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Comment on Hunt et al., "Feasibility of magnetic resonance guided radiotherapy for the treatment of bladder cancer"

We thank Yavas et al, for their interest in our recent work [1], and are happy to have the opportunity to respond to the comments they raise. We have addressed each of their points individually and hope that the clarification helps better understanding of the technique we described.

- The PTV dose constraints to be achieved at planning are as described in Supplementary Table 1. The PTV dose – volume metrics are as used in phase II randomised control trial protocol which is available open access and referenced within the paper [2]. They are in accordance with ICRU recommendation for photon IMRT planning [3]. We describe the target volumes constraints as a percentage of the prescribed dose and are therefore applicable irrespective of the prescription used i.e. 36 Gy in 6 fractions or 30 Gy in 5 fractions. The justification for these prescriptions in those unsuitable for radical daily bladder radiotherapy have been described elsewhere [4–7]. The D50% is used to for reporting of the prescription, as it reflects median absorbed dose for a homogeneously irradiated target [3].

- The PTV is a statistical construct to ensure that dose is successfully delivered to the CTV [3]. Therefore for an on-line reoptimisation workflow in bladder cancer, the PTV margin predominantly accommodates for the uncertainty of intra-fraction motion [8]. To determine whether the CTV (whole bladder) actually receives an adequate absorbed dose, CTV coverage is assessed on both the verification ($MRI_{verification}$) and post treatment image (MRI_{post}) as a function of the total prescription dose. Acceptable CTV coverage was defined as 95% of CTV receiving $\geq$95% of prescribed dose. The purpose is to demonstrate that the PTV is fit for purpose and that the CTV fills into the PTV during the time it takes to deliver the complete on-line workflow but not beyond it. Evaluating dose to the bladder CTV is consistent with reporting of target coverage in other adaptive bladder radiotherapy trials [9,10].

- In the methods we described that patients are asked to void their bladder prior to set-up. No other patient preparation methods were adopted.

- In the discussion section of the paper we describe how the margins to accommodate the intra-fraction margin were derived. The coverage of varying PTV sizes/margins was evaluated off line in a cohort of patients in whom bladder filling was observed over 30 min [5,9]. Based on this analysis we identified that a 0.5 cm isotropic PTV margin would only encompass 68% of intra-fractional excursions over 30 min. Whereas anisotropic margins used in the paper encompassed >90% of the intra-fraction bladder change over 30 min.

- In the on-line setting, we also have scope to shift the plan relative to the isocentre and recalculate dose on the MR session if the bladder CTV is not optimally within the PTV on MRI verification, i.e. perform an 'Adapt-to-Position' (ATP) workflow following the initial 'Adapt to Shape' (ATS). For these reasons the anisotropic margins described were taken forward for use in the clinical protocol. Larger margins would have reduced opportunity for improved normal tissue sparing, and a smaller margin would have provided inadequate coverage.

- If ATP following ATS did not sufficiently cover the bladder target, then we would have expected to remove the patient from the couch, asked them to void their bladder again, and initiated a new online workflow. ATP would now be preferentially considered to avoid repeat of the situation at this fraction. Patient factors contributing to rapid bladder filling such as pre-treatment diuretic or excessive hydration would be explored and managed prior to the next fraction [9,11]. If this were a routine occurrence then we would have reviewed and increased our intra-fraction margin [8].

- Statistical uncertainty is an important factor to decide dose calculation accuracy and on-line calculation time. For the treatment discussed in our manuscript we felt that a 2% statistical uncertainty offered the best compromise between these two competing demands.

- Move to adopt 55 Gy in 20 fractions (with concurrent chemotherapy) as standard of care fractionation for those suitable for daily treatment is informed by the recent individual patient data meta-analysis of two trials (BC2001 and BCON) which showed superiority of 55 Gy in 20f over 64 Gy in 32f for invasive loco-regional control and non-inferiority for overall survival, and late toxicity [12,13].

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S. Hafeez [a,b,*]
A. Dunlop [c]
A. Mitchell [c]
S. Nill [c]

[a] *Divsion of Radiotherapy and Imaging, The Institute of Cancer Research, London, UK*

[b] *Department of Radiotherapy, The Royal Marsden NHS Foundation Trust, London, UK*

[c] *The Joint Department of Physics at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, UK*

* Corresponding author at: The Royal Marsden NHS Foundation Trust, Downs Road, Sutton, Surrey SM2 5PT, UK.
E-mail address: shaista.hafeez@icr.ac.uk (S. Hafeez)

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