Elsevier required licence: © 2020

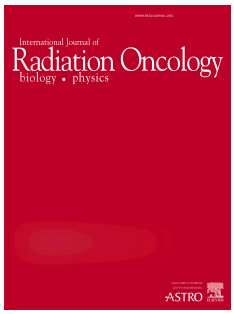
This manuscript version is made available under the
CC-BY-NC-ND 4.0 license

http://creativecommons.org/licenses/by-nc-nd/4.0/

The definitive publisher version is available online at

https://doi.org/10.1016/j.ijrobp.2020.03.014

Journal Pre-proof



Real-Time Image-Guided Ablative Prostate Cancer Radiation Therapy: Results from the TROG 15.01 SPARK Trial

Paul Keall, PhD, Doan Trang Nguyen, PhD, Ricky O'Brien, PhD, Emily Hewson, MMedPhys, Helen Ball, PhD, Per Poulsen, PhD, Jeremy Booth, PhD, Peter Greer, PhD, Perry Hunter, BSc, Lee Wilton, BMedRadiatSci, Regina Bromley, MSc, John Kipritidis, PhD, Thomas Eade, FRANZCR, Andrew Kneebone, FRANZCR, George Hruby, FRANZCR, Trevor Moodie, MSc, Amy Hayden, FRANZCR, Sandra Turner, FRANZCR, Sankar Arumugam, PhD, Mark Sidhom, FRANZCR, Nicholas Hardcastle, PhD, Shankar Siva, FRANZCR, Keen-Hun Tai, FRANZCR, Val Gebski, MStat, Jarad Martin, FRANZCR

PII: S0360-3016(20)30937-8

DOI: https://doi.org/10.1016/j.ijrobp.2020.03.014

Reference: ROB 26250

To appear in: *International Journal of Radiation Oncology • Biology • Physics*

Received Date: 6 August 2019

Revised Date: 9 March 2020

Accepted Date: 11 March 2020

Please cite this article as: Keall P, Nguyen DT, O'Brien R, Hewson E, Ball H, Poulsen P, Booth J, Greer P, Hunter P, Wilton L, Bromley R, Kipritidis J, Eade T, Kneebone A, Hruby G, Moodie T, Hayden A, Turner S, Arumugam S, Sidhom M, Hardcastle N, Siva S, Tai K-H, Gebski V, Martin J, Real-Time Image-Guided Ablative Prostate Cancer Radiation Therapy: Results from the TROG 15.01 SPARK Trial *International Journal of Radiation Oncology • Biology • Physics* (2020), doi: https://doi.org/10.1016/j.ijrobp.2020.03.014.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Elsevier Inc. All rights reserved.

Journal Pre-proof

Real-Time Image-Guided Ablative Prostate Cancer Radiation Therapy: Results from the TROG 15.01 SPARK Trial

Paul Keall PhD[a], Doan Trang Nguyen PhD[a,b], Ricky O'Brien PhD[a], Emily Hewson MMedPhys[a], Helen Ball PhD[a], Per Poulsen PhD[c], Jeremy Booth PhD[d,e], Peter Greer PhD[f,g], Perry Hunter BSc[f], Lee Wilton BMedRadiatSci[f], Regina Bromley MSc[d], John Kipritidis PhD[d], Thomas Eade FRANZCR[d,h] Andrew Kneebone FRANZCR[d,h], George Hruby FRANZCR[d,h], Trevor Moodie MSc[i], Amy Hayden FRANZCR[i], Sandra Turner FRANZCR[i], Sankar Arumugam PhD[j], Mark Sidhom FRANZCR[j], Nicholas Hardcastle PhD[k,l], Shankar Siva FRANZCR[m], Keen-Hun Tai FRANZCR[m], Val Gebski MStat[n], Jarad Martin FRANZCR[f,g]

Affiliations

[a]University of Sydney, ACRF Image X Institute, Sydney, Australia.

[b]University of Technology Sydney, School of Biomedical Engineering, Sydney, Australia

[c]Aarhus University Hospital, Department of Oncology and Danish Center for Particle Therapy, Aarhus, Denmark.

[d]Royal North Shore Hospital, Northern Sydney Cancer Centre, Sydney, Australia.

[e]University of Sydney, School of Physics, Sydney, Australia

[f]Calvary Mater Newcastle Hospital, Department of Radiation Oncology, Newcastle, Australia

[g]University of Newcastle, Newcastle, Australia

[h]University of Sydney, Northern Clinical School, Sydney, Australia

[i]Westmead Hospital, Crown Princess Mary Cancer Centre, Sydney, Australia.

[j]Liverpool Hospital, Liverpool and Macarthur Cancer Therapy Centres, Sydney, Australia.

[k]Peter MacCallum Cancer Centre, Department of Physical Sciences, Melbourne, Australia

[l]University of Sydney, Institute of Medical Physics, Sydney, Australia

[m]Peter MacCallum Cancer Centre, Sir Peter MacCallum Department of Oncology, University of Melbourne, Australia.

[n]University of Sydney, NHMRC Clinical Trials Centre, Sydney, Australia.

Corresponding author

Journal Pre-proof

Paul Keall PhD

ACRF Image X Institute, University of Sydney, Camperdown, 2006, NSW, Australia

Tel : 612 8627 1159 Email: paul.keall@sydney.edu.au

Author responsible for statistical analysis

Val Gebski MStat

NHMRC Clinical Trials Centre

Tel: 9562 5000 Email: val.gebski@sydney.edu.au

Running Title

Real-time IGRT improves radiation dose accuracy

Conflict of Interest Notification

Related to the SPARK trial, PK and PP are inventors of a KIM-related patent that has been licensed to Varian Medical Systems by Stanford University and PK is an inventor of an MLC tracking patent licensed to Leo Cancer Care by the University of Sydney. PK, DTN, RO and PP are inventors of additional unlicensed patents. PK founded Leo Cancer Care but has no ownership interest. PP has a research agreement with Varian Medical Systems through Aarhus University. JB reports a research agreement with Varian Medical Systems allowing RNSH to utilise MLC tracking and KIM for clinical application of the SPARK protocol. NH has had travel expenses paid by Varian Medical Systems for MLC tracking in lung. All other authors declare no competing interests.

Funding Statement

Supported by Cancer Australia, the Prostate Cancer Foundation of Australia and the National Health & Medical Research Council of Australia.

Acknowledgements

The authors thank the patient participants in this trial who entrusted their care to an emerging technology. Many additional radiation oncologists, medical physicists, radiation therapists, nurses and clinical trial coordinators were involved in and essential to the completion of the SPARK trial. The TROG team, especially Angie Chung, Brita Lehmann and Alisha Moore, provided critical support throughout the trial. Trial funding from Cancer

Journal Pre-proof

Journal Pre-proof

Australia (APP1081534), the Prostate Cancer Foundation of Australia and the NHMRC (APP1112096, APP1138807) is gratefully acknowledged.

Journal Pre-proof

Journal Pre-proof

Abstract

Purpose

Kilovoltage Intrafraction Monitoring (KIM) is a novel software platform implemented on standard radiation therapy systems enabling real-time image-guided radiation therapy (IGRT). In a multi-institutional prospective trial, we investigated whether real-time IGRT improved the accuracy of the dose prostate cancer patients received during radiation therapy.

Methods and Materials

Forty-eight patients with prostate cancer were treated with KIM-guided Stereotactic Ablative Radiation Therapy (SABR) with 36.25 Gy in five fractions. During KIM-guided treatment the prostate motion was corrected for by either beam gating with couch shifts or multileaf collimator tracking. A dose reconstruction method was used to evaluate the dose delivered to the target and organs at risk with and without real-time IGRT. Primary outcome was the effect of real-time IGRT on dose distributions. Secondary outcomes included patient-reported outcomes and toxicity.

Results

Motion correction occurred in ≥1 treatment for 88% of patients (42/48) and 51% of treatments (121/235). With real-time IGRT, no treatments had prostate CTV D98% dose 5% less than planned. Without real-time IGRT, 13 treatments (5·5%) had prostate CTV D98% doses 5% less than planned. The prostate CTV D98% dose with real-time IGRT was closer to the plan by an average of 1·0% (range -2·8% to 20·3%). Patient outcomes show no change in the 12-month patient reported outcomes compared with baseline and no grade ≥3 GU or GI toxicities.

Conclusion

Real-time IGRT is clinically effective for prostate cancer SABR.

Journal Pre-proof

88 Keywords: Prostate cancer; real-time image-guided radiation therapy; stereotactic ablative
89 radiation therapy

90

Journal Pre-proof

Journal Pre-proof

Introduction

Radiation therapy is an effective treatment option in the management of prostate cancer.[1] Accurate delivery of radiation dose is of fundamental importance in radiation oncology. Technical advances in radiation therapy technology have improved cancer treatment outcomes. These advances are evident for prostate cancer where image-guided radiation therapy (IGRT) and intensity modulated radiation therapy (IMRT) have independently demonstrated improved tumor control and lower rates of late rectal toxicity.[2-6] However, prostate motion during radiation therapy may shift the tumor outside the beam, simultaneously reducing target dose and exposing normal tissues to increased radiation doses. The deleterious effects of motion for prostate cancer has led the American Society for Radiation Oncology to recommend '*A precise ability to localize the target tumor is essential to fully benefit from stereotactic body radiation therapy techniques'*.[7] As the duration of prostate radiation therapy is compressed initially from around 40 treatments, to closer to 20, and more recently down towards five or fewer treatments, the importance of accurate treatment grows.[8-10] Clinical trials seeking to validate stereotactic ablative radiation therapy (SABR) approaches are underway.[11]

Correction for interfraction motion has become standard of care, but management of intrafraction motion is not widely used despite evidence of prostate movement even over the few minutes which treatment takes.[12] Real-time IGRT, where the cancer target position is continuously monitored during treatment, was clinically pioneered over 20 years ago.[13] Prostate cancer patients treated with real-time IGRT showed significantly lower bowel morbidity and improved health-related quality of life than a comparator cohort treated without real-time IGRT.[14] Similarly, prostate cancer patients treated with real-time IGRT had

Journal Pre-proof

115 superior target dose coverage compared to if they had been treated without real-time
116 IGRT.[15,16]
117
118 Several commercially available technologies have been developed to perform real-time
119 IGRT[17] but require extra hardware and/or per patient expendables. To improve widespread
120 access, real-time IGRT would ideally be performed using the equipment that already exists
121 on standard linear accelerators (linacs). A review of real-time IGRT on standard-equipped
122 cancer radiation therapy systems identified three clinically applied technologies for prostate
123 and liver cancer SABR patients with further methods under development that could be
124 clinically used for real-time IGRT.[17] More recently real-time IGRT for spinal SABR was
125 implemented on a standard linac.[18] Together these advances demonstrate a trajectory of real-
126 time IGRT becoming more widely available for patients receiving SABR.
127
128 One of these clinically applied technologies, Kilovoltage Intrafraction Monitoring (KIM), the
129 technology under investigation in this trial, uses the existing x-ray system to measure the
130 target translation and rotation during radiation therapy.[19] KIM is an in-house developed
131 software-based medical device. It is integrated into Elekta and Varian linacs using a computer
132 connected to the linac to read the images and treatment data in real-time and give the target
133 position and rotation measurements, along with the decision of whether a couch shift is
134 needed when gating is used, or directly sending the target position measurements to the
135 multileaf collimator (MLC) tracking system when this correction method is used. In an
136 analysis of the accuracy and precision of the KIM system, the in-treatment measurements of
137 44 patients were analysed using the kV and MV images acquired during treatment using
138 triangulation. The centroid geometric accuracy and precision of the KIM system during the
139 patient treatments was 0.0 ± 0.5, 0.0 ± 0.4 and 0.1 ± 0.3 mm for translation, and -0.1 ± 0.6°, -

Journal Pre-proof

140 0.1 ± 1.4° and -0.1 ± 1.0° for rotation in the AP, LR and SI directions respectively.[20] The
141 measured latency is 350 ms.[21] When KIM is used with gating the correction workflow
142 depends on the type of linac used. For Elekta Synergy and Varian Trilogy linacs, KIM
143 computes the couch shift based on the last known prostate position, and the radiation
144 therapists shift to the couch to the new coordinates. On Varian TrueBeam linacs, the system
145 requires additional kV-kV imaging prior to implementing the shift. When KIM is used with
146 MLC tracking KIM's 3D position is streamed to the MLC tracking program. This program
147 combines the position information with the plan to adjust the MLC leaf positions to the
148 moving target.[19] The promising findings of the use of KIM in a single institution pilot study
149 (NCT01742403) stimulated the development of the multi-institutional Trans-Tasman
150 Radiation Oncology Group (TROG) 15.01 Stereotactic Prostate Ablative Radiation Therapy
151 with KIM (SPARK) trial (NCT02397317).[22]
152
153 In this study we investigated whether real-time IGRT improved the accuracy of the dose
154 prostate cancer patients received during SABR.

Journal Pre-proof

Journal Pre-proof

Methods and Materials

Trial design

The SPARK trial was based on the KIM real-time IGRT method for treatments requiring correction for target motion, with the protocol published separately.[22] We considered a treatment with KIM-guided motion correction (real-time IGRT) a success if the estimated delivered patient dose distribution was closer to the planned values than the estimated dose distribution without real-time IGRT. The dose metric for reporting target doses in the presence of motion is not explicitly detailed in ICRU Report 83,[23] so the prostate dose values assessed were the dose to 98% (D98%) of the clinical target volume (CTV). The rectal and bladder doses were chosen to be the volume of the rectum receiving above 30 Gy (V30Gy). To put the results into context, a 5% dose difference between the planned dose and that delivered to the patient has long been considered clinically meaningful.[24]

The trial was approved by a human research ethics committee (HREC/15/HNE/216**)**, prospectively registered and all patients provided written informed consent.

Radiation treatment and dose assessment details

All patients had three intraprostatic gold markers inserted. Patients were prescribed 36.25 Gy to the PTV in five treatments. Patients were treated with multi-arc VMAT with 6 MV or 10 MV energy beams on Elekta Synergy, Varian Trilogy or Varian TrueBeam linacs with KIM implemented. Prior to each treatment the patient anatomy acquired with CBCT was aligned to the radiation beam via their gold markers. During treatment, the target motion was corrected in real-time by implementing either beam gating with couch shifts if motion exceeded 2-3 mm motion thresholds for ≥5 seconds or MLC tracking.[25] The gating thresholds were chosen because of the CTV to PTV margin of 3 mm posteriorly and 5 mm in other directions. MLC

Journal Pre-proof

tracking has no correction threshold and any detected motion results in a beam shift. MLC tracking was only available at one institution for the study and was used to correct for motion for all 10 patients treated at that institution. The remaining 34 patients treated at four separate institutions used beam gating with couch shifts to correct for motion. For 44/48 patients the estimated dose distribution that was delivered to the patients with real-time IGRT was estimated by generating motion-encoded plans that mimicked prostate motion as multiple isocenter shifts and replaced the planned MLC positions with actual positions for MLC tracking.[26] The motion-encoded plans were recalculated by the treatment planning system on the planning CT scans. For the remaining four patients where a different treatment planning system was used, the dose reconstruction was performed by measuring the mean position of the target with respect to the isocenter for each treatment arc. To compute the dose to the patient in simulated treatments without real-time IGRT, the KIM-measured prostate motion without couch corrections was used as the input to the dose reconstruction method. This process resulted in three dose distributions for each treatment – the planned dose, the estimated delivered dose with real-time IGRT and the estimated delivered dose without real-time IGRT. As such, every treatment was able to act as both a case and an internal control for comparative purposes.

The dose reconstruction was performed on the planning CT scan rather than the daily CBCT scan for each fraction. The advantage of using the planning CT is that deformable registration is not required, and the dose calculation issues on CBCT are avoided. However, the disadvantage is that the changes in the target and organs-at-risk are ignored. Nevertheless, the use of the planning CT scan for the dose reconstruction is a limitation. Had the CBCT scan been used, the motion that occurred during the treatment after the CBCT scan means that the CBCT is still not representative of the anatomy whilst the treatment beam is on.

Journal Pre-proof

Ideally this process would be based on volumetric imaging information at each time point during the treatment, with robust deformable registration and dose calculation. Until real-time volumetric imaging during treatment becomes a reality, there will be limitations in the dose accumulation process. The QUANTEC vision reference on dose accumulation highlights the need for accelerated research and development into auto-segmentation, deformation, modeling, dose accumulation, dose calculation in complex environments, and methods of estimating the uncertainty in the accumulated dose distribution over the course of therapy. [27]

To improve anatomic consistency between simulation and treatment the trial's Radiotherapy Planning, Delivery and Quality Assurance procedures document recommended both a bladder protocol to regulate bladder volume and a bowel protocol. The implementation of the protocols was according to each institution's practice.

A quality assurance program was implemented for each of the three novel technologies used in this trial, KIM,[21] MLC tracking[28] and time-resolved dose reconstruction.[26]

Patient outcomes

A secondary outcome of the SPARK trial was to measure patient treatment outcomes (PROs) using the Expanded Prostate Cancer Index Composite (EPIC)-26[29] instrument. Genitourinary (GU) and gastrointestinal (GI) physician-graded toxicity were measured using the Common Terminology Criteria for Adverse Events (CTCAE) v4·0 scale.[30] Prostate-specific antigen (PSA) levels were recorded with biochemical PSA failure defined using the ASTRO Phoenix definition (any rise in the PSA >2 ng/mL above the nadir).[31]

Journal Pre-proof

Results

Patient characteristics

Forty-eight patients with prostate cancer were treated with KIM-guided SABR at five institutions. The patient characteristics and treatment information are summarized in Table 1.

Patient dose results

The scheme used in the SPARK trial is shown in Figure 1. KIM was used in 235 SPARK trial treatments. Five treatments were delivered without KIM because of technical issues: hard drive full (two treatments), pre-treatment/KIM position discrepancy, overlapping markers and imaging noise. For the treatment with the pre-treatment/KIM position discrepancy there was >1 mm positioning difference between KIM and the kV/kV match. For this treatment, the clinical decision was made to treat the patient using the standard of care (triggered imaging) rather than using KIM. As the kV/kV match was performed at a different time than the KIM positioning, the probable cause of this discrepancy was prostate motion. Real-time IGRT using KIM-guided motion correction occurred in at least one treatment for 88% of the patients (42/48) and 51% of the treatments (121/235).

Waterfall plots of the dose-volume points with and without real-time IGRT for the prostate (CTV D98%), rectum (V30Gy) and bladder (V30Gy) are shown in Figure 2 for the 121 treatments with real-time IGRT. With real-time IGRT, the number of treatments with the prostate CTV dose 5% less, or the rectal or bladder dose 5% more than the planned dose was 0, 0 and 0, respectively. Without real-time IGRT, the number of treatments with the prostate CTV dose 5% less, or the rectal and bladder dose 5% more than the planned dose was 13, 4 and 14, respectively. The estimated dose distributions for the individual treatments where the

Journal Pre-proof

target dose coverage and rectal sparing were largest with real-time IGRT are shown in Figure 3.

The prostate CTV D98% dose with real-time IGRT was closer to the plan in 51% (62/121) of the treatments by an average of 1·0% (range -2·8% to 20·3%). The rectal V30Gy dose with real-time IGRT was closer to the plan in 86% (104/121) of the treatments by an average of 1·5% (range -1·2% to 9·7%). The bladder V30Gy dosewith real-time IGRT was closer to the plan in 90% (109/121) of the treatments by an average of 1·8% with the range from -2·3% to 14%. When the dose with real-time IGRT was worse, the difference was small, for the three metrics above the maximum detriment was -2·8%. When the dose with real-time IGRT was better, large improvements were observed for the outlier treatments. Of the three metrics above, the largest benefit over 20%. The prostate PTV D95% results are shown in the supplementary material.

The treatment delivery times with MLC tracking were similar to that of the original VMAT plan as there is negligible overhead with the MLC tracking software used. The treatment times were increased when using beam gating with couch shifts. This increase varied by the type of linac used, ranging from 30 seconds to 2 minutes per couch shift. There were 92 gating events for the treatments of the 38 patients treated with the couch correction strategy.

Patient outcomes

One-year PROs, GU and GI physician-graded toxicity and PSA measurements are shown in Figure 4 with at least 43 of the 48 patients included. For the PROs in some domains there is a short-term drop, however by 12 months the outcomes are the same as baseline. Two grade 2 GU and two grade 2 GI toxicities (4%) were observed at 12 months. No grade ≥3 GU or GI

Journal Pre-proof

toxicity was observed. All adverse events are included even if not considered to be related to treatment. Biochemical failure has been observed in one patient 42 months post-treatment. Assessment via PSMA-PET showed widespread lymphadenopathy and a solitary bone metastasis. There was no evidence of disease in the patient's prostate.

Journal Pre-proof

Journal Pre-proof

Discussion

We employed KIM to enable real-time IGRT on a standard linac for the treatment of 48 prostate cancer SABR patients. We investigated where the dose delivered to patients with real-time IGRT was better than the dose that would have been delivered to patients without real-time IGRT. First, we showed that this technology can be successfully implemented across several centers, vendors and clinical platforms, demonstrating both the flexibility and practicality of the KIM software device in transforming standard cancer radiation therapy systems into real-time IGRT systems that continuously monitor the target position and rotation during treatment. Second, in 42 of the 48 patients and half (51%) of the treatments, significant movement occurred during the treatment that would have been undetected without real-time IGRT. Third, the trial outcome was positive: with real-time IGRT, the number of treatments with the prostate CTV dose 5% less, or the rectal and bladder dose 5% more, than the planned dose was 0, 0 and 0, respectively, compared with 13, 4 and 14, without real-time IGRT (Figure 2). These results give confidence that with real-time IGRT the delivered dose is similar to the planned dose. When coupled with the promising early PROs that compare favorably with the five-treatment arm of the recently reported RTOG 0938 trial,[32] we believe this trial demonstrates the value of real-time IGRT in delivering more accurate radiation therapy.

SABR is an emerging option for prostate radiation therapy, and the evidence base continues to grow. A recent meta-analysis of ten series including 2142 patients with a median of 7 years follow-up showed overall biochemical control rates of over 90% for a low to intermediate risk population, and very low rates of severe toxicities.[9] The Scandinavian HYPO-RT-PC randomized trial of 1180 men has shown no differences in efficacy or toxicity

Journal Pre-proof

between a conventional regimen or a seven treatment SABR alternative.[33] Given the multiple randomized studies maturing in this area, we expect the evidence base to only get stronger.[11]

Management of organ motion is critical for accurate delivery of prostate SABR, and also in other tumor sites where respiratory motion is present, such as liver and pancreas tumors. We are currently exploring expanding the use of KIM for enabling real-time IGRT into these other tumor sites. Two limitations of the KIM real-time IGRT method are the reliance on implanted markers and the imaging dose (estimated to be 440 mGy for the entire treatment[34]). A planned future development is to use deep learning to personalize the KIM system to minimize the marker sizes and imaging doses whilst retaining robustness and accuracy for each patient. Ultimately, developing accurate solutions to target internal tumors without implanted markers using standard cancer radiation therapy systems would further reduce barriers to the widespread adoption of real-time IGRT technologies such as KIM.

One feature of the SPARK clinical trial is the use of an estimate of the delivered dose to the patient as a surrogate for clinical outcome. The ability to compute the estimated delivered dose during each treatment is a byproduct of measuring real-time target motion from systems such as KIM. Jaffray *et al*. describe the importance of accurately estimating the dose delivered to the patient during a treatment, rather than the assumption that the delivered dose to the patient equaled the treatment plan.[35,36] Accurate patient dose estimation not only improves radiation outcomes modelling but will also address the technical demands of the adaptive radiation therapy paradigm. A broader limitation of our study is that it is not randomized. However, given that each patient can effectively act as their own control in modelling their dose, the study has validity since it controls for other inter-patient geometric

Journal Pre-proof

heterogeneity. Further data maturation will be needed to report efficacy and toxicity endpoints.

Another feature of the KIM system is the ability to measure rotation of the target in real-time in addition to translational displacement. In the SPARK trial, rotation observed prior to treatment was corrected at some centers via a six degree of freedom couch, and in other centers by realigning the patient. We have modelled the dosimetric impact of uncorrected rotations, but given the prostate approximates a sphere, with a relative sphericity of ~0.8 , the dosimetric impact of rotation is smaller than for more elongated tumor volumes.[37] If an elongated tumor rotates, it is more likely the tumor will move outside the planned margins where the dose drops off quickly. If an approximately spherical tumor rotates, the rotated tumor is more likely to be inside the planned margins and remain in the high dose volume. Rotation may prove to be important as KIM is implemented for real-time IGRT of other tumor sites.

In this study two forms of correction for motion were used, either beam gating with couch shifts or MLC tracking. Future work could include an analysis of the dosimetric and workflow differences between these two motion correction strategies.

Conclusion

The SPARK trial primary outcome showed that real-time IGRT is clinically useful in improving the accuracy of the prostate and rectum dose in the presence of target motion. With the use of KIM enabling real-time IGRT on a standard linac, this approach holds promise for making real-time IGRT widely accessible for prostate cancer treatments.

Journal Pre-proof

355

Journal Pre-proof

Journal Pre-proof

References

1. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med.* 2016;375(15):1415-1424.
2. Gill S, Thomas J, Fox C, et al. Acute toxicity in prostate cancer patients treated with and without image-guided radiotherapy. *Radiat Oncol.* 2011;6(1):145.
3. Ratnayake G, Martin J, Plank A, Wong W. Incremental changes verses a technological quantum leap: The additional value of intensity-modulated radiotherapy beyond image-guided radiotherapy for prostate irradiation. *J Med Imaging Radiat Oncol.* 2014:503-510.
4. Singh J, Greer PB, White MA, et al. Treatment-Related Morbidity in Prostate Cancer: A Comparison of 3-Dimensional Conformal Radiation Therapy With and Without Image Guidance Using Implanted Fiducial Markers. *Int J Radiat Oncol Biol Phys.* 2013;85(4):1018-1023.
5. Zelefsky MJ, Kollmeier M, Cox B, et al. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2012;84(1):125-129.
6. de Crevoisier R, Bayar MA, Pommier P, et al. Daily versus weekly prostate cancer image guided radiation therapy: Phase 3 multicenter randomized trial. *Int J Radiat Oncol Biol Phys.* 2018;102(5):1420-1429.
7. Report of the ASTRO Emerging Technology Committee. Stereotactic Body Radiotherapy (SBRT) For Primary Management of Early-Stage, Low-Intermediate Risk Prostate Cancer. 2008.
8. Catton CN, Lukka H, Gu CS, et al. Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer. *J Clin Oncol.* 2017;35(17):1884-1890.
9. Kishan AU, Dang A, Katz AJ, et al. Long-term Outcomes of Stereotactic Body Radiotherapy for Low-Risk and Intermediate-Risk Prostate Cancer. *JAMA Netw Open.* 2019;2(2):e188006-e188006.
10. Martin JM, Supiot S, Keall PJ, Catton CN. Moderately hypofractionated prostate external-beam radiotherapy: an emerging standard. *Br J Radiol.* 2018;91(1086):20170807.
11. Catton CN, Lukka H, Martin J. Prostate Cancer Radiotherapy: An Evolving Paradigm. *J Clin Oncol.* 2018;36(29):2909-2913.
12. Langen KM, Willoughby TR, Meeks SL, et al. Observations on real-time prostate gland motion using electromagnetic tracking. *Int J Radiat Oncol Biol Phys.* 2008;71(4):1084-1090.
13. Shirato H, Shimizu S, Shimizu T, Nishioka T, Miyasaka K. Real-time tumour-tracking radiotherapy. *Lancet.* 1999;353(9161):1331-1332.
14. Sandler HM, Liu P-Y, Dunn RL, et al. Reduction in Patient-reported Acute Morbidity in Prostate Cancer Patients Treated With 81-Gy Intensity-modulated Radiotherapy Using Reduced Planning Target Volume Margins and Electromagnetic Tracking: Assessing the Impact of Margin Reduction Study. *Urology.* 2010;75(5):1004-1008.
15. Colvill E, Booth JT, O'Brien R, et al. MLC Tracking Improves Dose Delivery for Prostate Cancer Radiotherapy: Results of the First Clinical Trial. *Int J Radiat Oncol Biol Phys.* 2015;92(5):1141-1147.
16. Lovelock DM, Messineo AP, Cox BW, Kollmeier MA, Zelefsky MJ. Continuous Monitoring and Intrafraction Target Position Correction During Treatment Improves Target Coverage for Patients Undergoing SBRT Prostate Therapy. *Int J Radiat Oncol Biol Phys.* 2015;91(3):588-594.
17. Keall PJ, Nguyen DT, O'Brien R, et al. Review of Real-Time 3-Dimensional Image Guided Radiation Therapy on Standard-Equipped Cancer Radiation Therapy Systems: Are We at the Tipping Point for the Era of Real-Time Radiation Therapy? *Int J Radiat Oncol Biol Phys.* 2018; 102(4):922-931.

Journal Pre-proof

18. Hazelaar C, Verbakel WF, Mostafavi H, van der Weide L, Slotman BJ, Dahele M. First Experience With Markerless Online 3D Spine Position Monitoring During SBRT Delivery Using a Conventional LINAC. *Int J Radiat Oncol Biol Phys.* 2018;101(5):1253-1258.
19. Kim J, Nguyen D, Booth J, et al. The Accuracy and Precision of KIM Six Degree-of-freedom Prostate Motion Measurements during Patient Treatments. *Radiother Oncol.* 2018;126(2):236-243.
20. Hewson EA, Nguyen DT, O'Brien R, et al. The accuracy and precision of the KIM motion monitoring system used in the multi-institutional TROG 15.01 Stereotactic Prostate Ablative Radiotherapy with KIM (SPARK) trial. *Med Phys.* 2019;46(11):4725-4737.
21. Ng J, Booth J, O'Brien R, et al. Quality assurance for the clinical implementation of kilovoltage intrafraction monitoring for prostate cancer VMAT. *Med Phys.* 2014;41(11):111712.
22. Keall P, Nguyen DT, O'Brien R, et al. Stereotactic Prostate Adaptive Radiotherapy utilising Kilovoltage Intrafraction Monitoring: the TROG 15.01 SPARK trial. *BMC Cancer.* 2017;17(1):180.
23. International Commission on Radiation Units and Measurements. Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT): Report 83. *J ICRU.* 2010;10(1):1-92.
24. International Commission on Radiation Units and Measurements. Determination of Absorbed Dose in a Patient Irradiated by Beams of X or Gamma Rays in Radiotherapy. 1976;Report #24.
25. Keall P, Nguyen D, O'Brien R, et al. The First Clinical Implementation of Real-time Image-Guided Adaptive Radiotherapy using a Standard Linear Accelerator. *Radiother Oncol.* 2018;127(1):6-11.
26. Poulsen PR, Schmidt ML, Keall P, Worm ES, Fledelius W, Hoffmann L. A method of dose reconstruction for moving targets compatible with dynamic treatments. *Med Phys.* 2012;39(10):6237-6246.
27. Jaffray DA, Lindsay PE, Brock KK, Deasy JO, Tomé WA. Accurate accumulation of dose for improved understanding of radiation effects in normal tissue. *International journal of radiation oncology, biology, physics.* 2010;76(3 Suppl):S135-S139.
28. Sawant A, Dieterich S, Svatos M, Keall P. Failure mode and effect analysis-based quality assurance for dynamic MLC tracking systems. *Med Phys.* 2010;37(12):6466-6479.
29. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology.* 2000;56(6):899-905.
30. Common Terminology Criteria for Adverse Events (CTCAE) v4·0 https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf.
31. Roach III M, Hanks G, Thames Jr H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys.* 2006;65(4):965-974.
32. Lukka HR, Pugh SL, Bruner DW, et al. Patient Reported Outcomes in NRG Oncology RTOG 0938, Evaluating Two Ultrahypofractionated Regimens for Prostate Cancer. *Int J Radiat Oncol Biol Phys.* 2018;102(2):287-295.
33. Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet.* 2019;394(10196):385-395.
34. Legge K, Greer PB, Keall PJ, et al. TROG 15.01 SPARK trial multi-institutional imaging dose measurement. *J Appl Clin Med Phys.* 2017;18(5):358-363.

Journal Pre-proof

35. Bentzen SM, Constine LS, Deasy JO, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys.* 2010;76(3):S3-S9.
36. Jaffray DA, Lindsay PE, Brock KK, Deasy JO, Tomé W. Accurate accumulation of dose for improved understanding of radiation effects in normal tissue. *Int J Radiat Oncol Biol Phys.* 2010;76(3):S135-S139.
37. Wolf J, Nicholls J, Hunter P, Nguyen DT, Keall P, Martin J. Dosimetric impact of intrafraction rotations in stereotactic prostate radiotherapy: A subset analysis of the TROG 15.01 SPARK trial. *Radiother Oncol.* 2019;136:143-147.

Journal Pre-proof

Journal Pre-proof

Figure Legends

Figure 1. The scheme used in the SPARK trial to investigate if real-time IGRT improves dose distributions for prostate cancer SABR patients.

Figure 2. Waterfall plots of the difference in dose from the plan for the treatments with interventions with real-time IGRT (blue) and without real-time IGRT (red) (A) prostate (CTV D98%), (B) rectum (V30Gy), and (C) bladder (V30Gy). The 5% dose difference line is shown.

Figure 3. (A) Isodose distributions showing the treatments with the largest benefit for real-time IGRT for the prostate target and rectal sparing. (B) and (C) Dose volume histograms with and without real-time IGRT for the patients from the isodose in (A) upper and lower panels respectively.

Figure 4. (A) Median and Interquartile range (IQR) of EPIC-26 patient reported outcomes, n=43-45 depending on domain. (B) Prostate Specific Antigen (PSA) levels (ng/ mL). Box plot represents median with IQR and whiskers are the minimum/maximum values, n=47. (C) CTCAE v4.0 genitourinary and (D) gastrointestinal toxicities, n=48. All adverse events are included even if not considered to be related to treatment.

Journal Pre-proof

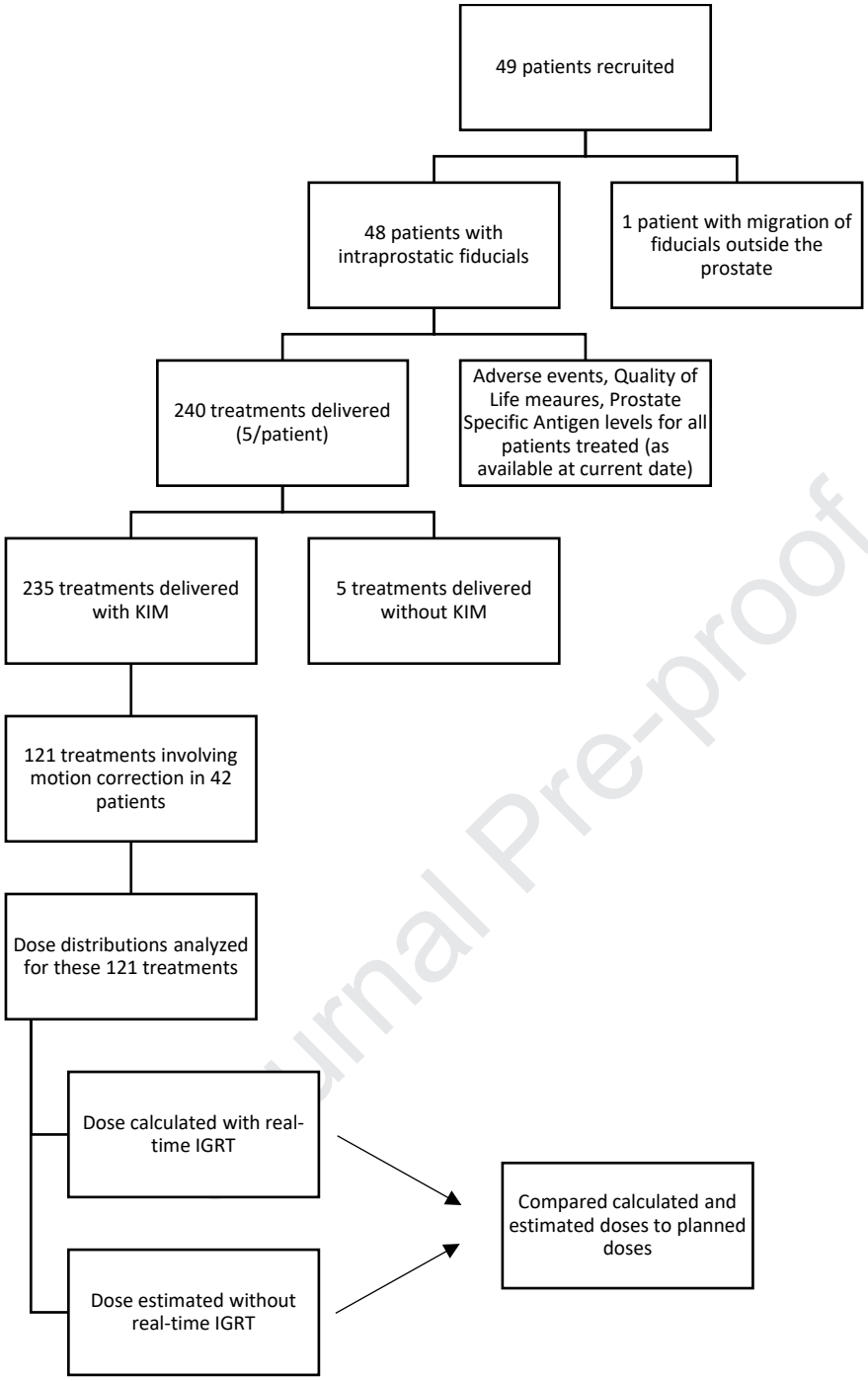
Journal Pre-proof

Table 1. Patient characteristics and treatment information for the "Blinded for review" trial.

Age in years at recruitment (median, range)	69 (57-81)
Risk status	
Low-risk Disease PSA<10 ng/mL, Gleason score 6 and stage T1 or T2a	2/48 (4%)
Intermediate-risk Disease PSA 10-20 ng/mL, Gleason score 7 or stage T2b-c	46/48 (96%)
Eastern Cooperative Oncology Group performance status	
0	45/48 (94%)
1	3/48 (6%)
KIM-guided motion correction strategy	
Gating with 2-3 mm threshold	38/48 (79%)
MLC adaptation	10/48 (21%)
Cancer radiation therapy system used with KIM	
Elekta Synergy	4/48 (8%)
Varian Trilogy	10/48 (21%)
Varian TrueBeam	34/48 (71%)

Journal Pre-proof

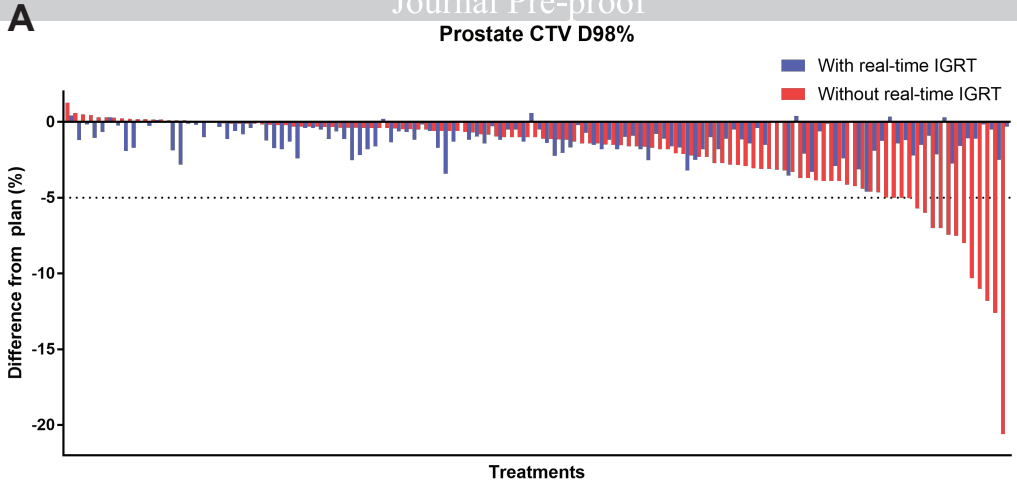
Journal Pre-proof



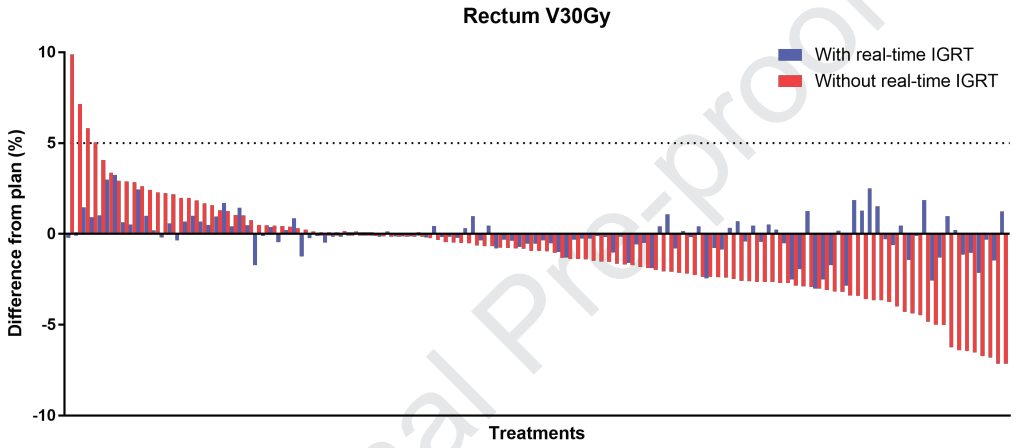
Journal Pre-proof

Journal Pre-proof

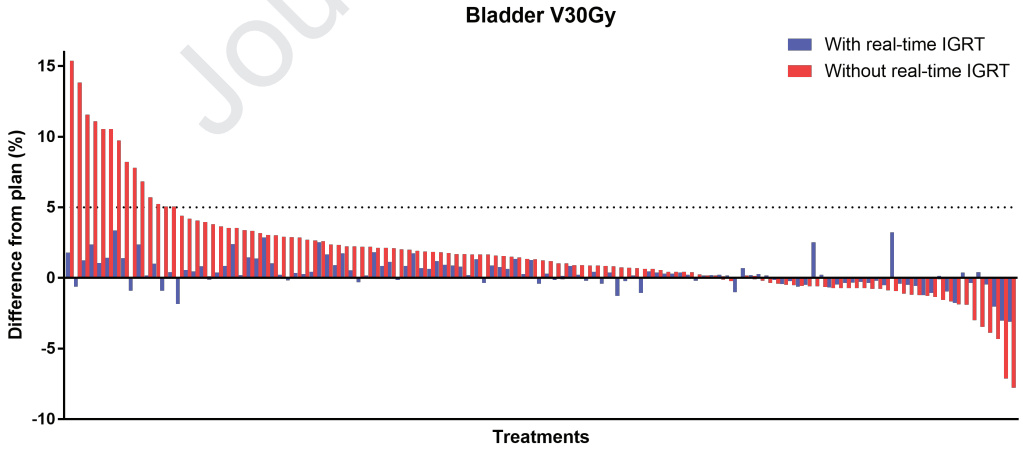
A



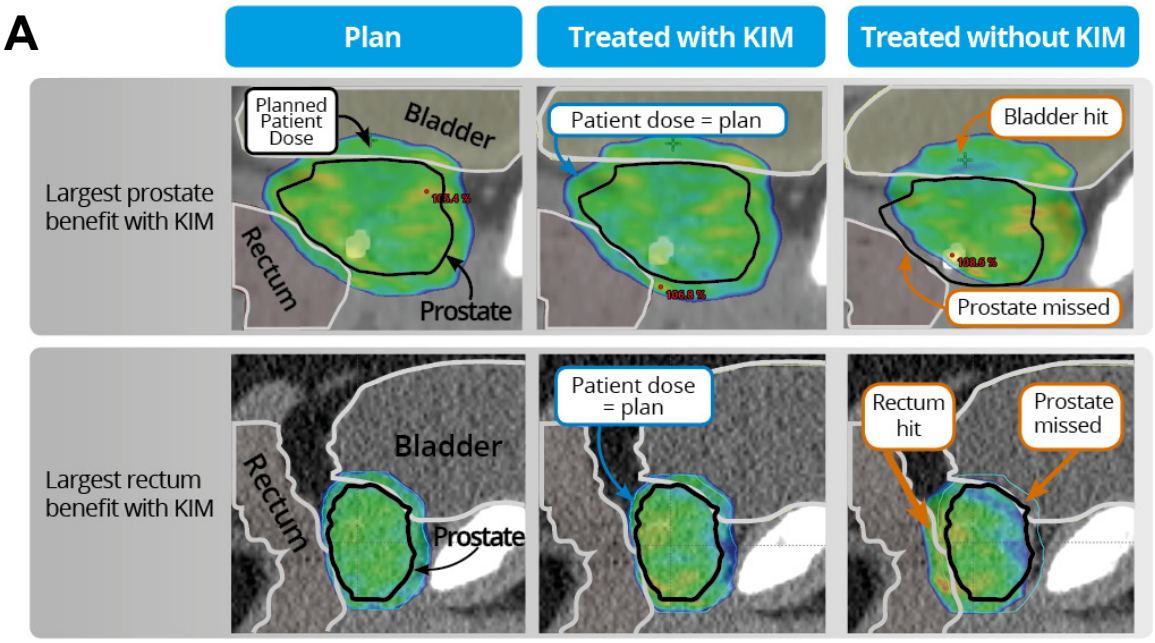
B

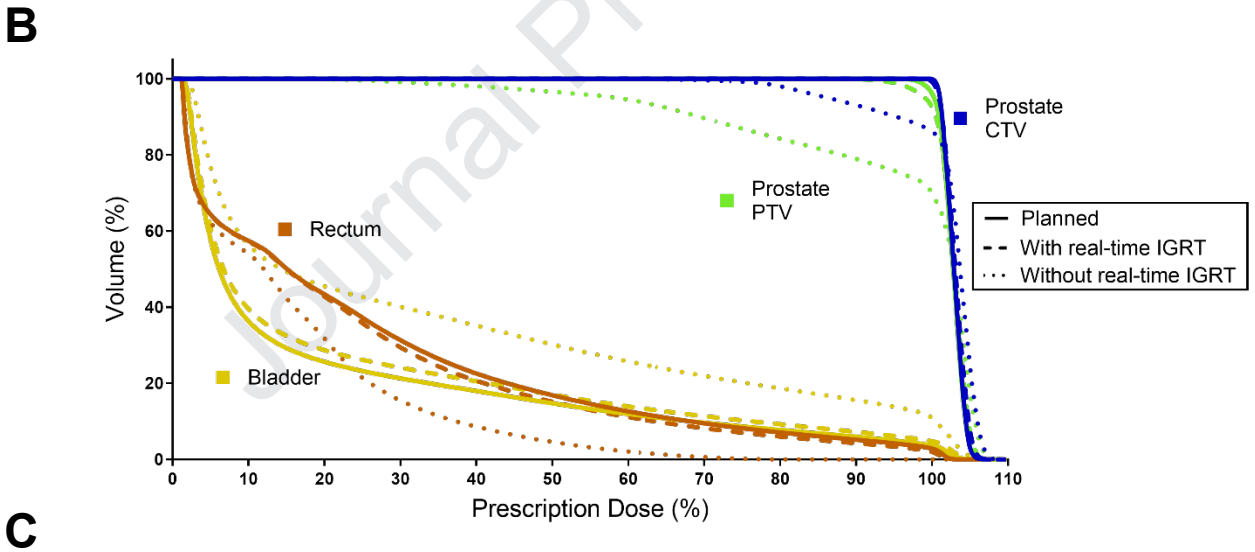


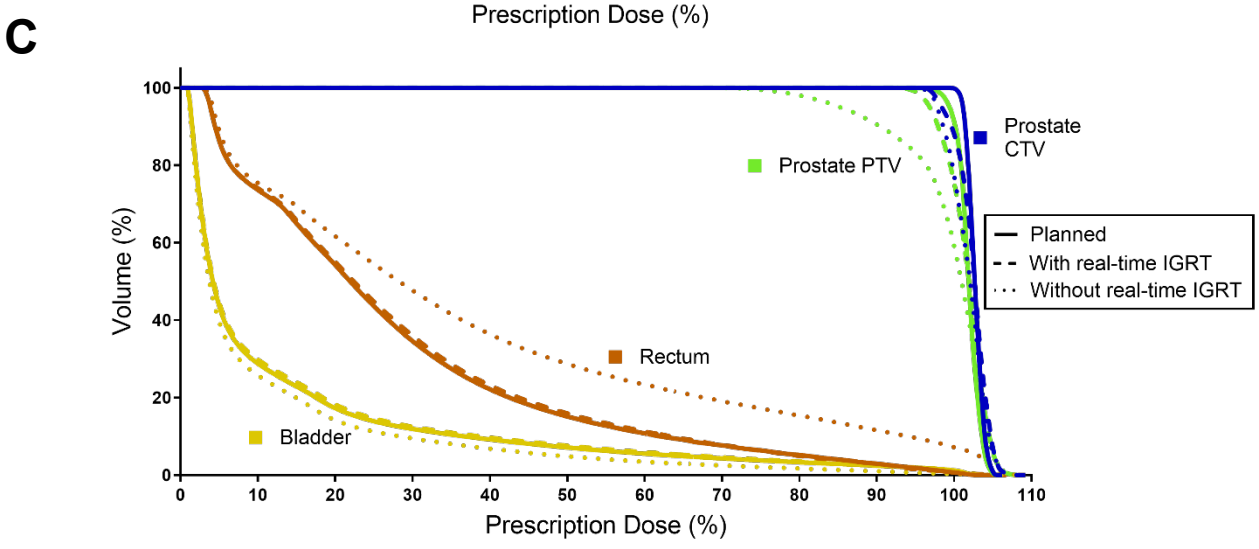
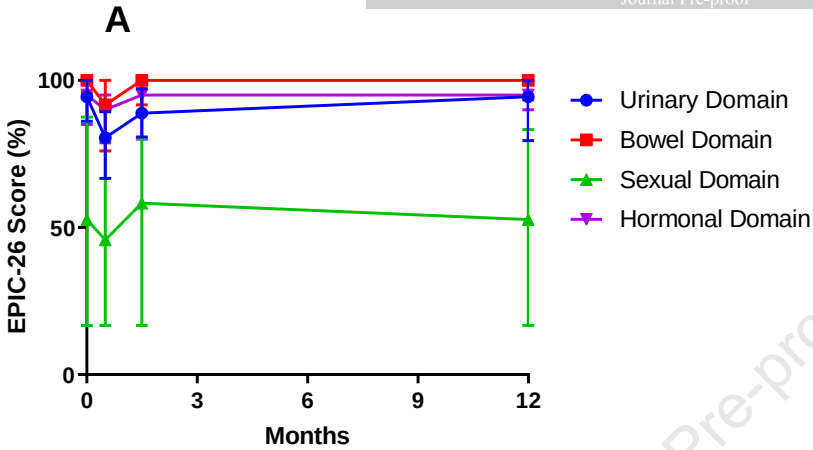
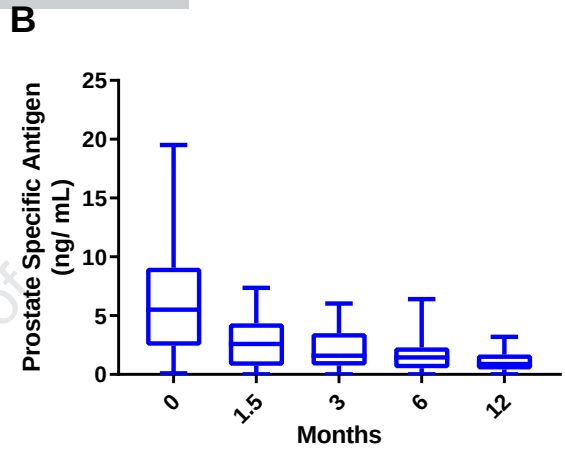
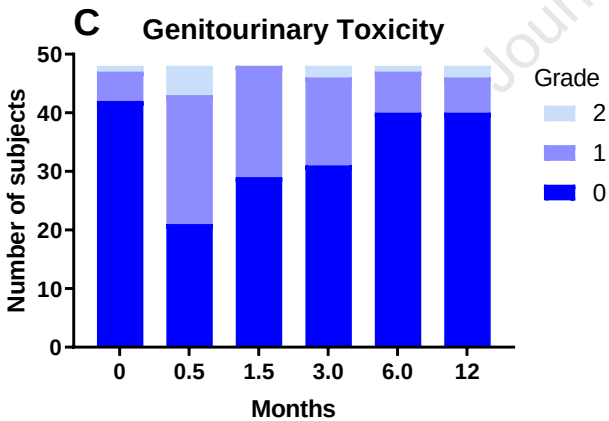
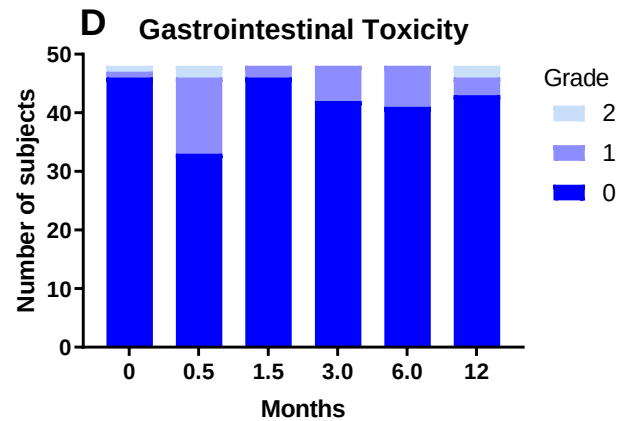
C



Journal Pre-proof


A
Plan
Treated with KIM
Treated without KIM
Largest prostate benefit with KIM
Planned Patient Dose
Bladder
Rectum
Prostate
Patient dose = plan
Bladder hit
Prostate missed
Largest rectum benefit with KIM
Bladder
Rectum
Prostate
Patient dose = plan
Rectum hit
Prostate missed


B
Volume (%)
Prescription Dose (%)
Prostate CTV
Prostate PTV
Rectum
Bladder
Planned
With real-time IGRT
Without real-time IGRT


C
Volume (%)
Prescription Dose (%)
Prostate CTV
Prostate PTV
Rectum
Bladder
Planned
With real-time IGRT
Without real-time IGRT

Journal Pre-proof