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Technical Note

Feasibility of tumour-focused adaptive radiotherapy for bladder cancer on the MR-linac

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ABSTRACT

Bladder tumour-focused magnetic resonance image-guided adaptive radiotherapy using a 1.5 Tesla MR-linac is feasible. A full online workflow adapting to anatomy at each fraction is achievable in approximately 30 min. Intra-fraction bladder filling did not compromise target coverage with the class solution employed.

Introduction

Adaptive radiotherapy techniques in bladder cancer aim to address inter-fraction target shape and size variation [1]. One developed solution is plan selection from a pre-prepared library of plans generated to capture the expected range of bladder filling [1]. However, this approach is limited as the selected plan conformity to the target on the day can be relatively poor [2]. Daily online re-optimisation at each fraction has the potential to improve this, and in turn reduce the volume of irradiated normal tissue [1,3–5].

Magnetic resonance imaging (MRI) scans acquired immediately prior to radiotherapy delivery on MR-linac systems enable treatment plans to be designed and delivered according to the patient's anatomy at each fraction with good visualisation of the target and organs-at-risk (OARs) [5–7]. The clinical feasibility of whole bladder online adaptation at each fraction with MR-guided adaptive radiotherapy (MRgART) delivered using an MR-linac platform has been successfully demonstrated [8].

A bladder tumour-focused, reduced high-dose volume has the potential to further improve normal tissue irradiation without adversely impacting on local disease control compared to standard whole bladder irradiation [5,9–11]. This is currently being investigated within the RAIDER trial (NCT02447549) at standard and escalated doses delivered on C-arm linacs using a library of three plans where plan selection is informed by target visualisation as seen on pre-treatment cone beam computed tomography (CBCT) verification imaging [12,13].

An MRgART solution to deliver tumour-focused reduced high-dose volume boost may be advantageous given improved tumour visualisation with MRI [5]. In this technical report we share the class solution and first clinical experience for online adaptive bladder tumour-focused radiotherapy using a 1.5 T MR-linac.

Methods and materials

Study population

Patients with T2-T3N0M0 unifocal bladder cancer of any histologic subtype scheduled to receive radical daily bladder radiotherapy on the MR-linac were considered eligible. Patients were consented to a prospective single centre clinical research and ethics committee approved study (Prospective Evaluation of Radiotherapy Using Magnetic Resonance Image Guided Treatment, PERMIT; NCT03727698) conducted in accordance with Good Clinical Practice and The Declaration of Helsinki. Radiotherapy was delivered on the Elekta Unity MR-linac system (Elekta AB, Stockholm, Sweden) with concomitant chemotherapy (weekly gemcitabine 75 mg/m^2).

Treatment planning

All patients underwent a non-contrast enhanced planning computed tomography (CT) scan ($CT_{planning}$) and 3D T2-weighted (T2w) planning

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MRI scan ($MRI_{planning}$), acquired on the MR-linac. Patients were required to void their bladder immediately prior to each planning scan. No drinking protocol was otherwise applied. The Combi Fix system (Oncology Systems Ltd, UK) was used for patient immobilisation during scanning.

Target volumes and OARs were delineated on both $CT_{planning}$ and $MRI_{planning}$. The gross tumour volume (GTV) was defined as the bladder tumour or bladder tumour bed including any extravesical extension. The clinical target volume (CTV) was contoured to encompass the whole bladder including the GTV and any extra-vesicle spread. If the GTV was at the bladder base or if distant carcinoma in situ was present, the CTV included 1.5 cm of the prostatic urethra (in males) or 1 cm of urethra (in females). The GTV and CTV were each expanded by 0.5 cm laterally and inferiorly, 1 cm posteriorly, and 1.5 cm anteriorly and superiorly to create the PTV_{tumour} and $PTV_{bladder}$ respectively [7,12].

The contoured OARs were the rectum, bowel (including both small and large bowel as a single structure), femoral heads, and the normal bladder outside PTV_{tumour}. Normal bladder outside PTV_{tumour} was created by subtracting PTV_{tumour} from the corresponding CTV. Details of target volume and OAR delineation have been previously described [12].

The initial reference plan was created on $MRI_{planning}$, utilising $CT_{planning}$ to derive the relative electron densities for bulk density override regions of interest (ROIs) to facilitate MRI-based dose calculation. The Monaco treatment planning system (v5.40.01 Elekta AB, Stockholm, Sweden), with a fast graphics processing unit (GPU)-based Monte Carlo dose (GPUMCD) engine, was used [14]. Treatment plans consisted of 11-field step-and-shoot intensity modulated radiation therapy (IMRT) with a field energy of 7MV FFF. Plans were calculated using a dose grid resolution and Monte Carlo statistical uncertainty of 0.3 cm and 2 % per calculation respectively. A volumetric modulated arc therapy (VMAT) back-up plan for C-arm linac use was also generated on $CT_{planning}$ in the event of MR-linac unavailability. The prescription dose (PTV D50%) was 55 Gy in 20 fractions to PTV_{tumour} and 46 Gy in 20 fractions to $PTV_{bladder}$. Dose constraints are given in Table 1. Planning template parameter details are provided in the Supplementary Material.

Table 1
Dose constraints for MR-linac bladder tumour-focused radiotherapy.

Structure	Metric				Optimal	Mandatory	Units
Targets							
PTV_{tumour}	D	99	%	>	–	49.5	Gy
	V	52.3	Gy	>	98	95	%
	D	50	%	>	–	54.4	Gy
	D	50	%	<	–	55.6	Gy
	D	5	%	<	–	57.8	Gy
	D	2	%	<	–	58.9	Gy
$PTV_{bladder\_edited}$	V	43.7	Gy	>	98	95	%
($PTV_{bladder}$ -	D	50	%	>	–	45.5	Gy
PTV_{tumour})	D	50	%	<	46.5	48.3	Gy
Organs at risk							
Rectum	V	28.0	Gy	<	50	80	%
	V	43.2	Gy	<	20	60	%
	V	52.0	Gy	<	15	50	%
	V	56.0	Gy	<	5	30	%
Bowel	V	28.0	Gy	<	149	178	cc
	V	39.8	Gy	<	116	139	cc
	V	43.2	Gy	<	104	127	cc
	V	48.0	Gy	<	91	115	cc
	V	52.0	Gy	<	73	98	cc
	V	56.0	Gy	<	23	40	cc
Uninvolved Bladder	V	50.0	Gy	<	50	80	%
	V	54.2	Gy	<	0	5	%
(CTV - PTV_{tumour})							
Left Femoral Joint	V	43.2	Gy	<	–	50	%
Right Femoral Joint	V	43.2	Gy	<	–	50	%
Normal Tissue	D	1	cc	<	57.8	60.5	Gy
(Patient - [PTV_{tumour} + $PTV_{bladder}$])							

Online workflow

Patients were asked to void their bladder prior to set up and were immobilised as per their planning scans. An online Adapt-to-Shape (ATS) workflow was adopted at each fraction whereby contours were propagated from $MRI_{planning}$ to the daily session MRI scan ($MRI_{session}$) and edited accordingly, with a new treatment plan optimised and delivered daily [8].

Following acquisition of the 2 min 3D T2w $MRI_{session}$, it was exported to Monaco and registered to $MRI_{planning}$, prioritising soft tissue matching of the GTV. The GTV contour was then propagated rigidly to $MRI_{session}$; CTV and OARs were propagated using deformable image registration. The target and OAR contours on $MRI_{session}$ were reviewed and amended by the clinician accordingly. Reduction in GTV size from initial $MRI_{planning}$ was avoided. GTV editing was permitted where bladder deformation or filling status impacted on GTV contour. OARs were amended within 2 cm of PTV_{tumour} and $PTV_{bladder}$ where required.

A new radiotherapy plan was optimised using $MRI_{session}$ contours and reference plan parameters. The optimisation was terminated once optimal target and mandatory OARs constraints were achieved rather than completion of pre-defined maximum number of segment shape optimisation loops defined by the planning template. A further 2 min T2w MRI ($MRI_{verification}$) was acquired prior to beam on to ensure appropriate target coverage was maintained. $MRI_{verification}$ acquisition was timed to coincide with optimisation termination.

If on $MRI_{verification}$ the GTV was not encompassed by PTV_{tumour}, a subsequent Adapt-to-Position (ATP) workflow was performed to ensure appropriate target coverage. During this process, the segment apertures from the ATS plan were shifted based on rigid registration translations between $MRI_{session}$ and $MRI_{verification}$, and the segment weightings were re-optimised. Dose calculation was performed on $MRI_{session}$.

Immediately prior to beam on, orthogonal 2D cine MRI scans were initiated to ensure that the bladder tumour was still being encompassed by PTV_{tumour}. An independent dose check was performed during treatment delivery. A final post-treatment 2 min T2w MRI (MRI_{post}) was acquired to coincide with end of dose delivery to assess intra-fractional change offline.

Offline assessment

For offline assessment, two clinicians (SH and MI) re-contoured the GTV, CTV, rectum, and bowel on the MRI_{post} images. The delivered treatment plans were then recalculated on the corresponding MRI_{post} image. Target dose coverage was deemed acceptable if 95% of the GTV and CTV received $\geq$ 95% of their respective prescribed doses. Doses were evaluated assuming each plan delivers the complete treatment course (20 fractions).

Results

Between April and November 2021, five patients (3 male and 2 female) were recruited. The median age was 71 years old (range 62 – 82 years). All patients had unifocal disease. All patients completed their scheduled 20 fraction treatment course. Of the 100 fractions delivered, 98 were delivered on the MR-linac; two patients were treated with their back-up plan on C-arm linac for a single fraction each due to machine breakdown. All 98 fractions were delivered using the ATS protocol. Six fractions required additional ATP planning after ATS. All mandatory OAR dose constraints were achieved on $MRI_{session}$ and MRI_{post} plans.

Target volume variation

Median (range) volume as defined on $MRI_{planning}$ of GTV and CTV were 14.8 cc (9.4 – 21.6 cc) and 72.0 cc (59.1 – 84.8 cc) respectively.

Median percentage volume changes between $MRI_{session}$ and MRI_{post} were −4.2 % and + 41.9 % for GTV and CTV respectively. Per patient inter and intra-fraction target volume variation is shown in Supplementary Fig. 1.

Target coverage

Target coverage of the GTV and CTV on $MRI_{session}$ and MRI_{post} are given in Figs. 1 and 2 respectively. All $MRI_{session}$ plans met their target prescription dose at every fraction.

On MRI_{post} plans, the median (range) GTV D95% was 53.7 Gy (43.4 – 55.6 Gy). 93/98 fractions met the target prescription dose. Of the 5/98 fractions achieving less than 95% of the prescribed dose, GTV D95% ranged between 43.4 Gy and 52.2 Gy with GTV V95% between 86.1 % and 94.9%. Of these 5 fractions, only one fraction also did not meet GTV target prescription dose on $MRI_{verification}$, in this instance GTV D95% was 49.9 Gy and V95% was 90.1%.

On MRI_{post} plans, the median (range) CTV D95% was 45.7 Gy (18.9 – 52.0 Gy). 91/98 fractions met the target prescription dose. Of the 7/98 fractions achieving less than 95% of the prescribed dose, CTV D95% ranged between 18.9 Gy and 43.3 Gy with CTV V95% between 81.8 % and 92.6 %. Of these 7 fractions, all met CTV target prescription dose on $MRI_{verification}$.

Timings

From completion of patient setup to end of treatment delivery, the median (range) time was 30.3 min (24.7 – 60.4 min). Individual patient timings are given in Fig. 3A, and the times for individual stages in the workflow are given in Fig. 3B. Online contouring represented the most variable duration of the workflow, with median (range) time of 5.6 min (1.4 – 14.4 min).

Overall workflow duration increase was associated with fractions where ATP was required following ATS (6/98 fractions). In 7 fractions an increase was associated with software or machine-related failures. In 2/98 fractions, duration increase was due to patient requirement to leave the treatment room following ATS planning when it was identified that the GTV was no longer encompassed by PTV_{tumour} on $MRI_{verification}$ and was not deemed correctable by ATP. In one instance, Patient 3 was asked to partially void their bladder. In the second instance, Patient 5 was asked to void their rectum of flatus. Here, the times from initial setup to end of treatment delivery were 60.4 min and 47.5 min respectively.

Discussion

We successfully demonstrate technical and clinical feasibility of an online re-optimisation adaptive radiotherapy strategy to deliver tumour-focused reduced high-dose volume bladder radiotherapy on an MR-linac.

To mitigate against the potential additional complexity increasing overall workflow time compared to the whole bladder adaptive MR-linac solution, several new considerations were made [8]. This included performing the initial reference plan on MRI rather than CT, ensuring acquisition of $MRI_{verification}$ was completed by the time ATS optimisation concluded, and sequencing the independent plan dose check during treatment delivery. The latter was deemed to be safe and acceptable following retrospective analysis and risk assessment of plan checking results from 115 prior whole bladder ATS fractions delivered on the MR-linac. These combined strategies successfully accelerated the online process such that median workflow times were 30 min, compared to 39 min for whole bladder, accepting in part higher dose per fraction

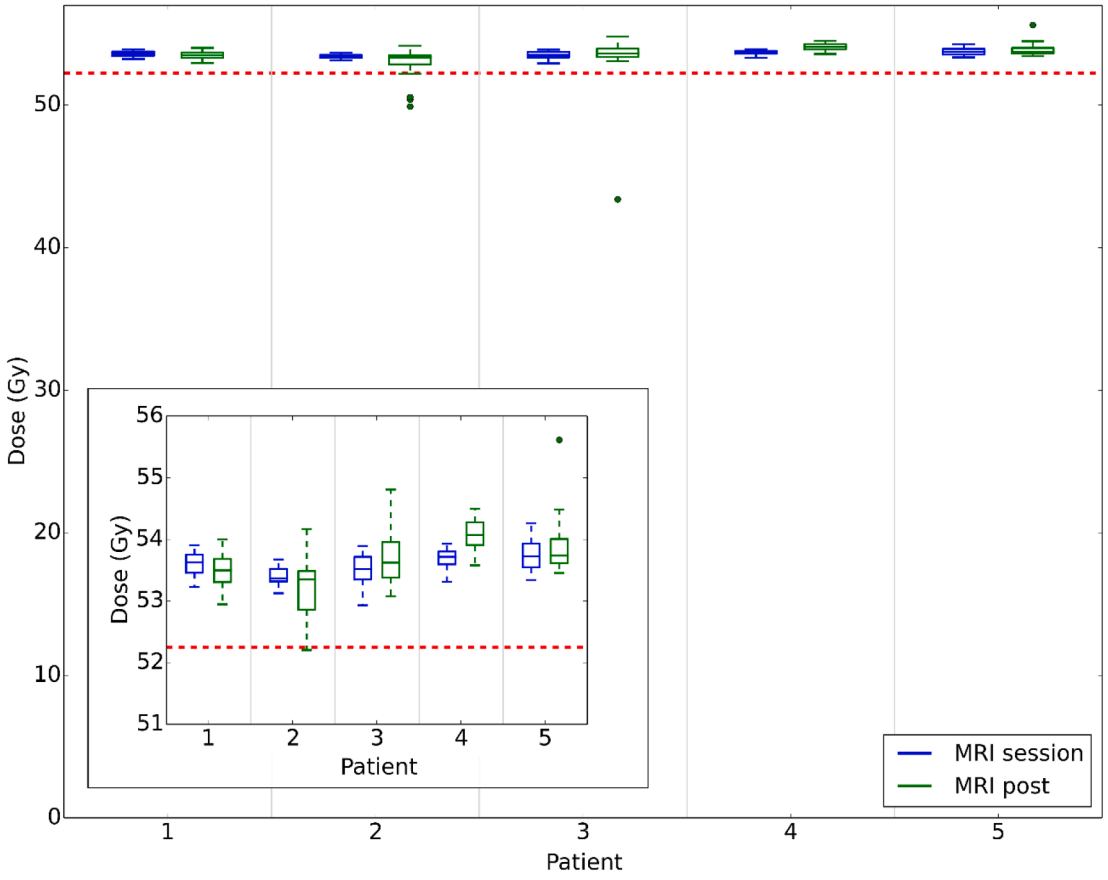

Fig. 1. GTV D95%, evaluated on $MRI_{session}$ and MRI_{post}. Red line indicates the mandatory dose constraint (52.3 Gy). Inset graph magnifies the higher doses.

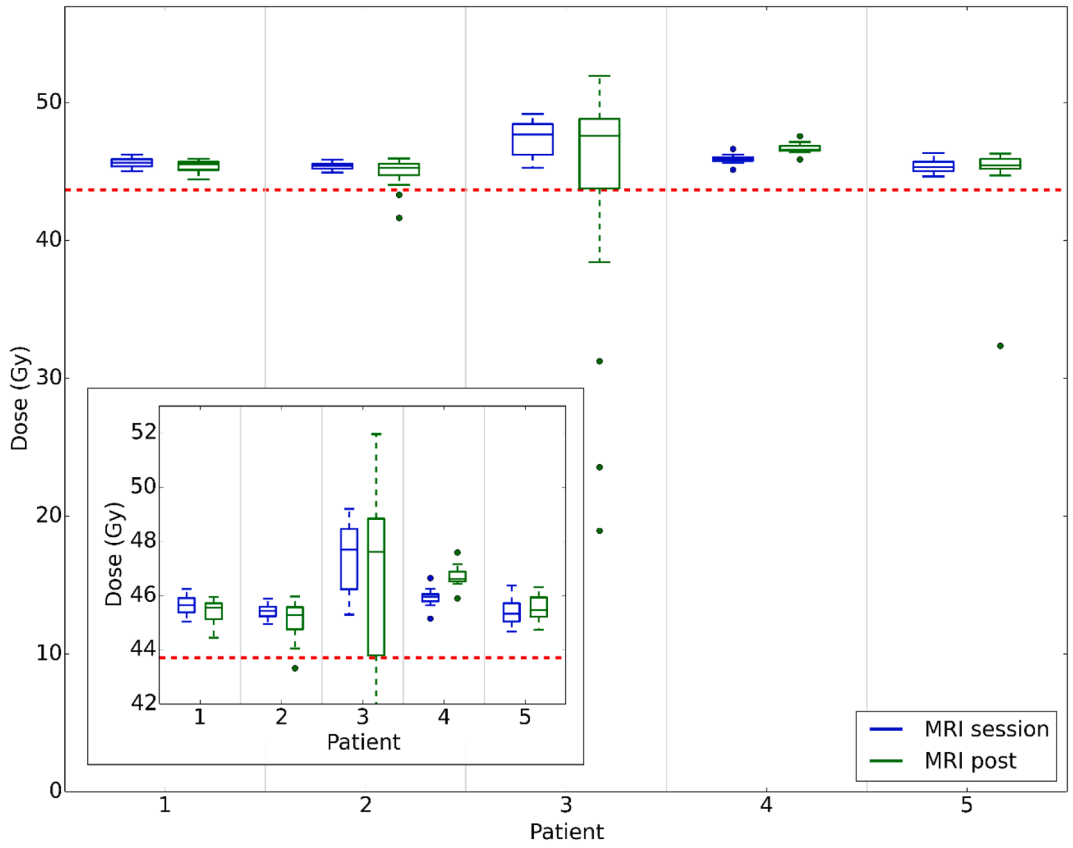

Fig. 2. CTV D95%, evaluated on $MRI_{session}$ and MRI_{post}. Red line indicates the mandatory dose constraint (43.7 Gy). Inset graph magnifies the higher doses.

will confound direct comparison (2.75 Gy compared to 6 Gy per fraction) [8]. Comparable workflow times are achieved when the measures described above were adopted for whole bladder patients receiving 55 Gy in 20 fractions (unpublished).

The anisotropic PTV margins were derived from a previous bladder radiotherapy study cohort, whereby intra-fraction bladder filling occurring over 30 min could be encompassed in 90% of cases [15]. These margins also successfully maintained target coverage for MR-linac whole bladder treatment [8]. It was therefore anticipated they would be adequate for tumour-focused reduced high-dose volume bladder radiotherapy if similar online workflow times could be achieved.

As PTV_{tumour} and $PTV_{bladder}$ are geometric constructs to ensure adequate dose is received by the GTV and CTV respectively, GTV and CTV target coverage were assessed on the post treatment image (MRI_{post}). This is consistent with reporting of target coverage in other adaptive bladder radiotherapy trials [2,4,16]. An accepted limitation is that it represents a potentially worst-case scenario time point when intra-fractional bladder filling and size are at their maximum so lending itself to underestimating target dose reporting. Despite this, GTV and CTV were covered by 95% of their respective prescription doses in > 90% of fractions.

When ATP following ATS was required to accommodate intra-fractional changes, the clinical decision was made to prioritise target coverage of the GTV over the uninvolved bladder (CTV). This contributed to 7% of fractions not meeting the mandatory CTV dose constraint. For example, Patient 3 required ATP following ATS to optimise GTV coverage at intentional expense of CTV coverage for 4/20 fractions (Fig. 2 and supplementary Fig. 1). It is anticipated that an overall faster workflow would mitigate instances where intra-fractional bladder filling compromises target coverage. Future work will also investigate predictors of individual patient bladder filling to determine personal minimum intra- fraction margin required to maintain target coverage.

In 2% of fractions the patient was removed from the treatment room to optimise anatomy because ATP following ATS was not deemed suitable to achieve adequate target coverage. This is marginally better than observed rate (3%) with library of plans to deliver tumour-focused reduced high-dose volume bladder radiotherapy [2].

Online re-optimisation has also demonstrated improved conformity over library of plans [2,8]. Modelling work to date demonstrates that MRI-defined bladder tumour is up to 50% smaller than CT which translates to significant reduction of dose to bowel and normal bladder while enabling dose escalation to the bladder tumour with anisotropic PTV_{tumour} margin described [17].

Reduction in PTV margin and further normal tissue sparing is anticipated with reduced workflow times. Utilisation of MRI sequences with shorter acquisition times and smaller datasets would improve overall system and optimisation speeds. These sequences would require a multi-disciplinary approach to evaluate their suitability for contouring, registration, and planning, as well as MR safety and geometric image fidelity. This work is in progress.

The clinical delivery of the online workflow described required the presence of a clinical (radiation) oncologist, a physicist, and two treatment radiographers (RTTs). However we anticipate less resource intensive treatment delivery with further role and responsibility expansion by appropriately trained treatment radiographers in the near future [18].

Conclusion

The MR-linac system can be used to deliver online adaptive bladder tumour-focused radiotherapy. It is feasible to successfully deliver this workflow in approximately 30 min without compromise to target coverage.

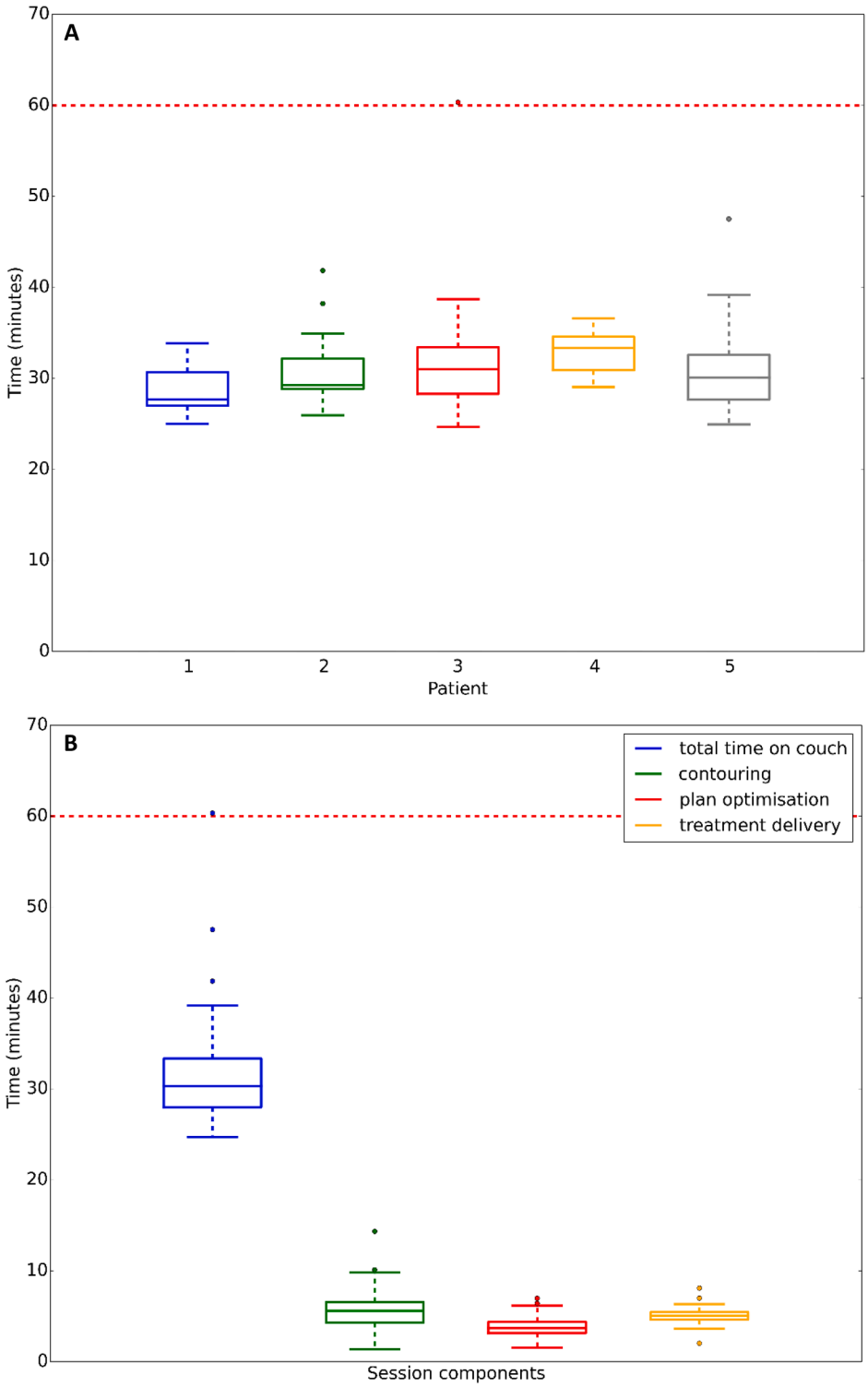

Fig. 3. Timings summary. Panel A: individual patient workflow times. Panel B: time taken for key workflow stages. Red line indicates the currently allocated treatment slot duration of 60 min.

Contributions

All authors meet at least of one the criteria recommended by the ICMJE. A.M., A.D., and S.H. wrote the first draft of the manuscript. All authors contributed to subsequent revisions of the manuscript.

Declaration of interest

The Royal Marsden Hospital, and The Institute of Cancer Research are members of the Elekta MR-linac Consortium, which aims to coordinate international collaborative research relating to the Elekta Unity (MR-linac). Elekta (Elekta AB, Stockholm, Sweden) and Philips (Philips, Best, Netherlands) are commercial members of the MR-linac

Consortium. Elekta financially supports consortium member institutions with research funding, education, and travel costs for consortium meetings. S.H. is bladder tumour site group lead within the MR-linac Consortium. No commercial financial support was received from any organisation for the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.04.008.

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