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Technical Note

MRI-guided adaptive radiotherapy for prostate cancer: When do we need to account for intra-fraction motion?

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ABSTRACT

A shift of the daily plan can mitigate target position changes that occur between daily MR acquisition and treatment for MR-linac radiotherapy, but increases the session time. We demonstrated that our workflow strategy and decision-making process, to determine whether a subsequent shift is necessary, is appropriate.

Introduction

Magnetic resonance image guided radiotherapy (MRgRT) delivered with the Unity MR-Linac (Elekta AB, Stockholm, Sweden), utilises an integrated 7MV flattening filter free (FFF) Elekta linear accelerator (linac) and a Philips 1.5T Magnetic resonance imaging (MRI) scanner, enabling online adaptive radiotherapy and real-time imaging [1].

Patients with low and intermediate risk prostate cancer were treated with radical radiotherapy on the MR-Linac within the Prostate Radiotherapy Integrated with Simultaneous MRI (PRISM) trial (NCT03658525). Two online workflow planning strategies were used, 'Adapt to Shape' ('ATS') and 'Adapt to Position of the ATS' ('ATP-of-ATS') [2]. In ATS a new plan is created online by creating new contours on the initial daily MR image ($MR_{session}$) and for ATP-of-ATS a subsequent modification or 'shift' (adjustment of the treatment field apertures) of the daily ATS plan is performed to correct for motion [3]. Intra-fraction motion, resulting from bladder filling, patient movement, or rectal changes may occur during the MR-Linac treatment session [4], which are typically longer than those on conventional linacs [5,6]. A MRI acquired immediately prior to treatment (MR_verification) can determine such motion by a rigid registration with the MR_session image. Any intra-fraction motion can be accounted for, by performing an ATP-of-ATS at the expense of further increasing session time.

Although ATS strategies have been demonstrated to be acceptable [7], there have been reported cases where ATP-of-ATS would have improved dosimetry, albeit in only 4 % of fractions [8]. The additional time needed to perform ATP after ATS for all fractions would impact patient throughput and increase the potential for further intra-fraction motion. We have investigated whether criteria implemented to perform ATP-of-ATS was appropriate and evaluated the predicted dosimetric benefits, if any, of using an ATP-of-ATS compared with ATS only.

Methods

This study was approved by the Royal Marsden NHS Foundation Trust audit committee. The first seven patients consented to the PRISM MR-Linac Trial (NCT03658525) for prostate cancer treatment with daily MRgRT, treated between October 2018 and March 2019 were included. Patient preparation and treatment planning parameters and procedures have been previously described [3].

Treatment planning was performed using the Monaco Treatment Planning System (TPS) (Elekta AB, Stockholm, Sweden, v5.40.00). The primary clinical target volume (CTV), Prostate CTV, was defined as the prostate plus proximal 1 cm of seminal vesicles (SV) with an elective CTV ('SV CTV') consisting of the proximal 2 cm of seminal vesicles exterior to the prostate. The primary Planning Target Volume (PTV_6000) was a 5 mm left, right, superior, inferior, anterior and 3 mm

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posterior expansion of the prostate CTV, and elective PTV_4860 was defined as a 5 mm isotropic expansion of the combined prostate and SV CTVs. PTV_6000 and PTV_4860 were prescribed to 60 Gy and 48.6 Gy in 20 fractions, respectively.

Online workflow

Following patient set-up [9] a 2-minute T2 weighted MRI was acquired ($MRI_{session}$). Organs at Risk (OARs) and target volumes were propagated from a reference image (either CT or MRI) onto the $MR_{session}$. The target volumes and OARs were amended by a clinician where required. PTVs were regrown based on the updated CTVs and a daily plan was created on the $MR_{session}$ with the updated volumes. MRI-based dose calculation was facilitated via bulk density overrides [3].

A second 2-minute T2 weighted MRI ($MR_{verification}$) was acquired, following plan creation, immediately prior to treatment delivery. The volumes defined on the $MR_{session}$ were overlaid and reviewed on the $MR_{verification}$. If the visible prostate was within the corresponding PTV, the 'ATS' treatment was delivered. However, if intra-fraction motion was observed such that the PTV was no longer encompassing the prostate, an 'ATP-of-ATS' was performed prior.

The use of an 'ATS' plan or an 'ATP-of-ATS' plan for any given fraction was recorded (treated workflow). The alternative workflow was simulated offline for all 20 fractions (alternative workflow). For each fraction both the treated and alternative workflow plans were recalculated on the $MR_{verification}$ as a surrogate for delivered fractional dose. Target volumes and OARs were delineated by one clinician (KS) using the RayStation TPS (RaySearch Laboratories, Development Software v8.0.0.61). The Monaco dose cubes for both the treated and alternative workflow plans were exported to the RayStation TPS for dosimetric analysis. The delivered fractional dose estimations were scaled to the full prescription, i.e. 20 fractions, in order to appraise the distributions against established target and OAR clinical goals.

Data analysis

The frequency of using an 'ATP-of-ATS' was determined. Overall daily plan compliance was determined by permitting two variations in the clinical goals, following strategies implemented for trials such as the PACE C (NCT01584258) [10] (Table 1), with 14/16 passing clinical goals deemed an acceptable online plan if failed clinical goals were approved by a clinician. Clinical goal compliance for treated and alternative workflows was assessed for all fractions.

Results

Of the seven patients treated between October 2018 and March 2019 five patients were included with 94 fractions available for analysis. The workflow described was not implemented for the first treated patient and another patient excluded due to bladder voiding during the workflow for over half the fractions. Six fractions were unable to be analysed because of disruptions to the MRLinac workflow for example bladder voiding (n = 4) and software issues (n = 2). Patients included were allocated numbers 1–5.

'ATP-of-ATS' was used for treatment in 25 % (23/94) of fractions, with 'ATS' used for treatment in the remaining 75 % (71/94). Of the 23 fractions treated using ATP-of-ATS, the majority (22) were spread evenly between three patients. ATS-treated fractions achieved equivalent predicted clinical goal compliance of 95 % and similar rates of overall plan acceptability (92 % compared to 93 %) compared to the alternative workflow (Table 2). For fractions where 'ATP-of-ATS' was used, a greater percentage of predicted clinical goals were achieved (93 %) and a greater number of plans considered acceptable (96 %) compared to the alternative workflow where the ATS was delivered without an ATP (89 % and 70 %, respectively). Two fractions treated with ATS would have benefited from ATP-of- ATS, in terms of clinical goal compliance. No fractions that were treated ATP-of-ATS would have benefited from the alternative workflow – with ATS alone.

Fig. 1 displays estimated delivered dose for a fraction where the patient demonstrated gross intra-fraction motion. For this fraction the patient was treated with an 'ATP-of-ATS' workflow (Fig. 1, left) with D95% of CTV Prostate predicted to be 57.2 Gy (>57.0 Gy) when scaled to twenty fractions. Had the alternative workflow been used (ATS, Fig. 1, right) D95% of CTV Prostate was predicted to be lower at 54.7 Gy.

For Patient 1, as identified on reference planning imaging, the bowel often abutted the primary target (CTV Prostate) on the $MR_{session}$. This meant that for 13 fractions during online plan optimisation the target coverage was intentionally compromised to ensure cumulative OAR doses over the entire treatment course remained within constraints. Therefore, to ensure intentional target compromise (and corresponding predicted clinical goal failures) did not influence the interpretation of the data, the results were analysed with data for Patient 1 removed. For ATS-treated fractions there was no predicted dosimetry benefit had the alternative workflow been used, with total clinical goal compliance and overall plan acceptability being higher for the ATS-treated plan compared to alternative ATP-of-ATS workflow. For fractions where ATP-of-ATS was used, a greater percentage of predicted clinical goals were achieved (96 %) and a greater number of plans considered acceptable (100 %) compared to the ATS alternative workflow (92 % and 81 %, respectively) (Table 3). With Patient 1 removed from the analysis, 100 % of clinically delivered workflows passed with at least 14/16 clinical goal compliance (Table 3).

Discussion

We have shown that visual assessment of the prostate on the $MR_{verification}$, with $MR_{session}$ -defined PTVs overlaid, is an effective decision-making tool to determine the necessity of a ATP-of-ATS. The workflow strategy of using an 'ATP-of-ATS' where the CTV was not covered by the PTV at verification has been reported, but the frequency and impact of doing so not described [11]. We found that for fractions treated with the 'ATP-of-ATS' workflow, a greater percentage of clinical goals were achieved, and a greater number of daily plans deemed acceptable, compared to an ATS workflow. Conversely, there was no

Table 1
Clinical target volumes and Organs at risk clinical goals.

CTV Clinical Goals	OAR Mandatory Clinical Goals
Prostate CTV D95% >57.0 Gy	Bladder V60.8 Gy < 25 %
Prostate CTV D98% > 55.8 Gy	Bladder V56.8 Gy < 35 %
SV CTV D95% > 46.2 Gy	Bladder V52.7 Gy < 50 %
SV CTV D98% > 45.2 Gy	Bowel V52.7 Gy < 0.01 cc
	Bowel V48.7 Gy < 6 cc
	Bowel V44.6 Gy < 28 cc
	Penile Bulb V40.5 Gy < 50 %
	Rectum V60.8 Gy < 5 %
	Rectum V56.8 Gy < 15 %
	Rectum V52.7 Gy < 30 %
	Rectum V48.6 Gy < 50 %
	Rectum V40.5 Gy < 60 %

Table 2
Clinical goal compliance for clinically treated and alternative workflows (e.g. for the ATS clinically delivered workflow, the offline alternative is ATP-of-ATS.

All 94 fractions analysed		Total clinical goals achieved		Plans which pass at least 14/16 clinical goal compliance	
Clinically delivered workflow	Fractions Treated	Online treated	Offline alternative	Online treated	Offline alternative
ATS	71 (75 %)	95 %	95 %	92 %	93 %
ATP-of-ATS	23 (25 %)	93 %	89 %	96 %	70 %

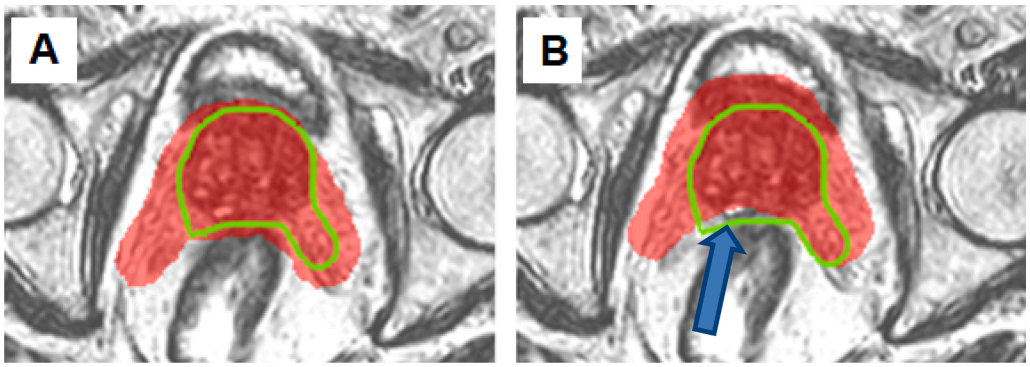

Fig. 1. Clinically delivered estimated fraction dose for Patient 1 fraction 8 using ATP-of-ATS workflow left (A) and alternative workflow (ATS) shown right (B). Red colourwash represents 95 % of primary prescription dose (57 Gy when scaled to full twenty fractions) when plans recalculated on $MR_{\_verification}$. Green contour represents the Prostate CTV as re-contoured on the $MR_{\_verification}$, this falls outside the PTV with the ATS alone workflow (blue arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Clinical goal compliance for clinically treated and alternative workflows (Patient 1 removed) e.g. for the ATS clinically delivered workflow, the offline alternative is ATP-of-ATS.

Patient 1 removed, results from remaining 75 fractions	
Total clinical goals achieved	
Plans which pass at least 14/16 clinical goal compliance	
Clinically delivered workflow	
Fractions Treated	
Online	
treated	
Offline alternative	
Online	
treated	
Offline alternative	
ATS	
59 (79 %)	
97 %	
96 %	
100 %	
98 %	
ATP-of-ATS	
16 (21 %)	
96 %	
92 %	
100 %	
81 %	

appreciable difference in these metrics between the two workflows for fractions where ATS-only was used, indicating that for these fractions a subsequent ATP-of-ATS adaption would have prolonged the overall session time, by approximately 5–10 min, without a predicted dosimetric benefit.

The CTV prostate D95% constraints for the clinically treated plan were met in all but one fraction in four of the five patients. A retrospective assessment of this fraction indicated that the visible prostate on the $MR_{\_verification}$ was outside the $MR_{\_session}$ -defined PTV so that although an ATS strategy was used for this fraction, ATP-of-ATS, which would have been predicted to improve target coverage, would have been appropriate in this case.

The online challenges of ATP-of-ATS must also be considered. Performing an ATP-of-ATS further extends the already prolonged treatment session, increasing the likelihood of additional motion[12,13]. An alternative would be to always perform an ATP-of-ATS, to streamline the workflow and exclude the decision-making process. However, we have shown ATP-of-ATS is only necessary in <30 % of fractions and was not necessary in all patients. One patient did not require ATP-of-ATS and another only required ATP-of-ATS for one fraction.

Other centres have reported an ATS only workflow to be effective, with no excursion of the prostate beyond the PTV reported, in 20 patients receiving 5 fractions with 3 mm PTV margins [7] and only required in 4 of 100 fractions in 5 patients receiving 20 fractions with 5 mm margins [13]. ATP-of-ATS was used more frequently in our study. The reason for the difference between our results and these previous studies is not clear. Patient preparation and the workflow time was similar [7]. The small number of patients may have been a contributing factor, or the different PTV margin used (5 mm posterior margin as opposed to 3 mm) [13].

The delivered fractional dose estimations were scaled to the full prescription, i.e. 20 fractions, in order to appraise daily distributions against established target and OAR clinical goals. Appraising plan acceptability, in this way may have limited clinical significance. For example, if the bowel was far away from the target for the majority of fractions and abutting the target on a small number of days, if we failed the scaled bowel V52.7 Gy constraint on the daily plans when it abutted the target, the predicted accumulated bowel V52.7 Gy dose across all fractions would still be expected to be achieved. Thus, appraising each daily plan to 1/20th of the total course constraint may be overly cautious. With adaptive radiotherapy techniques, where we can visualise targets and OARs during treatment, we can now explore compromises between tumour control and toxicity more precisely in the future.

Following methods used in our previous studies [3], we used the recalculated dose on the $MR_{\_verification}$ as a surrogate for delivered dose. This is a limitation because intra-fraction motion occurring after $MR_{\_verification}$ acquisition and during beam delivery is not accounted for. The time between the and $MR_{\_verification}$ acquisitions was, approximately 25 min, compared to <5 mins between the $MR_{\_verification}$ and start of treatment delivery. Further work could be carried out to ascertain an internal margin which would account for the anticipated intra-fraction motion between the verification image and beam on, creating an alternative expansion of the prostate target, smaller than the PTV, to be used in the decision-making process and determining if an ATP-of-ATS was necessary. This was beyond the scope of this study.

We have described two online planning strategy workflows, ATS and ATP-of-ATS. Although other workflows are available for the MR-linac such as ATP-only, we have shown previously that for this patient cohort, a subset of patients are predicted to benefit, dosimetrically, from daily online adaption [3]. Therefore, we have not considered workflows that do not adapt to anatomy online.

The conclusions made are only valid for the protocol used to treat the patients included in this study. Any variation of dose constraints, target margins, and treatment planning solutions may impact the effectiveness of the decision-making process. Continuous audit of online decision-making tools should be undertaken to ensure patients are treated as intended.

Conclusion

We have demonstrated that our workflow strategy decision-making process, verifying if the visible prostate was within the corresponding PTV was appropriate to determine whether a subsequent ATP-of-ATS workflow is necessary for any given fraction. The dose calculated on

the image immediately prior to delivery was used as a surrogate for delivered dose to quantify the process.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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