumour coverage, taken as the DVH with the steepest slope between D5 and D95, for T1 was achieved for a field of (5×4 , 5×3 , 5×3 mm²). The same analysis for all seven treatments resulted in the seven best case scenarios that were shown in Table 3 and in Figure 4. The “shoot-through” technique, with a similar beam arrangement as in the photon plan (Figure 2a), would be expected to give a better coverage of the target. However, the use of a single spot beam resulted in a non-uniformity of the dose distribution in the lateral direction. Using an optimizer and smaller side-by-side-beams may improve this result.

For benchmarking, a photon plan (Figure 2a) was made by a commercially available treatment planning system for small-animal research. In contrast, in this work, single spot proton beams

Figure 7. Fraction of protons that arrive at the exit window in an open field (no collimation) as function of the energy (a), and as function of the energy and field size (b). The field sizes used: 5, 10, 12.5, 15, 17.5, 20, 25 mm², correspond to an adaptive aperture opening of 5 × 1, 5 × 2, 5 × 2.5, 5 × 3, 5 × 3.5, 5 × 4 and 5 × 5 mm², respectively.

with equal weight were aimed at the isocentre. Nevertheless, Figure 4 and Table 3 show that the proton plans could be used for animal irradiation with a less optimal tumour coverage, but for most cases with an improved sparing of the OARs. Specifically, 32% of the right lung volume receives 90% of the prescribed dose in the photon plan, which decreases to 12% in T3 and T4 proton plans. Furthermore, in Figure 2a it is possible to observe a very high photon dose (three times the prescribed dose) in bone tissues, due to the predominance of the photoelectric effect for

Figure 8. Beam-on time to deliver 2 Gy as function of the energy and field sizes.

low energy X-ray beams. Protons in tissue also have a higher mass stopping power for bone, but only a factor 1.6 higher than water, in contrast with the factor of about three higher mass-energy absorption coefficient at low energy photon beams.

The proton treatments designed in this study used two strategies: low energy fields that stop in the tumour or high energy beams to shoot through. Dose differences show that the former allows for a decrease in dose to healthy tissues observed in the Figure 5d-f, with respect to the “shoot through” strategy. This would allow to study potential RBE effects.¹⁰ The latter has the potential interest of performing small animal proton CT imaging that could be used for pre-treatment position verification or to improve range uncertainty by directly measuring the animal relative stopping power maps.¹⁹

A special component of this beamline is the EMS, which is characterized by a constant range straggling at the Bragg peak for all energies. This might be a disadvantage for pre-clinical work, since it prevents the easy production of sharper beams. Another effect of the EMS is the increase in lateral beam spot size with the decrease in energy, caused by the many plates in front of the beam. For the low energies used in this work (T1–T6), the beam spot size, taken as the standard deviation of a double Gaussian fit, is approximately 16 mm. The AA can collimate the beam, however there is an intrinsic loss in efficiency by using large spot sizes with small fields, since most of the beam will be absorbed by the AA, clearly seen in Figure 7b. The central beam axis also suffers a decrease in intensity (Figure 6b–f), since the very small angular deflections in proton trajectories are not negligible for small fields. Nevertheless, Figure 8 shows the estimated irradiation time needed to deliver a 2 Gy dose with different energies and field sizes. For the lowest energy (29.14 MeV) and the

smallest field size ($5 \times 1 \text{ mm}^2$), the prescribed dose can be delivered in less than 5 s. The high dose rate of this system allows for 30 Gy to be delivered in less than a minute.

CONCLUSION

The feasibility of the Mevion S250i with HYPERSCAN proton irradiation system for pre-clinical research was affirmatively

tested, using different strategies in the choice of energies, field directions and sizes. Moreover, the system would be able to give very high doses in a short period of time, due to the system's high beam current. With the use of a movable platform equipped with μ CBCT imaging and a table with accurate positioning, the clinical proton system could be used to perform proton irradiation in small animals for a wide range of studies.

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