Technical Note: The first live treatment on a 1.0 Tesla inline MRI-linac

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Purpose: This work describes the first live imaging and radiation delivery performed on a prototype 1.0 Tesla inline MRI-Linac system in a rat brain tumour model, which was conducted on 29th January 2019.

Methods: A human scale 1.0 Tesla MRI-Linac was adapted to be suitable for animal studies via a specially constructed open 6-channel receiver radiofrequency (RF) coil. A Fischer rat injected with 9L glioma cells in the right hemisphere was imaged and irradiated at day 11 post surgery as part of a larger cohort survival study. The rat was anaesthetized and positioned at the isocentre of the MRI-Linac. Imaging was used to localize the brain and confirm the presence of a tumour following the administration of a gadolinium nanoparticle contrast agent. A single dose of 10 Gy was delivered using a 2.25 x 2.90 cm radiation field covering the whole brain and verified with radiosensitive film in situ. Real-time imaging was used throughout the irradiation period to monitor the animal and target position.

Results: The signal-to-noise ratio (SNR) measured in the rat brain was 38. Post-contrast imaging was able to demonstrate a tumour of 5 mm diameter in the upper right hemisphere of the brain approximately 45 minutes after administration of the nanoparticles. The radiation beam had no impact on SNR and images at the rate of 2 Hz were effective in monitoring both respiration and intrafractional motion. In vivo film dosimetry confirmed the intended dose delivery. The total procedure time was 35 minutes.

Conclusions: We have successfully used MRI guidance to localize and subsequently deliver a radiation field to the whole brain of a rat with a right hemispheric tumour. Real-time imaging during beam-on was of sufficient quality to monitor breathing and perform exception gating of the treatment. This represents the first live use of a high field inline MRI-Linac.

Keywords: MRI-Linac, Radiotherapy, MRI.
1. Introduction

MRI-Linac systems are hybrid radiotherapy devices that combine a linear accelerator with the ability to use MR imaging at the time of treatment, allowing for real-time guidance and adaption of treatment dose. A number of mutual interactions exist between the x-ray beam and the imaging system and these challenges have led to four unique MRI-Linac system designs and different magnetic field strengths being developed [1-4]. Two of these systems (Elekta Unity & Viewray MRIdian) have the beam orientated in a perpendicular direction to the magnetic field. These systems are now commercially available and performed the first human treatments in May [5] and July 2017 [6] respectively. The two remaining designs (University of Alberta & Australian MRI-Linac) are at the research prototype stage. These are described as ‘inline’, where the radiation beam is parallel to the magnetic field, and offer a different approach. In particular, the system described here has an open bore design, which would permit vertical treatments, and the inline configuration could be important for MR-guided charged particle beams.

The Australian MRI-Linac group has previously reported its first beam-on images in phantoms and imaging-only studies in humans [7]. In this report, we describe the first ever live treatment on this system, which is also the first time an inline system has been employed in a therapeutic use. The work is part of a larger pre-clinical trial investigating the efficacy of radiation sensitisation using polysiloxane-gadolinium chelated nanoparticles (AGuIX®, NH Theraguix, France) [8], which will be reported at a later date. The pilot phase of this trial was used to develop and test the imaging part of the protocol separately in live rats and also included dosimetry work-up in phantoms and in a single euthanized animal. The culmination of the pilot phase was the first live treatment which was performed on 29th January 2019 and is reported here.

2. Methods

The prototype inline MRI-Linac system has been described in detail previously [7] but is briefly summarised as follows.

The treatment beam is provided by a linear accelerator unit (Linatron, Varex, USA) which can produce two x-ray energies of 4 and 6 MV. The unit is mounted to a stainless steel table together with a clinical 120-leaf (Millennium, Varian) multi-leaf collimator (MLC) on a rail system enabling source-to-isocentre (SID) variation. The output stability has previously been measured to be 1.87% (standard deviation over ten days).
The magnet is a 1.0 Tesla open bore design (Agilent, UK) with a 50 cm gap and 60 cm bore to permit beam and patient entry in either inline or perpendicular orientations. Dedicated imaging gradient coils (Tesla, UK) and a volume radiofrequency (RF) body coil (Magnetica Pty Ltd, Australia) are integrated into the magnet while maintaining access from both sides of the central gap and the bore. The RF coil can be used in transceiver mode, as is in normal operation for human imaging [7], but in this animal study it was used as transmit only in combination with a second smaller receiver RF coil to increase signal-to-noise ratio (SNR). Imaging has previously been shown to have no impact on dose in simultaneous irradiations [7].

2.1 Animal tumour model

All animal experiments were approved by the Animal Care and Ethics committee of Western Sydney University (ACEC number A12431) and were conducted in accordance with the ‘Australian Code for the Care and Use of Animals for Scientific Purposes (2013)’ and the ‘New South Wales Animal Research Act 1985’.

Approximately $1 \times 10^4$ 9L glioma cells were injected into the right caudate nucleus of a F344 rat; injection was at the bregma, 3.5 mm lateral to the midline in the right hemisphere, at 6 mm depth from the skull surface using a stereotactic device. The tumour was allowed to grow for 11 days before scheduled irradiation.

Prior to imaging and irradiation the rat was anaesthetised with intraperitoneal injection of 66 mg/kg ketamine, 5.5 mg/kg xylazine in solution with 5 ml/kg saline. The nanoparticle contrast agent (AguIX®, NH Theraguix, France) was administered intravenously by tail vein injection approximately 30 minutes before the start of the examination in a 1ml volume of 100 mg/ml solution (approx. 400 mg/kg). The rat was transferred into the treatment room and placed on a heating pad for the duration of the procedure, which also acted as a water reference for subsequent RF coil tuning.

2.2 Imaging

All imaging was undertaken using a specially constructed 6-channel receive-only RF coil. This coil is a modified bird cage construction with a 26 cm diameter and a 24 cm $\times$ 17 cm lateral opening designed to work in either parallel or perpendicular orientations without obstructing the radiation beam. In the present study the coil was aligned along the patient table in the x-axis with the open beam-portal facing the linear accelerator x-ray head. The rat was positioned prone inside the coil with the right side to the beam and the brain aligned with lasers to the isocentre of the MRI-Linac system.
A sagittal $T_2$-weighted Turbo spin-echo (TSE) scan was acquired (TE/TR = 86/13493 ms) to localise the rat brain and verify the position of the target. An in-plane resolution of 1.3 mm was used with a slice thickness of 5 mm and acquired in 3 min 50 s. These images were subsequently displayed on the console and a visual grid was overlaid which superimposed both the position of the system isocentre and a graticule of 1 cm square in both directions in order to verify target position. SNR was measured in the brain region using the standard deviation of background signal as a noise estimate and applying the appropriate correction factor (= 0.7) for multiple coil elements [9].

While the first images were being reviewed for possible adjustment of the MLC, a second axial $T_1$-w scan was acquired through the brain using a fast gradient echo (FGR) sequence (TE/TR = 1.4/3.75 ms) in 4 min 54 s. The in-plane resolution was 1.3 mm and a slice thickness of 1.4 mm. The purpose of this scan was to verify that the implanted cells had developed into a viable tumour as demonstrated by the uptake of the nanoparticle agent. Contrast-to-noise ratio (CNR) was measured as the ratio of the signal difference between the enhancing and non-enhancing brain to the standard deviation of the signal in the background.

During irradiation a dynamic fast gradient-echo sequence was acquired to provide real-time visualisation of respiration and also to monitor any signs of intrafractional motion. In this case a single 10 mm slice was acquired in the coronal plane through the centre of the entire animal with a spatial resolution of 2.0 mm (TE/TR = 4.29/10 ms). A partial (6/8) Fourier technique was used to provide a temporal resolution of 0.5 s (2 Hz). These images were continued for 30 s after the treatment ended so that a SNR comparison could be made between the beam on and off periods. In this case the stochastic pixel variation method [10] was used which calculates $\text{SNR}(x,y)$ from the ratio of $\text{mean}(x,y)$ to standard deviation$(x,y)$ of the signal over time. Pixel-by-pixels maps were computed for two adjacent 30 s (beam on and off) periods and subsequently a region chosen above the lungs to obtain a value for mean SNR in each period. The percentage signal change in this region over the full time course was also calculated as a measure of image stability. Additionally, in a separate experiment, two noise acquisition scans [7] were performed using a water phantom with an identical experimental set-up to investigate any evidence of interference in the (k-space) raw data caused by the radiation.

2.3 Radiation delivery

In this study the Linac was fixed at a source-to-isocentre distance (SID) of 1.8 m. Based on imaging performed in the pilot phase of the study, a vertically off-axis rectangular field of $2.25 \times 2.90$ cm was defined by the MLC. The number of monitor units necessary to deliver the radiation dose of 10 Gy to the target as defined in the study protocol was determined using a microdiamond detector (60019,
PTW, Freiburg, Germany) cross-calibrated to a Farmer chamber (FC-65G, Scanditronix/Wellhoffer), previously calibrated in the magnetic field of 1.0 T [11]. The microdiamond was placed in a solid water block resembling the scatter conditions present in the animal irradiation: the block was 3 × 3 × 8 cm oriented sideways to the beam with the detector placed 1.5 cm from the tip. The number of monitor units was chosen to deliver 10 Gy at the position of the microdiamond detector. The set-up included a 2 cm slab of solid water proximal to the beam which serves two purposes; firstly it removes the enhanced skin dose from electron focussing that is observed with inline systems [12] and secondly it improves the dose homogeneity in the target, which is located 4-8 mm under the tissue surface, shifting it beyond the build-up region. The result was verified through film measurements in two experiments. Gafchromic films (EBT3, Ashlend, Bridgewater, USA) were irradiated in the same block geometry placed in air upstream of the block (proximal), at the beam entry surface, at beam exit surface and in air downstream of the block (distal) as shown in Figure 1 three times. Additionally, two films were irradiated placed on either side of a rat cadaver in the treatment position. The same method was used in the live experiment to provide an in vivo verification of dose and position.

3. Results

The delivered film doses in the solid water phantom, on the beam central axis, were 11.2 ± 0.1 Gy (proximal), 10.8 ± 0.5 Gy (entrance), 9.1 ± 0.6 Gy (exit) and 8.6 ± 1.1 Gy (distal) respectively. The dose recorded by the microdiamond detector at the phantom centre was 10.7 ± 0.2 Gy. The doses in the rat cadaver were 11.3 Gy in the proximal film and between 11.3 and 7.2 Gy in the distal film depending on the thickness of the tissue traversed by the beam.

In the live treatment, imaging was successfully used to localise and monitor the delivery of the intended radiation dose to completion. Figure 2 shows photographs of the animal inside the RF coil: The proximal and distal Gafchromic films can both be seen prior to irradiation (left) and the distal film can be seen after irradiation (middle and right).

The dose recorded in the proximal film was 11.5 Gy and in the distal film between 11 and 7 Gy. These films also confirmed that the delivery was to the correct location and radiation field size as can be seen in Figure 2 (middle & right). Figure 3 plots the dose profile in each film for the vertical direction. The dose penumbra (measured between 80 and 20% maximum dose) in the proximal film was equal to 4.9 mm (vertical) and 6.1 mm (horizontal).

Figure 4 shows example images acquired as part of the live treatment: In the sagittal view (left) there is visualisation of the brain leading into the spinal canal with high T2-w signal.
The SNR in the (brain) target region was 38. The lateral lung is also seen in this image with adequate contrast to visualise the diaphragm and liver inferiorly. There is also visualisation of the bowel loops filled with air and surrounding visceral fat. The congruence of the brain target and isocentre was confirmed from viewing the superimposed grid (not shown in Figure 4) and no adjustment of the MLC was required. The axial $T_1$-w image (Figure 4, right) was acquired approximately 45 minutes following contrast injection and demonstrates a small region of hyperintensity in the right hemisphere which measures 5 mm in diameter. The CNR in this enhancing mass was equal to 7.0.

In the real time coronal view (Figure 5, left) there is clear visualisation of both lung fields, liver and kidneys. The external body contour is also visualised. The dynamic images were able to adequately visualise respiration, and also confirmed that the target remained stationary during the course of the treatment. Figure 5 (right) shows a pixel-by-pixel map of maximum signal difference overlaid onto the first image which highlights regions of high variation secondary to respiratory motion. In contrast, regions that remained stationary (e.g. head and neck) showed a percentage signal change of -0.01 ± 0.7% during the beam on period. SNR in these images was unaffected by the radiation beam with values equal to 13.68 and 13.72 for the beam off and on respectively. This was also confirmed by the absence of any spikes in k-space data with the beam on, either using the experimental MLC field size or open MLC, therefore ruling out radiation induced current in the coil.

4. Discussion & Conclusion

This study describes the first use of an inline MRI-Linac with simultaneous imaging and radiation delivery in a living subject. The radiation was delivered according to the trial protocol and has demonstrated the feasibility of the on-going survival study.

Small field dosimetry work-up has been established in the pilot phase of this study to ensure correct dose delivery. Agreement within the specifications of the study protocol was achieved in the pre-treatment dose verification experiments using phantoms and excellent reproducibility was observed between the experiment with the euthanized animal and the subsequent in-vivo film measurements. Inline MRI-Linacs offer an interesting alternative to the current commercial systems in that they minimise or even exploit some of the effects of the magnetic field on the dose deposition: they do not cause an electron return effect, which reduces the dose perturbations at density interfaces and exhibit an electron focussing effect, which has been shown to offer some benefit in penumbral sharpening and lung tumour enhancement [13]. The latter, which is dependent on magnetic field strength and radiation field size, leads to a higher skin dose and can be removed in a number of ways including off-centre irradiation [12]. In this study, a 2 cm solid water block was used primarily to improve dose

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homogeneity in the target, which is located just millimetres below the tissue surface, by shifting it beyond the dose build-up region, but also to remove contaminating electrons; We intend to use such a water block in human patients for this purpose.

Image quality was excellent with the open receiver coil and permitted good visualisation of the target and, in combination with the extended retention time of the nanoparticle agent, was able to discriminate a 5 mm diameter tumour. Images acquired during beam-on showed no change in signal-to-noise ratio or interference in raw data demonstrating the effectiveness of this novel open coil design compared to radio-opaque or radio-translucent coils that may be subject to radiation induced artefacts and beam attenuation [14,15].

The real-time images were of sufficient quality and frame rate to monitor respiration of the animal, which for rats is typically reduced from 80 to 62 breaths per minute under anaesthesia. These images also allowed the target position to be observed during treatment and will serve as a method of exception gating in the larger trial. In one case during the pilot phase, an animal recovered consciousness and was seen to move on these images; during live treatment the beam will be paused and a decision will be made whether to increase anaesthesia and continue with the remainder of the intended delivery.

In conclusion, we have reported on the first live treatment conducted on our prototype inline system, which we also believe is the first animal treatment on any MRI-Linac. The ability to perform pre-clinical animal work on a human system is important for the development of new imaging and therapy agents. A larger cohort study is currently underway comparing no treatment against radiation alone, nanoparticles alone and radiation plus nanoparticles, to investigate the efficacy of radioenhancement using this theranostic contrast agent. The results of the full study will be reported at a later date.

This animal work paves the way for first human trials on our system anticipated later this year; initially this will be conducted by re-positioning of the patient to recreate the desired number of beam angles prior to the installation of an automated rotating couch for full conformal therapy [16].

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Conflict of Interest
The authors have no conflicts to disclose.

References


Figure Legends

**Figure 1:** Photograph showing the film and detector arrangement used in the small solid water phantom to confirm the intended dose with four Gafchromic films and the microdiamond detector.

**Figure 2:** Photographs illustrating the experimental set-up; (left) before irradiation showing the positions of solid water and two films either side of the rat; (middle) view inside the MRI-Linac along the beam axis post irradiation shows laser alignment at isocentre with respect to a vertically off-axis irradiation, and; (right) a close up view confirms the position of the radiation field over the rat brain.

**Figure 3:** Plot of vertical dose profile in the proximal (higher values) and distal (lower values) films. The shaded regions indicate where the penumbra is calculated.

**Figure 4:** Example images from the first live treatment; (left) A sagittal T2-weighted image used to localise the rat brain. The region of high signal underneath the animal is from the heating pad (wrapped in a towel in Figure 2). (right) An axial post-contrast T1-w scan through the centre of the brain confirms the presence of a 5 mm diameter tumour in the right hemisphere (arrow).

**Figure 5:** (left) A single coronal frame taken from a series of dynamic real-time images acquired during irradiation and used for the monitoring of respiration and verification of target position. (right) An overlay of the maximum signal difference during beam on which highlights motion seen in the diaphragm, lung and kidneys.
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