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Title: A randomised assessment of image guided radiotherapy within a phase 3 trial of Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer

Article Type: Full Length Article

Keywords: prostate, image-guided radiotherapy, toxicity, dosimetry

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Abstract: Background and purpose

Image-guided radiotherapy (IGRT) improves treatment set-up accuracy and provides the opportunity to reduce target volume margins. We introduced IGRT methods using standard (IGRT-S) or reduced (IGRT-R) margins in a randomised phase 2 substudy within CHHiP trial. We present a pre-planned analysis of the impact of IGRT on dosimetry and acute/late pelvic side effects using gastrointestinal and genitourinary clinician and patient-reported outcomes (PRO) and evaluate efficacy.

Materials and methods

CHHiP is a randomised phase 3, non-inferiority trial for men with localised prostate cancer. 3216 patients were randomly assigned to conventional (74Gy in 2Gy/fraction (f) daily) or moderate hypofractionation (60 or 57Gy in 3Gy/f daily) between October 2002 and June 2011. The IGRT substudy included a second randomisation assigning to no-IGRT, IGRT-S (standard CTV-PTV margins), or IGRT-R (reduced CTV-PTV margins). Primary substudy endpoint was late RTOG bowel and urinary toxicity at 2 years post-radiotherapy.

Results

Between June 2010 to July 2011, 293 men were recruited from 16 centres. Median follow-up is 56.9(IQR 54.3-60.9)months. Rectal and bladder dose-volume and surface percentages were significantly lower in IGRT-R compared to IGRT-S group; ($p < 0.0001$). Cumulative proportion with RTOG grade > 2 toxicity reported to 2 years for bowel was 8.3(95% CI 3.2-20.7)%, 8.3(4.7-14.6)% and 5.8(2.6-12.4)% and for urinary 8.4(3.2-20.8)%, 4.6(2.1-9.9)% and 3.9(1.5-9.9)% in no IGRT, IGRT-S and IGRT-R groups respectively. In an exploratory analysis, treatment efficacy appeared similar in all three groups.

Conclusion

Introduction of IGRT was feasible in a national randomised trial and IGRT-R produced dosimetric benefits. Overall side effect profiles were acceptable in all groups but lowest with IGRT and reduced margins.

Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:

Data may only be released through completion of an ICR-CTSU data access form, approval of the CHHiP Trial Management Group (TMG) and Trial Steering Committee (TSC) and signed data sharing agreement.



Professor Michael Baumann

Editor-in-Chief, Radiotherapy and Oncology

23rd October 2019

Dear Professor Baumann,

RE: Revision of manuscript: A randomised assessment of image guided radiotherapy within a phase 3 trial of Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP)

The Institute of
Cancer Research

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Many thanks for allowing us to address the reviewers' comments, please find below our responses in italic text and revisions noted within the manuscript.

Registered office
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Reviewer #1: This is a nicely conducted substudy of the CHHiP trial which seeks to determine whether IGRT reduces rectal and urinary toxicity after two years of follow up. This report convincingly shows that IGRT achieved this.

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This was not a surprise for this reviewer because gold grain guided IGRT with insertion by a local urologist quickly demonstrated that IGRT reduced rectal and urinary toxicity at my centre. In fact, the better we became at using gold grains, the less our rectal and urinary toxicity became. We also sent a report of our experience to the Red Journal.

We agree with the reviewer and think it is important for these modern radiotherapy techniques to be reported and robustly evaluated.

Reviewer #3: Authors should be commended for their effort in conducting this substudy. The paper is well written, sound and the MM or Results sections do not require modifications.

However I have two major concerns:

1. regarding application of the findings, most guidelines now mandate daily IGRT so this trial will likely not affect the guidelines

Currently, NHS England guidelines for hypofractionated radiotherapy (60Gy/20F) mandate intensity modulated radiotherapy techniques with strict normal tissue dose constraints and recommend image guidance techniques. The use of IGRT is also recommended within the ASTRO/ASCO/AUA guideline for hypofractionated prostate radiotherapy. In addition, this study also evaluates the effect of a reduced PTV margin with image guidance.

2. more importantly, the authors claim that this is the first IGRT trial published so far, when in reality, to my knowledge, there are at least TWO randomized trials already published (de Crevoisier et al, IJROBP 2018 and Tondel et al, Radiother Oncol 2018) that the authors should discuss. Hence the discussion should be re-written to compare their findings with the ones from the other trials, which are different in many ways.

We have amended and clarified the sentence concerning this study in relation to other prostate IGRT trials, and it now reads 'To our knowledge, this is the only randomised study undertaken evaluating daily prostate image-guided IMRT with and without reduced PTV margins' (last sentence of Introduction). We are grateful to the reviewer for highlighting these trials and have included these studies within the discussion. These studies both showed no difference in clinician or patient reported acute toxicity between daily and weekly IGRT, with de Crevoisier study showing an improvement in biochemical progression and late rectal toxicity with daily IGRT. This study also cautiously suggested that there might be an increase in the incidence of 2nd cancers in the daily group and this will be reviewed in due course within the CHHiP study.

Reviewer #4: well written manuscript of a well conceived and well executed clinical trial. I had difficulty finding the exact normal tissue constraints and dose planning objectives despite the references given. please include a table of the normal tissue constraints utilized for the trial.

Was there central review of the treatment volumes and normal tissue volumes for patients enrolled?

Did all patients enrolled in the trial meet the dose constraints stipulated in the study?

Thank you to the reviewer for their comments. We agree that it is important for dose constraints to be available for readers and we have expanded Table S2 to include the normal tissue dose constraints for the 3Gy per fraction schedules.

Regarding the comment on quality assurance and central review of volumes, we did not have the personnel to review all outlining centrally. However, all centres underwent prospective case reviews of clinical outlining by the chief investigator for the first two

patients recruited per centre. An additional moderate-risk case was reviewed if the first two patients were low risk, and extra reviews were requested if significant errors persisted. Our quality assurance methods for CHHiP including this detail has been recently published and is now referenced within the manuscript (Naismith O, Mayles H. et al. Radiotherapy Quality Assurance for the CHHiP Trial: Conventional Versus Hypofractionated High-Dose Intensity-Modulated Radiotherapy in Prostate Cancer. Clinical Oncology 2019; 31: 611-620).

We are grateful for the question concerning the proportion of patients meeting the dose constraints within the study. We have included this information relating to rectum, bowel and bladder dose constraints as a statement within the results section, with further details in the supplementary information.

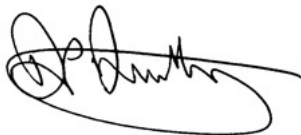
Editorial Office Comments:

- Please provide the Clinical Trial number below the abstract.
- The subheading "Conclusions" should be removed.

We have included the clinical trial number and removed the subheadings within the results section and removed the conclusions subheading.

If there are any questions, please do not hesitate to contact me.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'David Dearnaley', with a large, sweeping flourish at the end.

Prof David Dearnaley

Title page:

A randomised assessment of image guided radiotherapy within a phase 3 trial of Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer

Authors:

Julia Murray^{1,2}, Clare Griffin¹, Sarah Gulliford^{1,3}, Isabel Syndikus⁴, John Staffurth⁵, Miguel Panades⁶, Christopher Scrase⁷, Chris Parker^{1,2}, Vincent Khoo^{1,2}, Jamie Dean¹, Helen Mayles⁴, Philip Mayles⁴, Simon Thomas⁸, Olivia Naismith², Angela Baker⁹, Helen Mossop¹, Clare Cruickshank¹, Emma Hall¹, David Dearnaley^{1,2}, on behalf of CHHiP Investigators

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Highlights:

- Introduction of daily online prostate IGRT was feasible in a national randomised trial
- Dosimetric benefits seen in patients treated with IGRT and reduced CTV-PTV margins
- Overall side effect profiles were acceptable in all groups but lowest with IGRT and reduced margins

Keywords: prostate, image-guided radiotherapy, toxicity, dosimetry

Funding

Cancer Research UK, Department of Health, and the National Institute of Health Research Cancer Research Network

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Title page:

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4 **Background and purpose**
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7 Image-guided radiotherapy (IGRT) improves treatment set-up accuracy and provides
8
9 the opportunity to reduce target volume margins. We introduced IGRT methods
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13 substudy within CHHiP trial. We present a pre-planned analysis of the impact of
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24 **Materials and methods**
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27 CHHiP is a randomised phase 3, non-inferiority trial for men with localised prostate
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29 cancer. 3216 patients were randomly assigned to conventional (74Gy in 2Gy/fraction
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33 2002 and June 2011. The IGRT substudy included a second randomisation
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39 toxicity at 2 years post-radiotherapy.
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46 **Results**
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49 Between June 2010 to July 2011, 293 men were recruited from 16 centres. Median
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51 follow-up is 56.9(IQR 54.3-60.9)months. Rectal and bladder dose-volume and
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53 surface percentages were significantly lower in IGRT-R compared to IGRT-S
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1 for urinary 8.4(3.2-20.8)%, 4.6(2.1-9.9)% and 3.9(1.5-9.9)% in no IGRT, IGRT-S and
2 IGRT-R groups respectively. In an exploratory analysis, treatment efficacy appeared
3 similar in all three groups.
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9 **Conclusion**

10 Introduction of IGRT was feasible in a national randomised trial and IGRT-R
11 produced dosimetric benefits. Overall side effect profiles were acceptable in all
12 groups but lowest with IGRT and reduced margins.
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2 **Introduction**
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4 Intensity-modulated radiotherapy (IMRT) enables dose escalation to the prostate
5 target volume, with low gastrointestinal or genitourinary toxicity.¹⁻⁴ The success of
6 radical prostate radiotherapy depends on accurate delivery of high dose conformal
7 radiotherapy to a defined target volume. Image guided radiotherapy (IGRT) with daily
8 online imaging has the potential to improve prostate localisation, consequently
9 improving treatment accuracy and reducing the required clinical (CTV) to planning
10 (PTV) target volume margin.⁵ This may reduce the amount of normal tissue receiving
11 target doses, and consequently toxicity.⁶ Intrafraction motion and outlining
12 uncertainties still necessitate a small margin around the CTV.⁵
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29 In addition to optimising prostate radiotherapy techniques, there has been interest in
30 the exploitation of fraction sensitivity of prostate cancer through hypofractionation.⁷⁻⁹
31 This has been successfully examined within the UK multicentre randomised
32 controlled trial (Conventional or Hypofractionated High-dose Intensity Modulated
33 Radiotherapy in Prostate Cancer; CHHiP) which aimed to compare the efficacy and
34 toxicity of conventional and hypofractionated radiotherapy using high-quality
35 radiation techniques. Within the trial, 3216 patients were enrolled from 71 centres
36 within the UK between October 2002 and June 2011.¹⁰
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51 During the latter stages of the CHHiP trial, IGRT became available in participating
52 treatment centres. To assess this technology the CHHiP IGRT phase 2 substudy
53 was developed. We aimed to determine the feasibility and generalisability of IGRT in
54 the context of a multicentre trial and assess acute and late toxicity. A patient
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1 reported outcome (PRO) protocol was subsequently integrated into the substudy. To
2 our knowledge, this is the only randomised study undertaken evaluating daily
3 prostate image-guided IMRT with and without reduced PTV margins.
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10 11 **Materials and Methods**

12 13 14 15 16 *Study design and participants*

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19 CHHiP is a randomised phase 3, non-inferiority trial which recruited men with
20 localised prostate cancer (pT1b-T3aN0M0).¹⁰ Patients were randomly assigned
21 (1:1:1) to conventional 74 Gray (Gy) in 2Gy/fraction (f) daily or one of two
22 hypofractionated schedules giving 60Gy or 57Gy in 3Gy/f daily. Patients were all
23 treated with IMRT.¹¹
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34 The IGRT substudy was approved by Central London REC1 Research Ethics
35 Committee (10/H0718/31) and implemented in June 2010. Men who had entered the
36 CHHiP trial were eligible for the IGRT substudy with additional consent and provided
37 they had no contraindication to implanted fiducial markers or a hip prosthesis or
38 fixation which would interfere with positional imaging. Following dose/fractionation
39 randomisation in the main CHHiP trial, minimisation was used to assign IGRT
40 substudy patients in a 1:1:1 ratio to either no-IGRT – using standard CHHiP planning
41 margins, IGRT using standard CHHiP planning margins (IGRT-S), or IGRT with
42 reduced planning margins (IGRT-R). Radiotherapy centre and dose/fractionation
43 schedule were used as balancing factors. Neither patients nor clinicians were
44 blinded to allocation. Sixteen UK radiotherapy centres took part in the IGRT
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substudy. Centres could choose, depending on previous IGRT experience, to randomise to all three treatment technique options or to the 2-way randomisations: no IGRT versus IGRT-S or IGRT-S versus IGRT-R. Four centres used the 3-way randomisation, five centres randomised to no-IGRT vs IGRT-S and seven centres randomised to IGRT-S vs IGRT-R. In 2014, a patient reported outcomes (PRO) assessment was introduced to collect data at a single time point at least three years post randomisation. This separate protocol received ethical approval from the NRES Committee South West – Central Bristol (14/SW/1071).

Treatment

Patients randomised to treatment with IGRT, either had fiducial markers inserted into the prostate using trans-rectal ultrasound guidance or soft tissue matching if using the TomoTherapy® system. Fiducial markers were implanted with antibiotic cover approximately 2 weeks prior to the radiotherapy planning scan. Patient positioning was supine and target and treatment planning volumes have been previously described.¹¹ Radiotherapy was planned and delivered using an integrated simultaneous boost technique (SIB) with three different target volumes and dose levels as previously detailed¹² and illustrated in Table S1. In the no-IGRT and IGRT-S arms the standard CHHiP CTV to PTV posterior margins of 10mm/5mm/0mm were used. In the IGRT-R arm, these posterior margins were 6mm/3mm/0mm. Mandatory dose constraints were defined for both target coverage and avoidance of normal tissues including rectum, bowel, bladder and femoral heads (Table S2). Treatment was delivered with 6-15 MV photons with multileaf collimators to shape beams.

Patients randomised to no-IGRT had offline portal imaging to verify treatment accuracy; the match to bony landmarks was to be within 3mm. Patients receiving

1 IGRT had daily pre-treatment imaging and any observed set-up error ≥ 2 mm was
2 corrected prior to treatment. No post-correction imaging was taken. A prospective
3 quality-assurance programme was designed as an integral part of the study¹³
4 including specific aspects for the IGRT substudy (Supplementary material).
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10 *Trial assessments*

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12 Pre-trial staging investigations included PSA, lymph node assessment by MRI or CT,
13 and bone scan. Histology was assessed from diagnostic TRUS guided biopsies (or
14 TURP specimens) and reported using the Gleason system.
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17 Toxicity experienced from fiducial marker insertion was recorded using CTCAE
18 grading.¹⁴
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21 Pre-hormone and pre-radiotherapy clinical assessments used Late Effects of Normal
22 Tissues Subjective-Objective Management (LENT-SOM)¹⁵ and the Royal Marsden
23 Hospital (RMH) grading.¹⁶ Clinical assessment of acute toxicity was made weekly
24 during radiotherapy and at weeks 10, 12 and 18 from the start of radiotherapy using
25 the Radiation Therapy Oncology Group (RTOG) scoring system.¹⁷ Late toxicity was
26 assessed at 6, 12, 18 and 24 months then annually to 5 years using RTOG,
27 LENTSOM and RMH scoring systems.
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30 In the PRO substudy, data was collected at a single time point using the Expanded
31 Prostate Cancer Index Composite (EPIC) questionnaire, (EPIC-50 used for bowel
32 and urinary domains and EPIC-26 for sexual and hormonal domains),¹⁸ the Vaizey
33 Incontinence,¹⁹ Short Form 12 (SF-12)²⁰ and International Index of Erectile Function
34 (IIEF-5)²¹ questionnaires. Questionnaires were sent directly from participating
35 centres to patients (following confirmation of health status) who were at least three
36 years from completing treatment. A single reminder letter was sent.
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2 For each patient, treatment planning data (planning CT, dose distribution and organ
3 contours) were uploaded using dedicated analysis software (VODCA. MSS Medical
4 Software Solutions, Hagendorn, Switzerland). Using in-house code, all radiotherapy
5 plans were converted into equivalent dose in 2Gy per fraction, using Withers
6 formula²² with an α/β ratio of 3Gy for rectum and 5Gy for bladder for each dose cube
7 voxel. Dose volume (DVH) and dose-surface (DSH) histograms were generated for
8 rectum and bladder.
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22 *Statistical considerations*

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24 The IGRT substudy was non-comparative and powered to assess toxicity
25 independently within each treatment technique group using Simon single stage
26 design with exact p-values.²³ The primary endpoint was proportion of patients with
27 RTOG bladder or bowel toxicity of grade ≥ 2 at two years from starting radiotherapy.
28 Secondary endpoints included acute toxicity, prevalence of late radiation induced
29 toxicity, time to late radiation induced toxicity, toxicity associated with fiducials and
30 feasibility of delivery of IGRT in a multi-centre setting. Efficacy has been included as
31 exploratory analyses. Ninety-one patients were required (with 79 or more remaining
32 toxicity-free) in each group to give 80% power to detect a 10% RTOG bladder/bowel
33 grade ≥ 2 toxicity rate at 2 years with IGRT assuming a 20% toxicity rate with no
34 IGRT (alpha 3.4%). Sample size was not calculated for the PRO substudy, all
35 eligible IGRT substudy patients were invited to participate.
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54 *Analysis methods*

55 All analyses have been presented according to randomly allocated treatment
56 technique group. Analyses of side effects included all data available at each time
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1 point for patients who received at least one fraction of radiotherapy (unless otherwise
2 stated). Worst acute bladder and bowel toxicity was calculated using worst grade
3 reported during the first 18 weeks from start of radiotherapy. For the primary
4 endpoint, only patients with a 2-year RTOG toxicity assessment were included in the
5 denominator, although a sensitivity analysis was conducted using all randomised
6 patients. The proportion of patients with RTOG bladder or bowel toxicity of grade ≥ 2
7 at 2 years were presented together with exact binomial 95% confidence intervals.
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9 Time to first occurrence of late radiation induced side effects were analysed using
10 Kaplan Meier method to calculate the cumulative proportion with events reported on
11 2-year assessment form for each scoring system. Time was measured from start of
12 radiotherapy. Patients not experiencing an event were censored at date of last
13 toxicity assessment or at date of death for deceased patients. The log-rank test was
14 used to compare no IGRT versus IGRT-S and IGRT-S versus IGRT-R with a
15 significance level of 1%, to account for multiple comparisons. Biochemical/clinical
16 failure was defined as time to first PSA failure (PSA value greater than nadir +2ng/ml
17 with a consecutive confirmatory PSA value) or prostate cancer recurrence (local,
18 lymph node, pelvic or distant). Patients event free at the time of analysis were
19 censored at their last know PSA assessment.
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46 Statistical analyses were based on a data snapshot taken on 18th May 2016 (except
47 for efficacy analyses which were based on a snapshot taken on 3rd April 2018 to
48 maximise data maturity). All analyses were performed using STATA Version 13.1.
49 Patient reported outcomes were scored in accordance with the recommended
50 scoring manuals^{24,25} and presented as descriptive statistics by treatment group. The
51 Vaizey questionnaire is scored on a continuous scale, with minimum score, 0
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1 representing perfect continence and a maximum score, 24 representing total
2 incontinence.¹⁹ Patients were divided into 3 categories for Vaizey total score
3 according to tertiles and dose data presented. In health related quality of life, the
4 clinically meaningful change is defined as a mean change score exceeding half the
5 standard deviation of baseline value.²⁶ As there was no baseline data available for
6 this patient group, the mean and standard deviation values from the main CHHiP trial
7 QoL substudy²⁷ (Table S3) were used to define a threshold score for a meaningful
8 change for the EPIC bowel and urinary domain scores.
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21 **Results**

22 Two-hundred and ninety-three patients (48 no-IGRT, 137 IGRT-S and 108 IGRT-R)
23 from 16 radiotherapy centres across the UK were randomised between July 2010
24 and June 2011. Baseline characteristics were balanced between treatment
25 technique groups (Table 1) with median age of 71 (IQR 66-74), median pre-hormone
26 PSA of 9.5ng/ml (IQR 6.8-12.40) and 12%, 77% and 11% low, intermediate and high
27 risk respectively. At the time of the data snapshot for toxicity, median follow-up was
28 56.9 months (IQR 54.3-60.9) and for efficacy 73.3 (IQR 64.9-74.6) months.
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44 Three patients received no radiotherapy (one withdrew consent, one died and one
45 biochemically progressed prior to radiotherapy). Adherence to randomly allocated
46 treatment technique was high (Figure 1): three no-IGRT patients received IGRT, nine
47 IGRT-S patients did not receive standard CHHiP planning margins and four IGRT-R
48 patients did not have reduced margins. Two-hundred and twenty-five patients had
49 image guidance using fiducials, 11 patients were treated using TomoTherapy® and
50 six patients using CT on rails.
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1 Median (IQR) rectum volumes were 65 (59-77), 68 (56-86) and 67 (58-85) cm³ for
2 the no-IGRT, IGRT-S and IGRT-R groups respectively. Corresponding figures for
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4 bladder volumes were 277 (200-379), 249 (167-375) and 281 (180-386) cm³ (Table
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6 S4). A summary of DVH and DSH for rectum and bladder by treatment group are
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8 shown in Figure 2. Both rectal and bladder dose volume and surface percentages
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10 were consistently statistically lower in the IGRT-R compared to IGRT-S group (Table
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12 S5). Adherence to rectal dose constraints of 68% to 100% of prescribed dose and
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14 the bowel constraint was seen for 98% of patients, with all patients within the IGRT-
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16 R group achieving all these constraints (Table S6-S7).
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24 Toxicity associated with fiducial marker insertion was minimal with 19/190 (10%)
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26 reporting grade 1 and one patient reporting grade 2 haemorrhage. Six (3%) patients
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28 had an infection, three grade 1, two grade 2 and one grade 3. Worst RTOG bowel
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30 toxicity reported during 18 weeks from starting radiotherapy was grade ≥ 2 in 13/48
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32 (27%), 38/135 (28%) and 26/107 (24%) of no-IGRT, IGRT-S and IGRT-R patients
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34 respectively. Corresponding figures for RTOG bladder grade ≥ 2 were 21/48 (44%),
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36 71/135 (53%) and 48/107 (45%). By week 18, majority of toxicity had resolved with
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38 grade ≥ 2 bowel toxicity reported in 0% no-IGRT, 5% IGRT-S and 2% IGRT-R
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40 patients and RTOG bladder grade ≥ 2 reported in 3% no-IGRT, 8% IGRT-S and 4%
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42 IGRT-R patients (Figure 3).
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51 At two years, RTOG bowel and bladder toxicity was low across all treatment
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53 technique groups (Table S6) with 13 out of 274 (4.7%) patients assessed reporting
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55 any RTOG grade ≥ 2 toxicity, which was the primary endpoint of the substudy. The
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57 upper limits of 95% confidence intervals ruled out greater than 20% toxicity within
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1 each treatment technique group. Moderate to severe RTOG bowel toxicity was
2 similar across treatment groups, with 1/46 (2%), 3/125 (2%) and 2/103 (2%) no-
3 IGRT, IGRT-S and IGRT-R patients reporting grade ≥ 2 at 2 years. Cumulative
4 proportion with grade ≥ 2 RTOG bowel toxicity reported to 2 years was 8.3% (95%CI
5 3.2-20.7), 8.3% (4.7-14.6%) and 5.8% (2.6-12.4%) for no-IGRT, IGRT-S and IGRT-R
6 groups respectively (Figure 4A and Table S8). RMH and LENTSOM scales showed
7 similar low levels of moderate to severe bowel/rectum toxicity. RMH bowel grade ≥ 2
8 showed reduced toxicity in the IGRT-R group compared to IGRT-S with borderline
9 statistical significance (HR=0.39, 95%CI 0.18-0.83, p=0.012).
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24 Moderate to severe RTOG bladder toxicity was similar across treatment technique
25 groups, with 1/46 (2%), 4/125 (3%) and 2/103 (2%) no-IGRT, IGRT-S and IGRT-R
26 patients reporting grade ≥ 2 at 2 years. Cumulative proportion of RTOG bladder
27 grade ≥ 2 toxicity by 2 years was low for all groups with the least toxicity reported in
28 the IGRT-R group: 8.4 (3.2-20.8)%, 4.6 (2.1-9.9)% and 3.9 (1.5-9.9)% for no-IGRT,
29 IGRT-S and IGRT-R groups respectively (Figure 4B and Table S9). The RMH and
30 LENTSOM scales reported higher incidences of bladder toxicity compared to RTOG
31 but with a similar trend across groups. There was no evidence of significant
32 differences between treatment technique groups.
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48 A total of 193/265 (72.8%) PRO booklets were completed at a median of 50.3
49 months (IQR 47.8-52.0) from randomisation. Baseline characteristics were balanced
50 between treatment technique groups and there were no significant differences
51 between patients who did and did not complete the PRO booklet (Table S10). There
52 was no evidence of any differences between treatment technique groups for EPIC or
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Vaizey summary scores (Table 2), with no suggestion of a worsening of Vaizey score with increased dose volume or dose surface at any dose level (Table S11). Median DVH and DSH values were calculated for patients whose EPIC bowel and urinary scores were below and above the threshold level previously defined (Table S3). There was a trend that patients whose score were below the cut-point had higher dose volume or surface levels (Figure S1).

Thirty-three patients had biochemical/clinical failure reported (4, 20 and 9 in no IGRT, IGRT-S and IGRT-R groups respectively) (Table S12 and Figure S2). Five-year biochemical/clinical failure free survival was 91.1 (95% CI 77.9-96.6), 85.2 (95%CI 77.7-90.3) and 93.1 (95%CI 86.1-96.7) for no IGRT, IGRT-S and IGRT-R groups respectively. Fourteen patients had recommenced androgen deprivation therapy, nine had local recurrence, seven had lymph node/pelvic recurrence and seven had distant recurrence. Twenty-seven patients had died, three from prostate cancer, twenty-three from other reasons and one unknown.

Discussion

We have demonstrated that implementation of IGRT was feasible in a multi-centre trial in the UK. Recruitment of patients was swift and completed within one year. Accrual peaked at 45 patient/month, with 16 radiotherapy centres participating. Subsequently IGRT has become part of the national guidelines recommended treatment pathway. This emphasises the importance of clinical trials as a vehicle to introduce advanced radiotherapy technology. Limitations of this substudy include its relatively small size, uneven randomisation between treatment technique groups and PRO assessment at a single time point. Yet, to our knowledge, this is the only

1 randomised prospective study evaluating no-IGRT, IGRT and treatment margins
2 using the same planning techniques.
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4 We found minimal toxicity associated with insertion of fiducial markers. Dosimetric
5 assessments showed that reduced margins in the IGRT-R group resulted in rectal
6 and bladder volumes receiving 5-65Gy being significantly lower (<0.0001) than using
7 standard margins, this was also seen for surface dose. The mean dose to rectal
8 surface in the IGRT-S group was $33.9(\pm 5.1)$ Gy and similar to that previously
9 reported of $34.4(\pm 7.2)$ Gy using IG-IMRT²⁸ despite differences in dose prescription
10 and margining techniques. As expected, mean dose to rectum in the IGRT-R group
11 was significantly lower at $28.9(\pm 4.2)$ Gy. Similarly, mean dose to bladder surface was
12 $26.6(\pm 9.2)$ Gy / $20.5(\pm 6.6)$ Gy for IGRT-S / IGRT-R groups respectively, both lower
13 than previously reported (33.1 ± 10.9 Gy).²⁸ Late GI toxicity was consistently reported
14 less often using the three clinician based scores in the IGRT-R group. However, the
15 improved rectal dosimetry did not translate into a statistically significant benefit in
16 acute or late GI toxicity, with the possible exception of grade ≥ 2 RMH GI side-effects.
17 This perhaps unexpected result may relate to the low level of side-effects seen in all
18 randomised dose/fractionation groups in the main CHHiP trial which used strict
19 normal tissue dose constraints and a SIB technique limiting dose to the seminal
20 vesicles.¹⁰ The lack of reduction in acute and late GU side effects may relate to
21 similar doses to the urethra in all treatment technique groups. It may be the
22 combination of dose/volume/fractionation employed in the trial has reached a plateau
23 for radiotherapy side effects and other patient²⁹, radiogenomic³⁰ or microbiota³¹
24 related factors become more important in determining residual symptoms. We
25 believe it imprudent to extrapolate to treatments using higher doses, treating larger
26 target volumes or using more extreme forms of hypofractionation where the clinical
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1 benefits of IGRT-R might be more apparent. Previous non-randomised studies
2 comparing patient cohorts treated with IG-IMRT and 3D-CFRT^{28,29} have suggested
3 improvements in grade \geq 2 GU or GI side-effects using IGRT but are compromised by
4 differences in planning and delivery techniques as well as differing dose constraints.
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9 Two randomised trials have evaluated daily versus weekly image guided
10 radiotherapy. Tondel et al. reported no difference in acute patient reported
11 outcomes, despite dosimetric advantages seen with daily CBCT and reduced
12 margins, their late toxicity results are awaited.³² A further study by de Crevoisier et
13 al. showed no statistically significant difference in recurrence free survival, with also
14 no difference in acute toxicity.³³ A statistically significant difference in late rectal
15 toxicity and improvement in biochemical recurrence was reported, albeit with a short
16 median follow up of 4.1 years. We found no evidence to suggest that IGRT was
17 associated with a reduction in disease control. IGRT may increase accuracy and
18 reduce the chance of underdosage in the target volume, alternatively however it is
19 possible that the reduced margins might lower inadvertent dose outside the prostate
20 which has been suggested as a cause of treatment failure.³⁴

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39 The IGRT experience gained within this study has facilitated development of a new
40 national trial PIVOTALboost (CRUK/16/018) in which all patients receive IG-IMRT
41 and are randomised to receive pelvic lymph node IMRT or MR-directed dominant
42 lesion boosts using hypofractionated schedules as in the CHHiP study.
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51 We have shown it is feasible to introduce prostate IGRT in a national randomised
52 trial and that reduced margins translate into dosimetric benefits. Overall side effect
53 profiles were low with and without IGRT in the CHHiP trial and this substudy.
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2 **Figure legends**
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5 Figure 1: CONSORT diagram
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7 Figure 2: Boxplots illustrating dose volume and dose surface histograms, the
8 calculated volume and surface percentages for rectum (A) and bladder (B) normal
9 tissues by IGRT group and dose
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13 KEY: All doses are equivalent dose in 2Gy fractions. Red boxplots represent patients
14 treated with no IGRT, green boxplots are those patients treated with IGRT standard
15 margins and blue boxplots are those patients treated with IGRT reduced margins.
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19 Figure 3 – Acute RTOG bowel (A) and bladder (B) toxicity by timepoint and IGRT
20 group. Distribution of grade and prevalence
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24 Figure 4 – Bowel (A) and bladder (B) toxicity assessed using RTOG, RMH and
25 LENTSOM by timepoint and IGRT group. Distribution and cumulative proportion with
26 grade \geq 1 and grade \geq 2 radiation induced late toxicity.
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30 KEY: For cumulative proportion plots: red=No IGRT, Green= IGRT-S, Blue=IGRT-R.
31 Solid lines indicated grade \geq 1 events and dashed lines indicate grade \geq 2 events
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34 NB. Late toxicity data have been included in stacked bar charts if they were reported
35 within 6 weeks of the 6 month visit, within 3 months of the 12-24 month visits and
36 within 6 months of the 36 and 48 month visits.
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48 Table 1: Baseline characteristics by treatment group (n=293)
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51 Table 2: Bowel and urinary domain scores using EPIC questionnaire and scoring
52 system by treatment group at a median follow-up of 50.3 months (IQR: 47.8-52.0
53 months)
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2 **Supplementary material (online only)**
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5 Table S1: Margin definition and target isodose levels prescriptive to the planning
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7 Table S2: Normal tissue dose constraints
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10 Table S3: EPIC bowel domain mean and standard deviation scores from the CHHiP
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12 QoL substudy and the calculated threshold dose
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14 Table S4: Treatment planning data
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17 Table S5: P-values for statistical comparison of dose volume and dose surface
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19 histograms for No IGRT vs IGRT-S and IGRT-S vs IGRT-R. All doses are in
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21 equivalent dose in 2Gy fractions.
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24 **Table S6: Descriptive statistics given by IGRT treatment allocation for the rectum**
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26 **constraints**
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29 **Table S7: Descriptive statistics given by IGRT treatment allocation for the bladder**
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31 **constraints**
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34 **Table S8:** Number and proportion with RTOG grade \geq 2 toxicity at 2 years with 95%
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36 confidence intervals - by treatment group and randomisation strategy
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39 **Table S9:** Hazard ratios and cumulative proportion with G1+, G2+ and G3+ bowel
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41 and bladder toxicity at 2 years assessed by RTOG, RMH and LENTSOM scoring
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43 systems
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46 **Table S10:** Baseline characteristics for PRO responders and non-responders
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49 **Table S11:** Percentage volume and surface receiving each dose level according to
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51 Vaizey scores categorised as tertiles (Ter1=Vaizey score 0-2; Ter2=Vaizey total 3-5;
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53 Ter3=Vaizey score 6-20). All doses are equivalent dose in 2Gy fractions.
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56 **Table S12:** Efficacy data by IGRT substudy group
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Figure S1: Boxplots showing along the top row the dose volume histograms for patients whose EPIC bowel (A) and urinary (B) domain scores were above or below the defined thresholds. The dose surface histograms are shown along the bottom row for those patients whose EPIC bowel (A) and urinary (B) domain scores were above or below the defined thresholds. All doses are equivalent dose in 2Gy fractions.

Figure S2: Kaplan Meier for biochemical/clinical failure free survival by IGRT substudy group

Radiotherapy Quality Assurance in the CHHiP IGRT substudy

References:

1. Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E, et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53(5):1097–105.
2. Zietman AL, DeSilvio ML, Slater JD, Rossi Jr. CJ, Miller DW, Adams JA, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005;294(10):1233–9.
3. Zelefsky MJ, Yamada Y, Kollmeier MA, Shippy AM, Nedelka MA. Long-term outcome following three-dimensional conformal/intensity-modulated external-beam radiotherapy for clinical stage T3 prostate cancer. *Eur Urol* 2008;53(6):1172–9.
4. Al-Mamgani A, Heemsbergen WD, Peeters ST, Lebesque J V. Role of intensity-modulated radiotherapy in reducing toxicity in dose escalation for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;73(3):685–91.

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5. McNair HA, Hansen VN, Parker CC, Evans PM, Norman A, Miles E, et al. A comparison of the use of bony anatomy and internal markers for offline verification and an evaluation of the potential benefit of online and offline verification protocols for prostate radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;71(1):41–50.
6. Zelefsky MJ, Kollmeier M, Cox B, Fidaleo A, Sperling D, Pei X, 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):125–9
7. Brenner DJ, Martinez AA, Edmundson GK, Mitchell C, Thames HD, Armour EP. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. *Int J Radiat Oncol Biol Phys* 2002;52(1):6-13.
8. Yeoh EE, Botten RJ, Butters J, Di Matteo AC, Holloway RH, Fowler J. Hypofractionated versus conventionally fractionated radiotherapy for prostate carcinoma: final results of phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2011;81(5):1271–8.
9. Norkus D, Karklelyte A, Engels B, Versmessen H, Griskevicius R, De Ridder M, et al. A randomized hypofractionation dose escalation trial for high risk prostate cancer patients: interim analysis of acute toxicity and quality of life in 124 patients. *Radiat Oncol* 2013;8(1):206.
10. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* 2016;17(8):1047–60.

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11. South CP, Khoo VS, Naismith O, Norman A, Dearnaley DP. A comparison of treatment planning techniques used in two randomised UK external beam radiotherapy trials for localised prostate cancer. *Clin Oncol (R Coll Radiol)* 2008;20(1):15–21.
12. Dearnaley D, Syndikus I, Sumo G, Bidmead M, Bloomfield D, Clark C, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. *Lancet Oncol* 2012;13(1):43–54.
13. Naismith O, Mayles H, Bidmead M, Clark CH, Gulliford S, Hassan S, et al. Radiotherapy Quality Assurance for the CHHiP Trial: Conventional Versus Hypofractionated High-Dose Intensity-Modulated Radiotherapy in Prostate Cancer. *Clin Oncol (R Coll Radiol)*. 2019 Sep;31(9):611–20.
14. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003;13(3):176–81
15. Pavy JJ, Denekamp J, Letschert J, Littbrand B, Mornex F, Bernier J, et al. Late effects toxicity scoring: the SOMA scale. *Radiother Oncol*. 1995;35(1):11–5.
16. Dearnaley DP, Sydes MR, Langley RE, Graham JD, Huddart RA, Syndikus I, et al. The early toxicity of escalated versus standard dose conformal radiotherapy with neo-adjuvant androgen suppression for patients with localised prostate cancer: results from the MRC RT01 trial (ISRCTN47772397). *Radiother Oncol* 2007;83(1):31–41.
17. Pilepich M V., Asbell SO, Krall JM, Baerwald WH, Sause WT, Rubin P, et al. Correlation of radiotherapeutic parameters and treatment related morbidity-analysis of RTOG study 77-06. *Int J Radiat Oncol Biol Phys*. 1987;13(7):1007–

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18. Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology* 2010;76(5):1245–50.
 19. Vaizey CJ, Carapeti E, Cahill JA, Kamm MA. Prospective comparison of faecal incontinence grading systems. *Gut* 1999;44(1):77–80.
 20. Ware JJ, Kosinski MM, Keller SSD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care.* 1996;34(3):220–33.
 21. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999;11(6):319–26.
 22. Withers HR, Thames HD, Peters LJ. A new isoeffect curve for change in dose per fraction. *Radiother Oncol.* 1983;1(2):187–91.
 23. A'Hern RP. Sample size tables for exact single-stage phase II designs. *Stat Med.* 2001;20(6):859–66.
 24. Scoring instructions for the expanded prostate cancer index composite (EPIC) 2002. Available from: [http://medicine.umich.edu/sites/default/files/content/downloads/Scoring Instructions-EPIC.pdf](http://medicine.umich.edu/sites/default/files/content/downloads/Scoring%20Instructions-EPIC.pdf)
 25. Scoring Instructions for the Expanded Prostate cancer Index Composite Short Form (EPIC-26). 2002.
 26. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation.

Med Care 2003;41(5):582–92.

- 1
2 27. Wilkins A, Mossop H, Syndikus I, Khoo V, Bloomfield D, Parker C, et al.
3
4 Hypofractionated radiotherapy versus conventionally fractionated radiotherapy
5
6 for patients with intermediate-risk localised prostate cancer: 2-year patient-
7
8 reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial.
9
10
11
12 Lancet Oncol. 2015;16(16):1605–16.
13
- 14 28. Wortel RC, Incrocci L, Pos FJ, Lebesque J V., Witte MG, van der Heide UA, et
15
16 al. Acute Toxicity After Image-Guided Intensity Modulated Radiation Therapy
17
18 Compared to 3D Conformal Radiation Therapy in Prostate Cancer Patients. Int
19
20 J Radiat Oncol 2015 Mar;91(4):737–44.
21
22
- 23 29. Fellin G, Rancati T, Fiorino C, Vavassori V, Antognoni P, Baccolini M, et al.
24
25 Long term rectal function after high-dose prostatecancer radiotherapy: Results
26
27 from a prospective cohort study. Radiother Oncol. 2014;110(2):272–7.
28
29
30
- 31 30. Andreassen CN, Rosenstein BS, Kerns SL, Ostrer H, De Ruyscher D,
32
33 Cesaretti JA, et al. Individual patient data meta-analysis shows a significant
34
35 association between the ATM rs1801516 SNP and toxicity after radiotherapy in
36
37 5456 breast and prostate cancer patients. Radiother Oncol. 2016;121(3):431–
38
39 9.
40
41
- 42 31. Ferreira MR, Muls A, Dearnaley DP, Andreyev HJN. Microbiota and radiation-
43
44 induced bowel toxicity: Lessons from inflammatory bowel disease for the
45
46 radiation oncologist. Lancet Oncology. 2014; 15(3): e139-147
47
48
49
- 50 32. Tøndel H, Lund JÅ, Lydersen S, Wanderås AD, Aksnessæther B, Jensen CA,
51
52 et al. Radiotherapy for prostate cancer – Does daily image guidance with
53
54 tighter margins improve patient reported outcomes compared to weekly
55
56 orthogonal verified irradiation? Results from a randomized controlled trial.
57
58
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61
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Radiother Oncol. 2018; 126: 229-235.

33. de Crevoisier R, Bayar MA, Pommier P, Muracciole X, Pêne F, Dudouet 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.
34. Witte MG, Heemsbergen WD, Bohoslavsky R, Pos FJ, Al-Mamgani A, Lebesque J V., et al. Relating Dose Outside the Prostate With Freedom From Failure in the Dutch Trial 68 Gy vs. 78 Gy. *Int J Radiat Oncol Biol Phys.* 2010;77(1):131–8.

Title page:

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5 A randomised assessment of image guided radiotherapy within a phase 3 trial of
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7 Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for
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9 Prostate Cancer
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Highlights:

- Introduction of daily online prostate IGRT was feasible in a national randomised trial
- Dosimetric benefits seen in patients treated with IGRT and reduced CTV-PTV margins
- Overall side effect profiles were acceptable in all groups but lowest with IGRT and reduced margins

Keywords: prostate, image-guided radiotherapy, toxicity, dosimetry

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1
2 **Abstract**
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4 **Background and purpose**
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7 Image-guided radiotherapy (IGRT) improves treatment set-up accuracy and provides
8 the opportunity to reduce target volume margins. We introduced IGRT methods
9 using standard (IGRT-S) or reduced (IGRT-R) margins in a randomised phase 2
10 substudy within CHHiP trial. We present a pre-planned analysis of the impact of
11 IGRT on dosimetry and acute/late pelvic side effects using gastrointestinal and
12 genitourinary clinician and patient-reported outcomes (PRO) and evaluate efficacy.
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24 **Materials and methods**
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26 CHHiP is a randomised phase 3, non-inferiority trial for men with localised prostate
27 cancer. 3216 patients were randomly assigned to conventional (74Gy in 2Gy/fraction
28 (f) daily) or moderate hypofractionation (60 or 57Gy in 3Gy/f daily) between October
29 2002 and June 2011. The IGRT substudy included a second randomisation
30 assigning to no-IGRT, IGRT-S (standard CTV-PTV margins), or IGRT-R (reduced
31 CTV-PTV margins). Primary substudy endpoint was late RTOG bowel and urinary
32 toxicity at 2 years post-radiotherapy.
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46 **Results**
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48 Between June 2010 to July 2011, 293 men were recruited from 16 centres. Median
49 follow-up is 56.9(IQR 54.3-60.9)months. Rectal and bladder dose-volume and
50 surface percentages were significantly lower in IGRT-R compared to IGRT-S
51 group;(p<0.0001). Cumulative proportion with RTOG grade \geq 2 toxicity reported to 2
52 years for bowel was 8.3(95% CI 3.2-20.7)%, 8.3(4.7-14.6)% and 5.8(2.6-12.4)% and
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1 for urinary 8.4(3.2-20.8)%, 4.6(2.1-9.9)% and 3.9(1.5-9.9)% in no IGRT, IGRT-S and
2 IGRT-R groups respectively. In an exploratory analysis, treatment efficacy appeared
3 similar in all three groups.
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9 **Conclusion**

10 Introduction of IGRT was feasible in a national randomised trial and IGRT-R
11 produced dosimetric benefits. Overall side effect profiles were acceptable in all
12 groups but lowest with IGRT and reduced margins.
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2 **Introduction**
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4 Intensity-modulated radiotherapy (IMRT) enables dose escalation to the prostate
5 target volume, with low gastrointestinal or genitourinary toxicity.¹⁻⁴ The success of
6 radical prostate radiotherapy depends on accurate delivery of high dose conformal
7 radiotherapy to a defined target volume. Image guided radiotherapy (IGRT) with daily
8 online imaging has the potential to improve prostate localisation, consequently
9 improving treatment accuracy and reducing the required clinical (CTV) to planning
10 (PTV) target volume margin.⁵ This may reduce the amount of normal tissue receiving
11 target doses, and consequently toxicity.⁶ Intrafraction motion and outlining
12 uncertainties still necessitate a small margin around the CTV.⁵
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29 In addition to optimising prostate radiotherapy techniques, there has been interest in
30 the exploitation of fraction sensitivity of prostate cancer through hypofractionation.⁷⁻⁹
31 This has been successfully examined within the UK multicentre randomised
32 controlled trial (Conventional or Hypofractionated High-dose Intensity Modulated
33 Radiotherapy in Prostate Cancer; CHHiP) which aimed to compare the efficacy and
34 toxicity of conventional and hypofractionated radiotherapy using high-quality
35 radiation techniques. Within the trial, 3216 patients were enrolled from 71 centres
36 within the UK between October 2002 and June 2011.¹⁰
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51 During the latter stages of the CHHiP trial, IGRT became available in participating
52 treatment centres. To assess this technology the CHHiP IGRT phase 2 substudy
53 was developed. We aimed to determine the feasibility and generalisability of IGRT in
54 the context of a multicentre trial and assess acute and late toxicity. A patient
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1 reported outcome (PRO) protocol was subsequently integrated into the substudy. To
2 our knowledge, this is the only randomised study undertaken evaluating daily
3 prostate image-guided IMRT with and without reduced PTV margins.
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10 11 **Materials and Methods**

12 13 14 15 16 17 *Study design and participants*

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19 CHHiP is a randomised phase 3, non-inferiority trial which recruited men with
20 localised prostate cancer (pT1b-T3aN0M0).¹⁰ Patients were randomly assigned
21 (1:1:1) to conventional 74 Gray (Gy) in 2Gy/fraction (f) daily or one of two
22 hypofractionated schedules giving 60Gy or 57Gy in 3Gy/f daily. Patients were all
23 treated with IMRT.¹¹
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34 The IGRT substudy was approved by Central London REC1 Research Ethics
35 Committee (10/H0718/31) and implemented in June 2010. Men who had entered the
36 CHHiP trial were eligible for the IGRT substudy with additional consent and provided
37 they had no contraindication to implanted fiducial markers or a hip prosthesis or
38 fixation which would interfere with positional imaging. Following dose/fractionation
39 randomisation in the main CHHiP trial, minimisation was used to assign IGRT
40 substudy patients in a 1:1:1 ratio to either no-IGRT – using standard CHHiP planning
41 margins, IGRT using standard CHHiP planning margins (IGRT-S), or IGRT with
42 reduced planning margins (IGRT-R). Radiotherapy centre and dose/fractionation
43 schedule were used as balancing factors. Neither patients nor clinicians were
44 blinded to allocation. Sixteen UK radiotherapy centres took part in the IGRT
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substudy. Centres could choose, depending on previous IGRT experience, to randomise to all three treatment technique options or to the 2-way randomisations: no IGRT versus IGRT-S or IGRT-S versus IGRT-R. Four centres used the 3-way randomisation, five centres randomised to no-IGRT vs IGRT-S and seven centres randomised to IGRT-S vs IGRT-R. In 2014, a patient reported outcomes (PRO) assessment was introduced to collect data at a single time point at least three years post randomisation. This separate protocol received ethical approval from the NRES Committee South West – Central Bristol (14/SW/1071).

Treatment

Patients randomised to treatment with IGRT, either had fiducial markers inserted into the prostate using trans-rectal ultrasound guidance or soft tissue matching if using the TomoTherapy® system. Fiducial markers were implanted with antibiotic cover approximately 2 weeks prior to the radiotherapy planning scan. Patient positioning was supine and target and treatment planning volumes have been previously described.¹¹ Radiotherapy was planned and delivered using an integrated simultaneous boost technique (SIB) with three different target volumes and dose levels as previously detailed¹² and illustrated in Table S1. In the no-IGRT and IGRT-S arms the standard CHHiP CTV to PTV posterior margins of 10mm/5mm/0mm were used. In the IGRT-R arm, these posterior margins were 6mm/3mm/0mm. Mandatory dose constraints were defined for both target coverage and avoidance of normal tissues including rectum, bowel, bladder and femoral heads (Table S2). Treatment was delivered with 6-15 MV photons with multileaf collimators to shape beams.

Patients randomised to no-IGRT had offline portal imaging to verify treatment accuracy; the match to bony landmarks was to be within 3mm. Patients receiving

1 IGRT had daily pre-treatment imaging and any observed set-up error ≥ 2 mm was
2 corrected prior to treatment. No post-correction imaging was taken. A prospective
3 quality-assurance programme was designed as an integral part of the study¹³
4 including specific aspects for the IGRT substudy (Supplementary material).
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10 *Trial assessments*

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12 Pre-trial staging investigations included PSA, lymph node assessment by MRI or CT,
13 and bone scan. Histology was assessed from diagnostic TRUS guided biopsies (or
14 TURP specimens) and reported using the Gleason system.
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20 Toxicity experienced from fiducial marker insertion was recorded using CTCAE
21 grading.¹⁴
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26 Pre-hormone and pre-radiotherapy clinical assessments used Late Effects of Normal
27 Tissues Subjective-Objective Management (LENT-SOM)¹⁵ and the Royal Marsden
28 Hospital (RMH) grading.¹⁶ Clinical assessment of acute toxicity was made weekly
29 during radiotherapy and at weeks 10, 12 and 18 from the start of radiotherapy using
30 the Radiation Therapy Oncology Group (RTOG) scoring system.¹⁷ Late toxicity was
31 assessed at 6, 12, 18 and 24 months then annually to 5 years using RTOG,
32 LENTSOM and RMH scoring systems.
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43 In the PRO substudy, data was collected at a single time point using the Expanded
44 Prostate Cancer Index Composite (EPIC) questionnaire, (EPIC-50 used for bowel
45 and urinary domains and EPIC-26 for sexual and hormonal domains),¹⁸ the Vaizey
46 Incontinence,¹⁹ Short Form 12 (SF-12)²⁰ and International Index of Erectile Function
47 (IIEF-5)²¹ questionnaires. Questionnaires were sent directly from participating
48 centres to patients (following confirmation of health status) who were at least three
49 years from completing treatment. A single reminder letter was sent.
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2 For each patient, treatment planning data (planning CT, dose distribution and organ
3 contours) were uploaded using dedicated analysis software (VODCA. MSS Medical
4 Software Solutions, Hagendorn, Switzerland). Using in-house code, all radiotherapy
5 plans were converted into equivalent dose in 2Gy per fraction, using Withers
6 formula²² with an α/β ratio of 3Gy for rectum and 5Gy for bladder for each dose cube
7 voxel. Dose volume (DVH) and dose-surface (DSH) histograms were generated for
8 rectum and bladder.
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22 *Statistical considerations*

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24 The IGRT substudy was non-comparative and powered to assess toxicity
25 independently within each treatment technique group using Simon single stage
26 design with exact p-values.²³ The primary endpoint was proportion of patients with
27 RTOG bladder or bowel toxicity of grade ≥ 2 at two years from starting radiotherapy.
28 Secondary endpoints included acute toxicity, prevalence of late radiation induced
29 toxicity, time to late radiation induced toxicity, toxicity associated with fiducials and
30 feasibility of delivery of IGRT in a multi-centre setting. Efficacy has been included as
31 exploratory analyses. Ninety-one patients were required (with 79 or more remaining
32 toxicity-free) in each group to give 80% power to detect a 10% RTOG bladder/bowel
33 grade ≥ 2 toxicity rate at 2 years with IGRT assuming a 20% toxicity rate with no
34 IGRT (alpha 3.4%). Sample size was not calculated for the PRO substudy, all
35 eligible IGRT substudy patients were invited to participate.
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54 *Analysis methods*

55 All analyses have been presented according to randomly allocated treatment
56 technique group. Analyses of side effects included all data available at each time
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1 point for patients who received at least one fraction of radiotherapy (unless otherwise
2 stated). Worst acute bladder and bowel toxicity was calculated using worst grade
3 reported during the first 18 weeks from start of radiotherapy. For the primary
4 endpoint, only patients with a 2-year RTOG toxicity assessment were included in the
5 denominator, although a sensitivity analysis was conducted using all randomised
6 patients. The proportion of patients with RTOG bladder or bowel toxicity of grade ≥ 2
7 at 2 years were presented together with exact binomial 95% confidence intervals.
8
9 Time to first occurrence of late radiation induced side effects were analysed using
10 Kaplan Meier method to calculate the cumulative proportion with events reported on
11 2-year assessment form for each scoring system. Time was measured from start of
12 radiotherapy. Patients not experiencing an event were censored at date of last
13 toxicity assessment or at date of death for deceased patients. The log-rank test was
14 used to compare no IGRT versus IGRT-S and IGRT-S versus IGRT-R with a
15 significance level of 1%, to account for multiple comparisons. Biochemical/clinical
16 failure was defined as time to first PSA failure (PSA value greater than nadir +2ng/ml
17 with a consecutive confirmatory PSA value) or prostate cancer recurrence (local,
18 lymph node, pelvic or distant). Patients event free at the time of analysis were
19 censored at their last know PSA assessment.
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46 Statistical analyses were based on a data snapshot taken on 18th May 2016 (except
47 for efficacy analyses which were based on a snapshot taken on 3rd April 2018 to
48 maximise data maturity). All analyses were performed using STATA Version 13.1.
49 Patient reported outcomes were scored in accordance with the recommended
50 scoring manuals^{24,25} and presented as descriptive statistics by treatment group. The
51 Vaizey questionnaire is scored on a continuous scale, with minimum score, 0
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representing perfect continence and a maximum score, 24 representing total incontinence.¹⁹ Patients were divided into 3 categories for Vaizey total score according to tertiles and dose data presented. In health related quality of life, the clinically meaningful change is defined as a mean change score exceeding half the standard deviation of baseline value.²⁶ As there was no baseline data available for this patient group, the mean and standard deviation values from the main CHHiP trial QoL substudy²⁷ (Table S3) were used to define a threshold score for a meaningful change for the EPIC bowel and urinary domain scores.

Results

Two-hundred and ninety-three patients (48 no-IGRT, 137 IGRT-S and 108 IGRT-R) from 16 radiotherapy centres across the UK were randomised between July 2010 and June 2011. Baseline characteristics were balanced between treatment technique groups (Table 1) with median age of 71 (IQR 66-74), median pre-hormone PSA of 9.5ng/ml (IQR 6.8-12.40) and 12%, 77% and 11% low, intermediate and high risk respectively. At the time of the data snapshot for toxicity, median follow-up was 56.9 months (IQR 54.3-60.9) and for efficacy 73.3 (IQR 64.9-74.6) months.

Three patients received no radiotherapy (one withdrew consent, one died and one biochemically progressed prior to radiotherapy). Adherence to randomly allocated treatment technique was high (Figure 1): three no-IGRT patients received IGRT, nine IGRT-S patients did not receive standard CHHiP planning margins and four IGRT-R patients did not have reduced margins. Two-hundred and twenty-five patients had image guidance using fiducials, 11 patients were treated using TomoTherapy® and six patients using CT on rails.

1 Median (IQR) rectum volumes were 65 (59-77), 68 (56-86) and 67 (58-85) cm³ for
2 the no-IGRT, IGRT-S and IGRT-R groups respectively. Corresponding figures for
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4 bladder volumes were 277 (200-379), 249 (167-375) and 281 (180-386) cm³ (Table
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6 S4). A summary of DVH and DSH for rectum and bladder by treatment group are
7
8 shown in Figure 2. Both rectal and bladder dose volume and surface percentages
9
10 were consistently statistically lower in the IGRT-R compared to IGRT-S group (Table
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12 S5). Adherence to rectal dose constraints of 68% to 100% of prescribed dose and
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14 the bowel constraint was seen for 98% of patients, with all patients within the IGRT-
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16 R group achieving all these constraints (Table S6-S7).
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24 Toxicity associated with fiducial marker insertion was minimal with 19/190 (10%)
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26 reporting grade 1 and one patient reporting grade 2 haemorrhage. Six (3%) patients
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28 had an infection, three grade 1, two grade 2 and one grade 3. Worst RTOG bowel
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30 toxicity reported during 18 weeks from starting radiotherapy was grade ≥ 2 in 13/48
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32 (27%), 38/135 (28%) and 26/107 (24%) of no-IGRT, IGRT-S and IGRT-R patients
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34 respectively. Corresponding figures for RTOG bladder grade ≥ 2 were 21/48 (44%),
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36 71/135 (53%) and 48/107 (45%). By week 18, majority of toxicity had resolved with
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38 grade ≥ 2 bowel toxicity reported in 0% no-IGRT, 5% IGRT-S and 2% IGRT-R
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40 patients and RTOG bladder grade ≥ 2 reported in 3% no-IGRT, 8% IGRT-S and 4%
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42 IGRT-R patients (Figure 3).
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51 At two years, RTOG bowel and bladder toxicity was low across all treatment
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53 technique groups (Table S6) with 13 out of 274 (4.7%) patients assessed reporting
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55 any RTOG grade ≥ 2 toxicity, which was the primary endpoint of the substudy. The
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57 upper limits of 95% confidence intervals ruled out greater than 20% toxicity within
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1 each treatment technique group. Moderate to severe RTOG bowel toxicity was
2 similar across treatment groups, with 1/46 (2%), 3/125 (2%) and 2/103 (2%) no-
3 IGRT, IGRT-S and IGRT-R patients reporting grade ≥ 2 at 2 years. Cumulative
4 proportion with grade ≥ 2 RTOG bowel toxicity reported to 2 years was 8.3% (95%CI
5 3.2-20.7), 8.3% (4.7-14.6%) and 5.8% (2.6-12.4%) for no-IGRT, IGRT-S and IGRT-R
6 groups respectively (Figure 4A and Table S8). RMH and LENTSOM scales showed
7 similar low levels of moderate to severe bowel/rectum toxicity. RMH bowel grade ≥ 2
8 showed reduced toxicity in the IGRT-R group compared to IGRT-S with borderline
9 statistical significance (HR=0.39, 95%CI 0.18-0.83, p=0.012).
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24 Moderate to severe RTOG bladder toxicity was similar across treatment technique
25 groups, with 1/46 (2%), 4/125 (3%) and 2/103 (2%) no-IGRT, IGRT-S and IGRT-R
26 patients reporting grade ≥ 2 at 2 years. Cumulative proportion of RTOG bladder
27 grade ≥ 2 toxicity by 2 years was low for all groups with the least toxicity reported in
28 the IGRT-R group: 8.4 (3.2-20.8)%, 4.6 (2.1-9.9)% and 3.9 (1.5-9.9)% for no-IGRT,
29 IGRT-S and IGRT-R groups respectively (Figure 4B and Table S9). The RMH and
30 LENTSOM scales reported higher incidences of bladder toxicity compared to RTOG
31 but with a similar trend across groups. There was no evidence of significant
32 differences between treatment technique groups.
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48 A total of 193/265 (72.8%) PRO booklets were completed at a median of 50.3
49 months (IQR 47.8-52.0) from randomisation. Baseline characteristics were balanced
50 between treatment technique groups and there were no significant differences
51 between patients who did and did not complete the PRO booklet (Table S10). There
52 was no evidence of any differences between treatment technique groups for EPIC or
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Vaizey summary scores (Table 2), with no suggestion of a worsening of Vaizey score with increased dose volume or dose surface at any dose level (Table S11). Median DVH and DSH values were calculated for patients whose EPIC bowel and urinary scores were below and above the threshold level previously defined (Table S3). There was a trend that patients whose score were below the cut-point had higher dose volume or surface levels (Figure S1).

Thirty-three patients had biochemical/clinical failure reported (4, 20 and 9 in no IGRT, IGRT-S and IGRT-R groups respectively) (Table S12 and Figure S2). Five-year biochemical/clinical failure free survival was 91.1 (95% CI 77.9-96.6), 85.2 (95%CI 77.7-90.3) and 93.1 (95%CI 86.1-96.7) for no IGRT, IGRT-S and IGRT-R groups respectively. Fourteen patients had recommenced androgen deprivation therapy, nine had local recurrence, seven had lymph node/pelvic recurrence and seven had distant recurrence. Twenty-seven patients had died, three from prostate cancer, twenty-three from other reasons and one unknown.

Discussion

We have demonstrated that implementation of IGRT was feasible in a multi-centre trial in the UK. Recruitment of patients was swift and completed within one year. Accrual peaked at 45 patient/month, with 16 radiotherapy centres participating. Subsequently IGRT has become part of the national guidelines recommended treatment pathway. This emphasises the importance of clinical trials as a vehicle to introduce advanced radiotherapy technology. Limitations of this substudy include its relatively small size, uneven randomisation between treatment technique groups and PRO assessment at a single time point. Yet, to our knowledge, this is the only

1 randomised prospective study evaluating no-IGRT, IGRT and treatment margins
2 using the same planning techniques.
3

4 We found minimal toxicity associated with insertion of fiducial markers. Dosimetric
5 assessments showed that reduced margins in the IGRT-R group resulted in rectal
6 and bladder volumes receiving 5-65Gy being significantly lower (<0.0001) than using
7 standard margins, this was also seen for surface dose. The mean dose to rectal
8 surface in the IGRT-S group was $33.9(\pm 5.1)$ Gy and similar to that previously
9 reported of $34.4(\pm 7.2)$ Gy using IG-IMRT²⁸ despite differences in dose prescription
10 and margining techniques. As expected, mean dose to rectum in the IGRT-R group
11 was significantly lower at $28.9(\pm 4.2)$ Gy. Similarly, mean dose to bladder surface was
12 $26.6(\pm 9.2)$ Gy / $20.5(\pm 6.6)$ Gy for IGRT-S / IGRT-R groups respectively, both lower
13 than previously reported (33.1 ± 10.9 Gy).²⁸ Late GI toxicity was consistently reported
14 less often using the three clinician based scores in the IGRT-R group. However, the
15 improved rectal dosimetry did not translate into a statistically significant benefit in
16 acute or late GI toxicity, with the possible exception of grade ≥ 2 RMH GI side-effects.
17 This perhaps unexpected result may relate to the low level of side-effects seen in all
18 randomised dose/fractionation groups in the main CHHiP trial which used strict
19 normal tissue dose constraints and a SIB technique limiting dose to the seminal
20 vesicles.¹⁰ The lack of reduction in acute and late GU side effects may relate to
21 similar doses to the urethra in all treatment technique groups. It may be the
22 combination of dose/volume/fractionation employed in the trial has reached a plateau
23 for radiotherapy side effects and other patient²⁹, radiogenomic³⁰ or microbiota³¹
24 related factors become more important in determining residual symptoms. We
25 believe it imprudent to extrapolate to treatments using higher doses, treating larger
26 target volumes or using more extreme forms of hypofractionation where the clinical
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1 benefits of IGRT-R might be more apparent. Previous non-randomised studies
2 comparing patient cohorts treated with IG-IMRT and 3D-CFRT^{28,29} have suggested
3 improvements in grade \geq 2 GU or GI side-effects using IGRT but are compromised by
4 differences in planning and delivery techniques as well as differing dose constraints.
5
6 Two randomised trials have evaluated daily versus weekly image guided
7 radiotherapy. Tondel et al. reported no difference in acute patient reported
8 outcomes, despite dosimetric advantages seen with daily CBCT and reduced
9 margins, their late toxicity results are awaited.³² A further study by de Crevoisier et
10 al. showed no statistically significant difference in recurrence free survival, with also
11 no difference in acute toxicity.³³ A statistically significant difference in late rectal
12 toxicity and improvement in biochemical recurrence was reported, albeit with a short
13 median follow up of 4.1 years. We found no evidence to suggest that IGRT was
14 associated with a reduction in disease control. IGRT may increase accuracy and
15 reduce the chance of underdosage in the target volume, alternatively however it is
16 possible that the reduced margins might lower inadvertent dose outside the prostate
17 which has been suggested as a cause of treatment failure.³⁴

18
19 The IGRT experience gained within this study has facilitated development of a new
20 national trial PIVOTALboost (CRUK/16/018) in which all patients receive IG-IMRT
21 and are randomised to receive pelvic lymph node IMRT or MR-directed dominant
22 lesion boosts using hypofractionated schedules as in the CHHiP study.
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26 We have shown it is feasible to introduce prostate IGRT in a national randomised
27 trial and that reduced margins translate into dosimetric benefits. Overall side effect
28 profiles were low with and without IGRT in the CHHiP trial and this substudy.
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2 **Figure legends**
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5 Figure 1: CONSORT diagram
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7 Figure 2: Boxplots illustrating dose volume and dose surface histograms, the
8 calculated volume and surface percentages for rectum (A) and bladder (B) normal
9 tissues by IGRT group and dose
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13 KEY: All doses are equivalent dose in 2Gy fractions. Red boxplots represent patients
14 treated with no IGRT, green boxplots are those patients treated with IGRT standard
15 margins and blue boxplots are those patients treated with IGRT reduced margins.
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19 Figure 3 – Acute RTOG bowel (A) and bladder (B) toxicity by timepoint and IGRT
20 group. Distribution of grade and prevalence
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24 Figure 4 – Bowel (A) and bladder (B) toxicity assessed using RTOG, RMH and
25 LENTSOM by timepoint and IGRT group. Distribution and cumulative proportion with
26 grade \geq 1 and grade \geq 2 radiation induced late toxicity.
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30 KEY: For cumulative proportion plots: red=No IGRT, Green= IGRT-S, Blue=IGRT-R.
31 Solid lines indicated grade \geq 1 events and dashed lines indicate grade \geq 2 events
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34 NB. Late toxicity data have been included in stacked bar charts if they were reported
35 within 6 weeks of the 6 month visit, within 3 months of the 12-24 month visits and
36 within 6 months of the 36 and 48 month visits.
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48 Table 1: Baseline characteristics by treatment group (n=293)
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51 Table 2: Bowel and urinary domain scores using EPIC questionnaire and scoring
52 system by treatment group at a median follow-up of 50.3 months (IQR: 47.8-52.0
53 months)
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2 **Supplementary material (online only)**
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5 Table S1: Margin definition and target isodose levels prescriptive to the planning
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7 Table S2: Normal tissue dose constraints
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10 Table S3: EPIC bowel domain mean and standard deviation scores from the CHHiP
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12 QoL substudy and the calculated threshold dose
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14 Table S4: Treatment planning data
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17 Table S5: P-values for statistical comparison of dose volume and dose surface
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19 histograms for No IGRT vs IGRT-S and IGRT-S vs IGRT-R. All doses are in
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21 equivalent dose in 2Gy fractions.
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24 Table S6: Descriptive statistics given by IGRT treatment allocation for the rectum
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26 constraints
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29 Table S7: Descriptive statistics given by IGRT treatment allocation for the bladder
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31 constraints
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34 Table S8: Number and proportion with RTOG grade \geq 2 toxicity at 2 years with 95%
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36 confidence intervals - by treatment group and randomisation strategy
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39 Table S9: Hazard ratios and cumulative proportion with G1+, G2+ and G3+ bowel
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41 and bladder toxicity at 2 years assessed by RTOG, RMH and LENTSOM scoring
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43 systems
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45 Table S10: Baseline characteristics for PRO responders and non-responders
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48 Table S11: Percentage volume and surface receiving each dose level according to
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50 Vaizey scores categorised as tertiles (Ter1=Vaizey score 0-2; Ter2=Vaizey total 3-5;
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52 Ter3=Vaizey score 6-20). All doses are equivalent dose in 2Gy fractions.
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55 Table S12: Efficacy data by IGRT substudy group
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Figure S1: Boxplots showing along the top row the dose volume histograms for patients whose EPIC bowel (A) and urinary (B) domain scores were above or below the defined thresholds. The dose surface histograms are shown along the bottom row for those patients whose EPIC bowel (A) and urinary (B) domain scores were above or below the defined thresholds. All doses are equivalent dose in 2Gy fractions.

Figure S2: Kaplan Meier for biochemical/clinical failure free survival by IGRT substudy group

Radiotherapy Quality Assurance in the CHHiP IGRT substudy

References:

1. Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E, et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53(5):1097–105.
2. Zietman AL, DeSilvio ML, Slater JD, Rossi Jr. CJ, Miller DW, Adams JA, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005;294(10):1233–9.
3. Zelefsky MJ, Yamada Y, Kollmeier MA, Shippy AM, Nedelka MA. Long-term outcome following three-dimensional conformal/intensity-modulated external-beam radiotherapy for clinical stage T3 prostate cancer. *Eur Urol* 2008;53(6):1172–9.
4. Al-Mamgani A, Heemsbergen WD, Peeters ST, Lebesque J V. Role of intensity-modulated radiotherapy in reducing toxicity in dose escalation for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;73(3):685–91.

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5. McNair HA, Hansen VN, Parker CC, Evans PM, Norman A, Miles E, et al. A comparison of the use of bony anatomy and internal markers for offline verification and an evaluation of the potential benefit of online and offline verification protocols for prostate radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;71(1):41–50.
6. Zelefsky MJ, Kollmeier M, Cox B, Fidaleo A, Sperling D, Pei X, 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):125–9
7. Brenner DJ, Martinez AA, Edmundson GK, Mitchell C, Thames HD, Armour EP. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. *Int J Radiat Oncol Biol Phys* 2002;52(1):6-13.
8. Yeoh EE, Botten RJ, Butters J, Di Matteo AC, Holloway RH, Fowler J. Hypofractionated versus conventionally fractionated radiotherapy for prostate carcinoma: final results of phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2011;81(5):1271–8.
9. Norkus D, Karklelyte A, Engels B, Versmessen H, Griskevicius R, De Ridder M, et al. A randomized hypofractionation dose escalation trial for high risk prostate cancer patients: interim analysis of acute toxicity and quality of life in 124 patients. *Radiat Oncol* 2013;8(1):206.
10. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* 2016;17(8):1047–60.

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11. South CP, Khoo VS, Naismith O, Norman A, Dearnaley DP. A comparison of treatment planning techniques used in two randomised UK external beam radiotherapy trials for localised prostate cancer. *Clin Oncol (R Coll Radiol)* 2008;20(1):15–21.
12. Dearnaley D, Syndikus I, Sumo G, Bidmead M, Bloomfield D, Clark C, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. *Lancet Oncol* 2012;13(1):43–54.
13. Naismith O, Mayles H, Bidmead M, Clark CH, Gulliford S, Hassan S, et al. Radiotherapy Quality Assurance for the CHHiP Trial: Conventional Versus Hypofractionated High-Dose Intensity-Modulated Radiotherapy in Prostate Cancer. *Clin Oncol (R Coll Radiol)*. 2019 Sep;31(9):611–20.
14. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003;13(3):176–81
15. Pavy JJ, Denekamp J, Letschert J, Littbrand B, Mornex F, Bernier J, et al. Late effects toxicity scoring: the SOMA scale. *Radiother Oncol*. 1995;35(1):11–5.
16. Dearnaley DP, Sydes MR, Langley RE, Graham JD, Huddart RA, Syndikus I, et al. The early toxicity of escalated versus standard dose conformal radiotherapy with neo-adjuvant androgen suppression for patients with localised prostate cancer: results from the MRC RT01 trial (ISRCTN47772397). *Radiother Oncol* 2007;83(1):31–41.
17. Pilepich M V., Asbell SO, Krall JM, Baerwald WH, Sause WT, Rubin P, et al. Correlation of radiotherapeutic parameters and treatment related morbidity-analysis of RTOG study 77-06. *Int J Radiat Oncol Biol Phys*. 1987;13(7):1007–

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18. Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology* 2010;76(5):1245–50.
19. Vaizey CJ, Carapeti E, Cahill JA, Kamm MA. Prospective comparison of faecal incontinence grading systems. *Gut* 1999;44(1):77–80.
20. Ware JJ, Kosinski MM, Keller SSD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34(3):220–33.
21. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999;11(6):319–26.
22. Withers HR, Thames HD, Peters LJ. A new isoeffect curve for change in dose per fraction. *Radiother Oncol*. 1983;1(2):187–91.
23. A'Hern RP. Sample size tables for exact single-stage phase II designs. *Stat Med*. 2001;20(6):859–66.
24. Scoring instructions for the expanded prostate cancer index composite (EPIC) 2002. Available from: [http://medicine.umich.edu/sites/default/files/content/downloads/Scoring Instructions-EPIC.pdf](http://medicine.umich.edu/sites/default/files/content/downloads/Scoring%20Instructions-EPIC.pdf)
25. Scoring Instructions for the Expanded Prostate cancer Index Composite Short Form (EPIC-26). 2002.
26. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation.

Med Care 2003;41(5):582–92.

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58
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27. Wilkins A, Mossop H, Syndikus I, Khoo V, Bloomfield D, Parker C, et al. Hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate-risk localised prostate cancer: 2-year patient-reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol.* 2015;16(16):1605–16.
28. Wortel RC, Incrocci L, Pos FJ, Lebesque J V., Witte MG, van der Heide UA, et al. Acute Toxicity After Image-Guided Intensity Modulated Radiation Therapy Compared to 3D Conformal Radiation Therapy in Prostate Cancer Patients. *Int J Radiat Oncol* 2015 Mar;91(4):737–44.
29. Fellin G, Rancati T, Fiorino C, Vavassori V, Antognoni P, Baccolini M, et al. Long term rectal function after high-dose prostatecancer radiotherapy: Results from a prospective cohort study. *Radiother Oncol.* 2014;110(2):272–7.
30. Andreassen CN, Rosenstein BS, Kerns SL, Ostrer H, De Ruyscher D, Cesaretti JA, et al. Individual patient data meta-analysis shows a significant association between the ATM rs1801516 SNP and toxicity after radiotherapy in 5456 breast and prostate cancer patients. *Radiother Oncol.* 2016;121(3):431–9.
31. Ferreira MR, Muls A, Dearnaley DP, Andreyev HJN. Microbiota and radiation-induced bowel toxicity: Lessons from inflammatory bowel disease for the radiation oncologist. *Lancet Oncology.* 2014; 15(3): e139-147
32. Tøndel H, Lund JÅ, Lydersen S, Wanderås AD, Aksnessæther B, Jensen CA, et al. Radiotherapy for prostate cancer – Does daily image guidance with tighter margins improve patient reported outcomes compared to weekly orthogonal verified irradiation? Results from a randomized controlled trial.

Radiother Oncol. 2018; 126: 229-235.

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56
57
58
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62
63
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33. de Crevoisier R, Bayar MA, Pommier P, Muracciole X, Pêne F, Dudouet 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.
34. Witte MG, Heemsbergen WD, Bohoslavsky R, Pos FJ, Al-Mamgani A, Lebesque J V., et al. Relating Dose Outside the Prostate With Freedom From Failure in the Dutch Trial 68 Gy vs. 78 Gy. *Int J Radiat Oncol Biol Phys.* 2010;77(1):131–8.

Table 1: Baseline characteristics by treatment group (n=293)

	No IGRT N=48 n (%)	IGRT - S N=137 n (%)	IGRT - R N=108 n (%)
Randomisation option			
No IGRT v IGRT-S v IGRT-R	16 (33)	13 (9)	13 (12)
No IGRT v IGRT-S	32 (67)	32 (23)	-
IGRT-S v IGRT-R	-	92 (67)	95 (88)
Age at registration (years)			
Median (IQR)	71 (66-73)	72 (66-75)	71 (67-75)
Range	57-80	53-82	54-80
Time from histological confirmation of prostate cancer to randomisation (wks)			
Median (IQR)	16 (13-25)	17 (13-27)	18 (13-25)
Range	6-350	3-278	4-265
T stage (clinical assessment)			
T1	16 (33)	46 (34)	43 (40)
T2	27 (56)	83 (61)	56 (52)
T3	5 (10)	8 (6)	9 (8)
Grading group(Gleason score)			
1 (3+3)	13 (27)	42 (31)	31 (29)
2 (3+4)	30 (63)	61 (45)	55 (51)
3 (4+3)	4 (8)	32 (23)	19 (18)
4 (4+4, 3+5, 5+3)	1 (2)	2 (1)	3 (3)
PSA (pre-hormone treatment) (ng/ml)			
Median (IQR)	9.5 (6.8-15.2)	9.7 (6.9-12.5)	8.3 (6.9-11.4)
Mean (SD)	11.1 (4.9)	10.3 (4.6)	9.1 (3.8)
PSA (ng/ml)			
0.0-4.99	2 (4)	13 (10)	12 (11)
5.0-9.99	23 (48)	57 (42)	60 (56)
10.0-19.99	20 (42)	65 (48)	36 (33)
20.0-49.99	3 (6)	2 (2)	0
NCCN Risk group			
Low	2 (4)	16 (12)	17 (16)
Medium	38 (79)	109 (80)	80 (74)
High	8 (17)	12 (9)	11 (10)
CHHiP treatment allocation			
74Gy/37Fr	18 (38)	44 (32)	33 (31)
60Gy/20Fr	15 (31)	48 (35)	37 (34)
57Gy/19Fr	15 (31)	45 (33)	38 (35)

Table 2: Bowel and urinary domain scores using EPIC questionnaire and scoring system by treatment group at a median follow-up of 50.3 months (IQR: 47.8-52.0 months)

	No IGRT		IGRT-S		IGRT-R	
	No. of pts with data	Median (IQR)	No. of pts With data	Median (IQR)	No. of pts with data	Median (IQR)
Bowel function	29	96.4 (89.3-100)	89	92.9 (85.7-96.4)	75	96.4 (85.7-100)
P-value			0.210 ¹		0.500 ²	
Bowel bother	29	96.4 (87.5-100)	83	92.9 (85.7-100)	74	92.9 (85.7-100)
P-value			0.475 ¹		0.909 ²	
Bowel summary	29	94.6 (89.3-98.2)	84	94.6 (87.5-96.4)	74	92.9 (87.5-98.2)
P-value			0.218 ¹		0.586 ²	
Urinary function	28	97.5 (92.2-100)	87	100 (89.2-100)	75	95 (88.4-100)
P-value			0.941 ¹		0.409 ²	
Urinary bother	28	82.1 (74.1-93.8)	80	85.7 (71.4-92.9)	70	85.7 (75.9-92.9)
P-value			0.947 ¹		0.456 ²	
Urinary incontinence	27	100 (82.4-100)	79	93.8 (85.5-100)	71	93.8 (79.3-100)
P-value			0.985 ¹		0.473 ²	
Irritative/Obstructive	28	88.4 (78.6-96.0)	79	89.3 (80.7-92.9)	70	89.3 (85.7-96.4)
P-value			0.861 ¹		0.454 ²	
Urinary summary	27	88.9 (80.6-96.9)	79	88.9 (78.7-95.8)	71	89.6 (84-94.8)
P-value			0.945 ¹		0.733 ²	
Vaizey total score	27	4 (1-5.5)	84	4 (1-7)	72	4 (1-6)
			0.048 ¹		0.821 ²	

¹ Comparison of No IGRT and IGRT-S groups

² Comparison of IGRT-S and IGRT-R groups

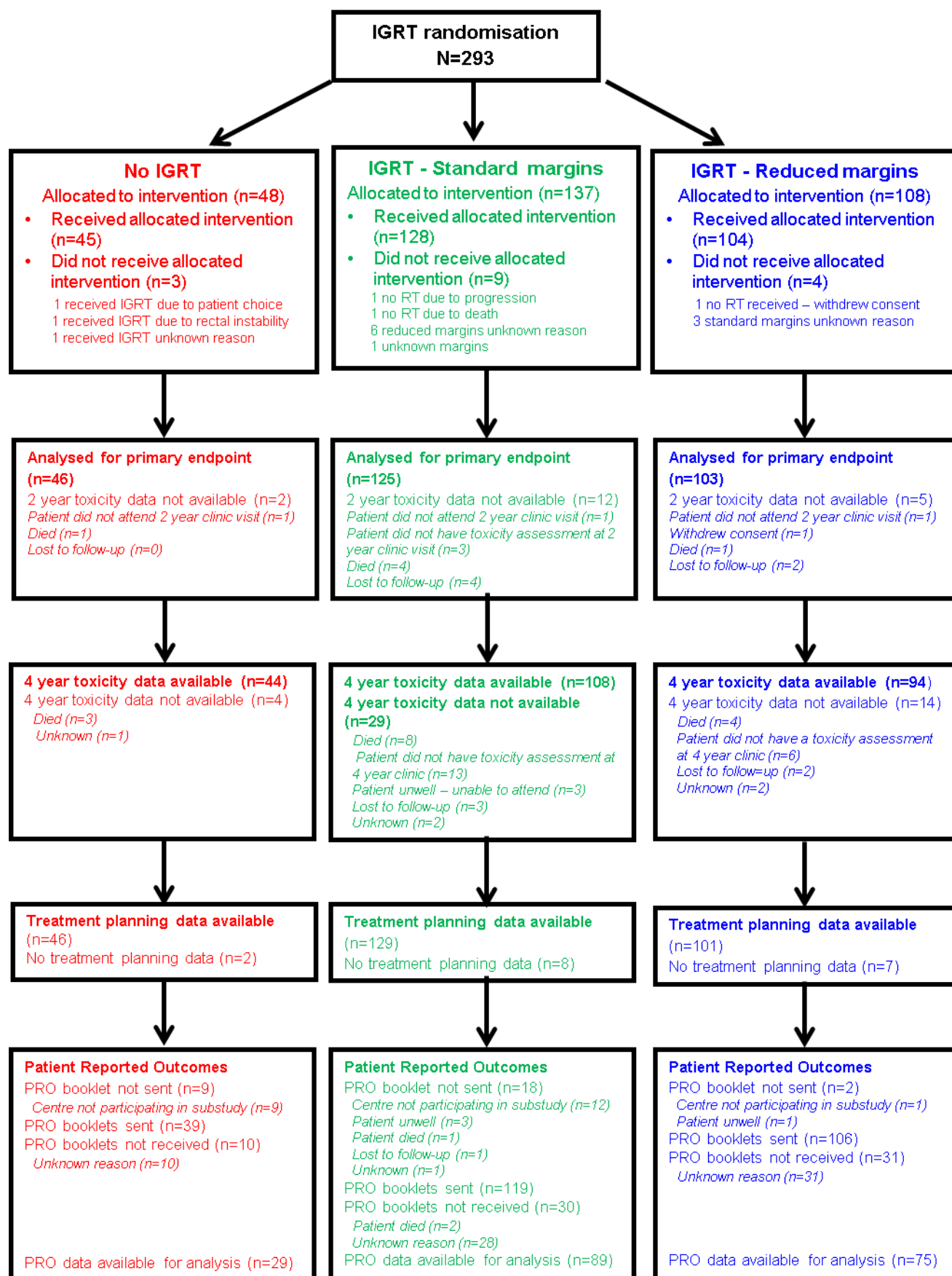
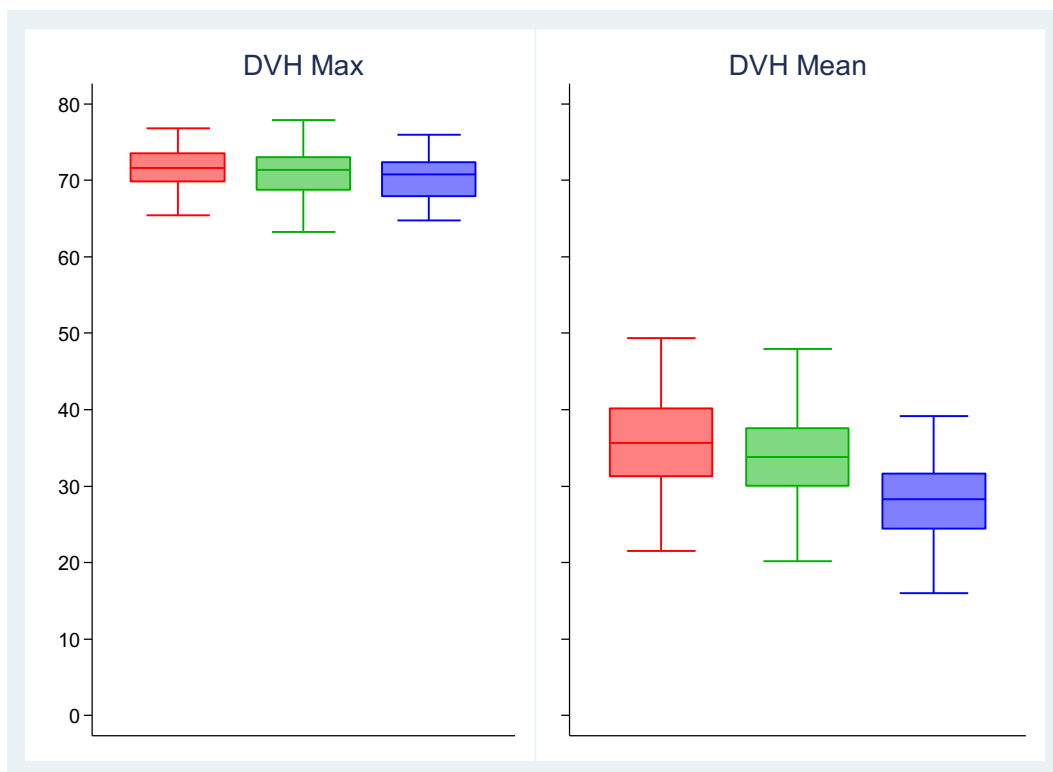
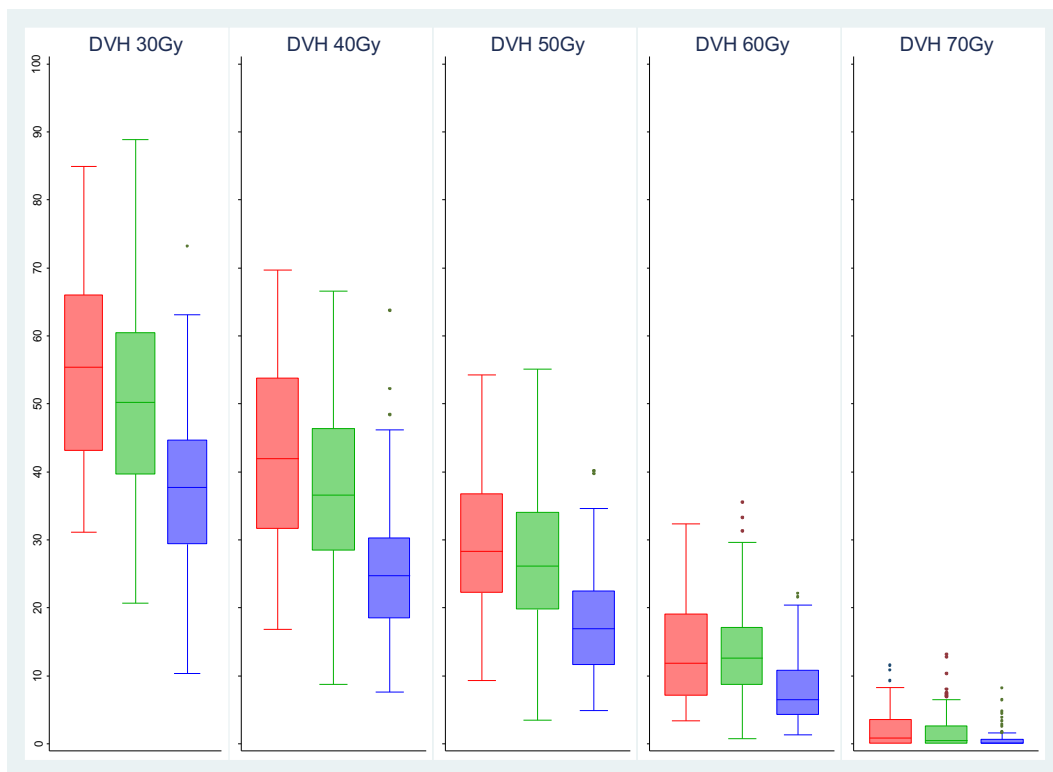


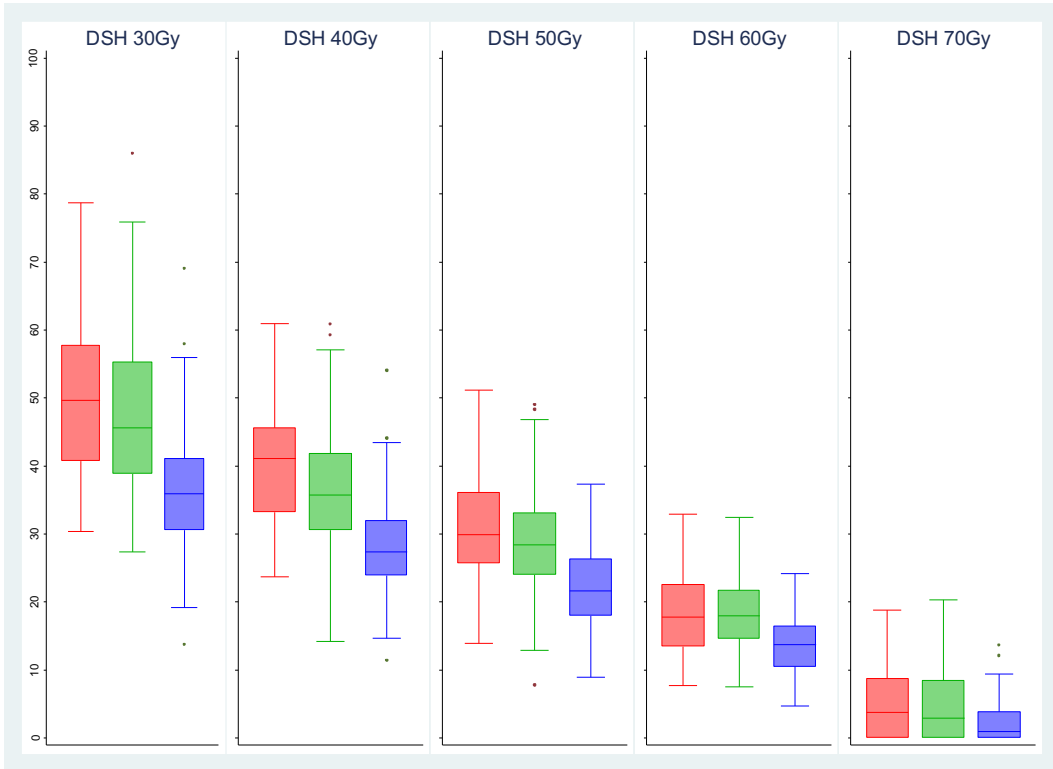
Figure 2

(A) RECTUM

DOSE VOLUME HISTOGRAMS

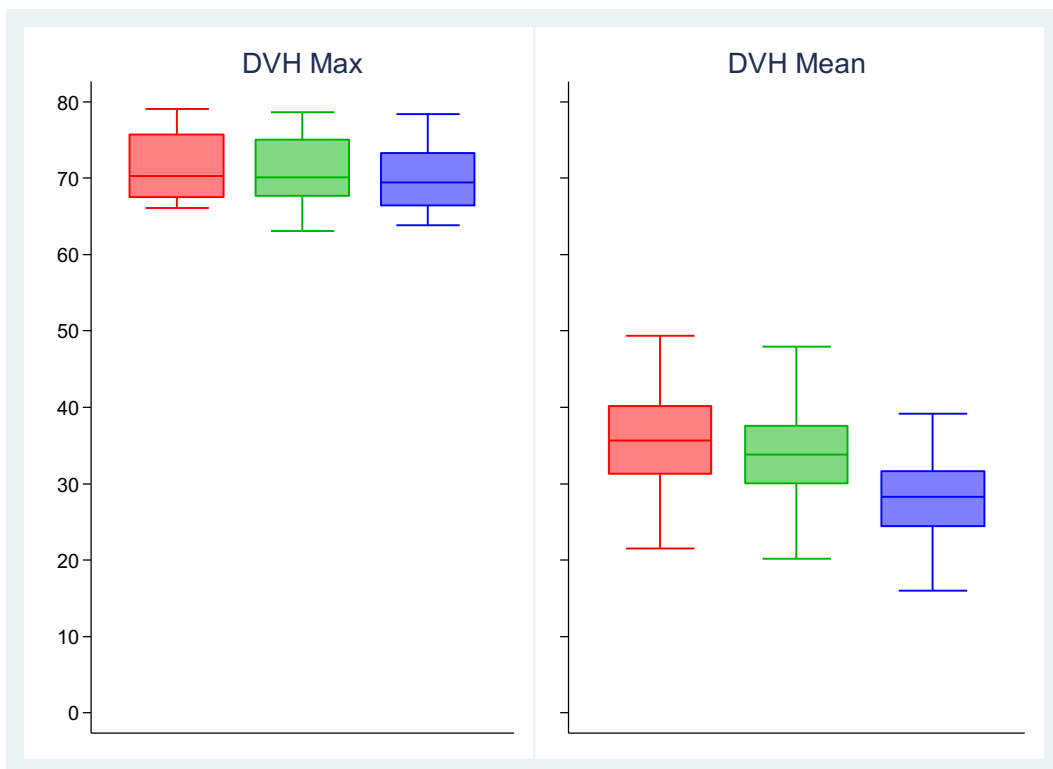
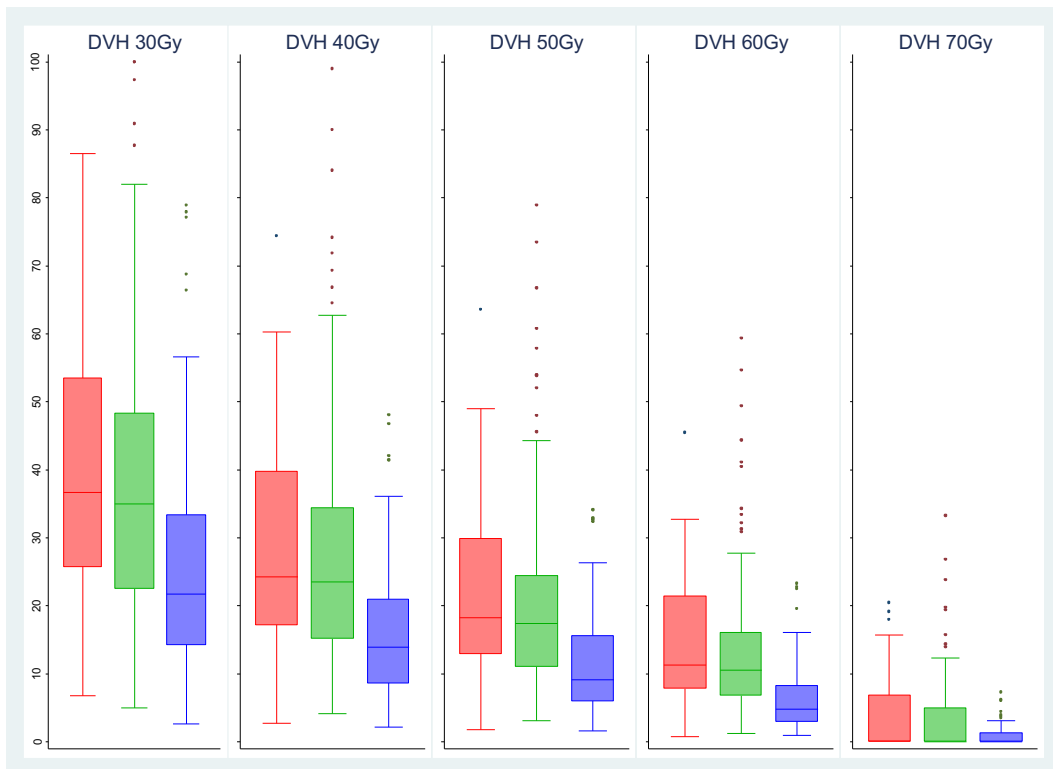


DOSE SURFACE HISTOGRAMS

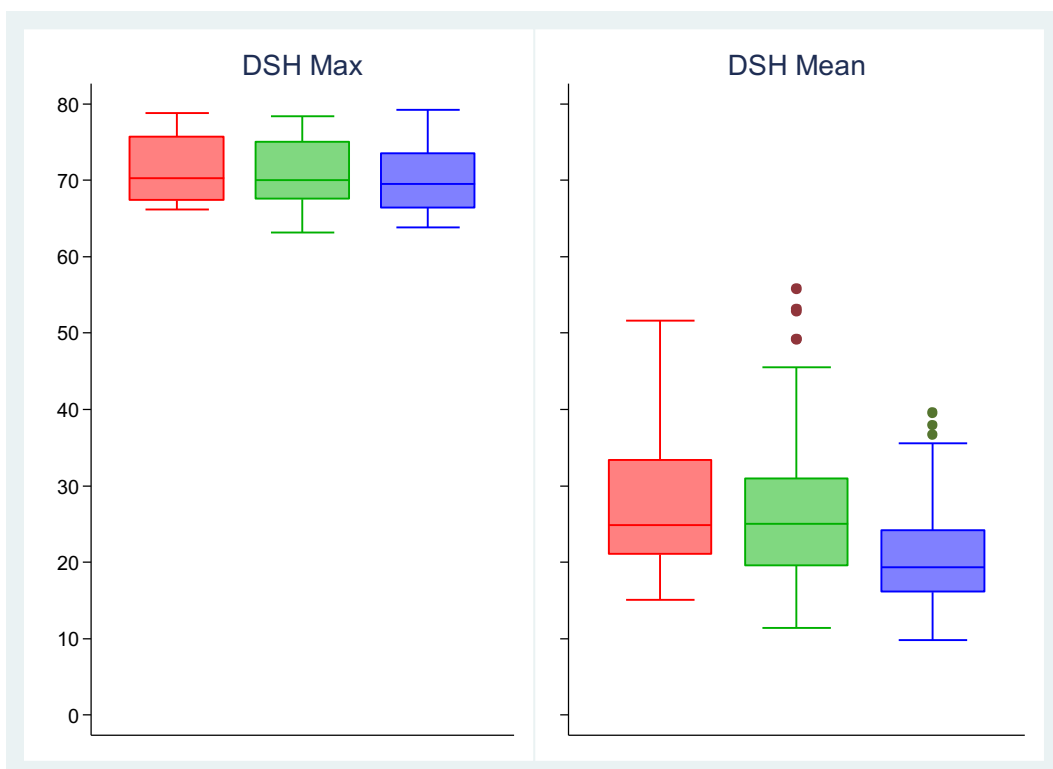
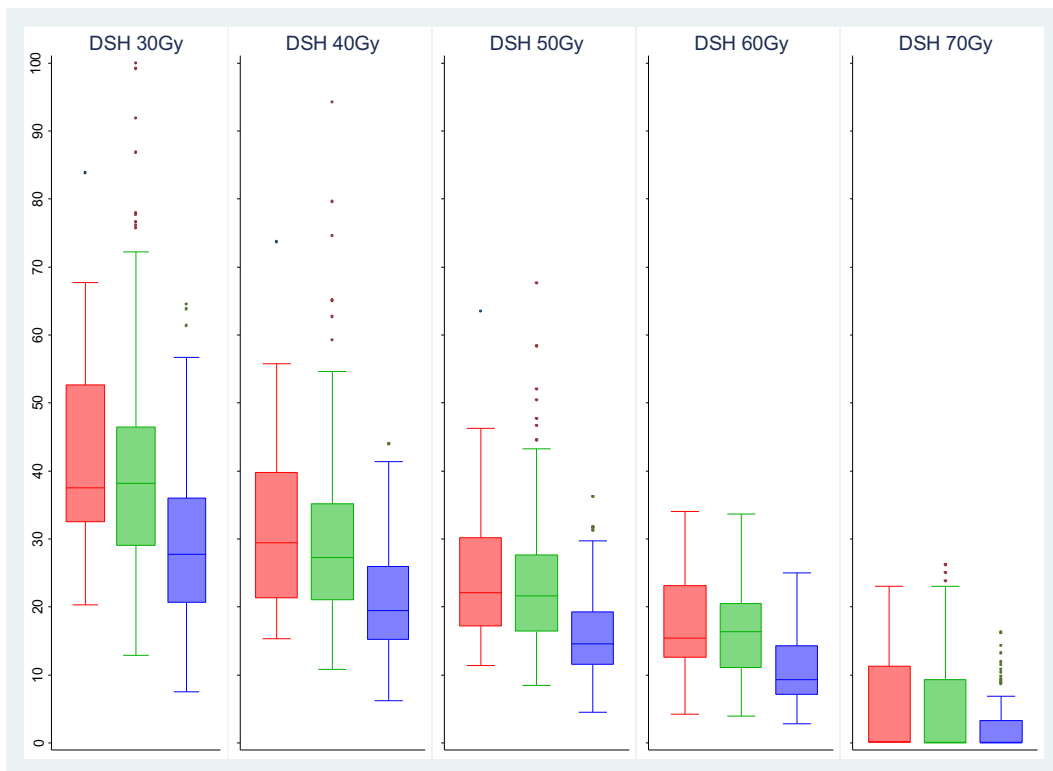


(B) BLADDER

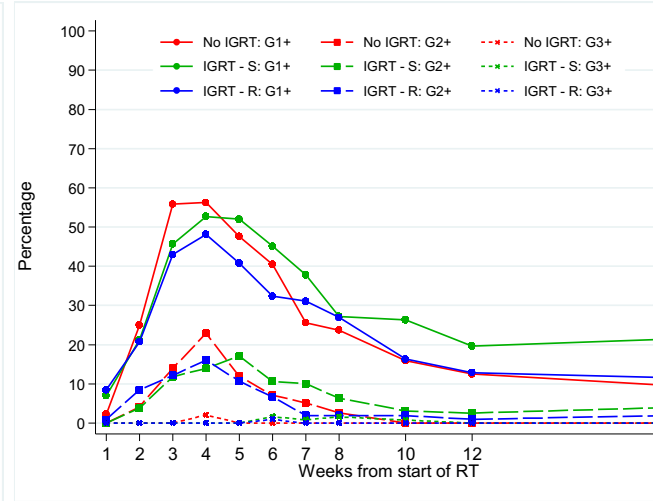
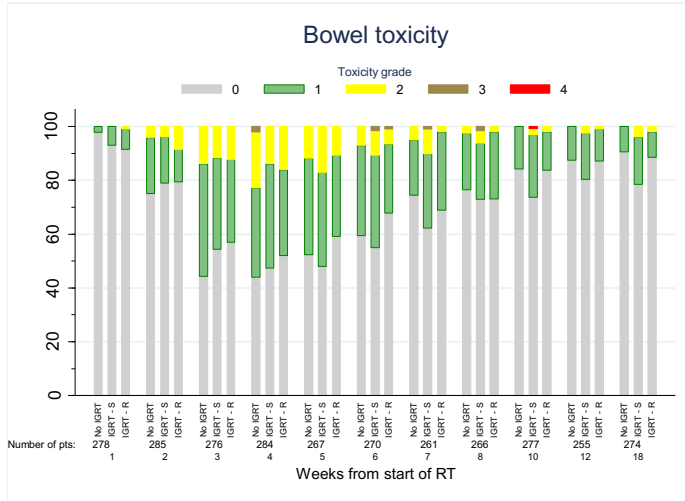
DOSE VOLUME HISTOGRAMS



DOSE SURFACE HISTOGRAM



(A) BOWEL



(B) BLADDER

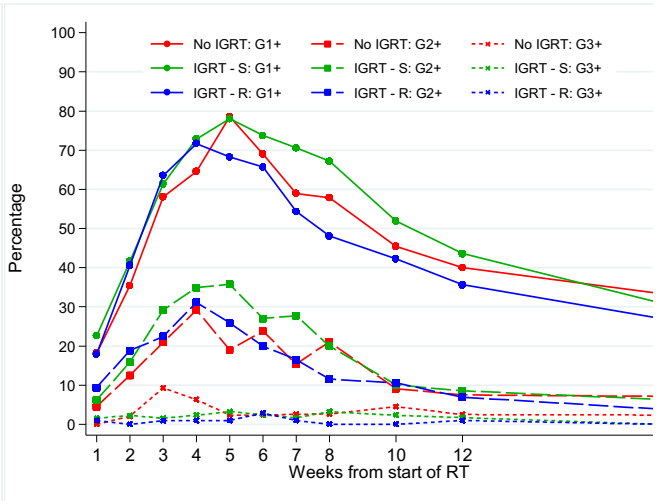
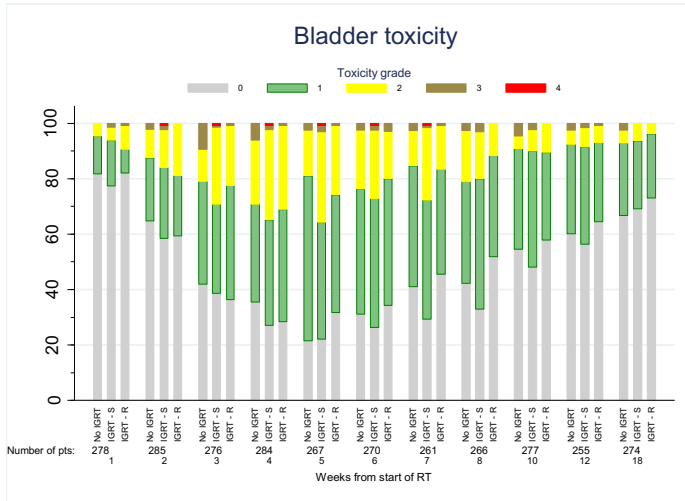
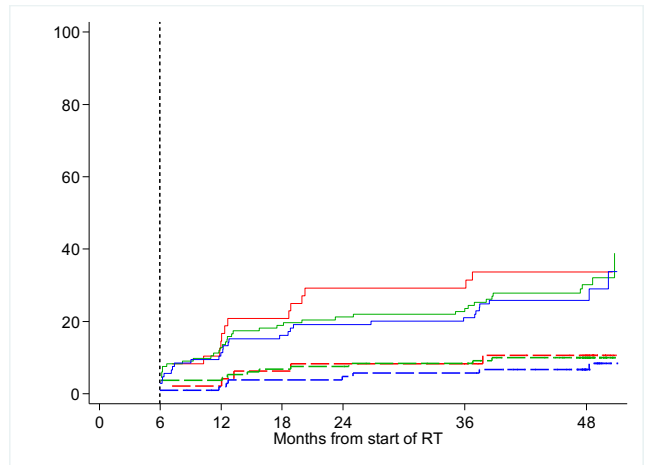
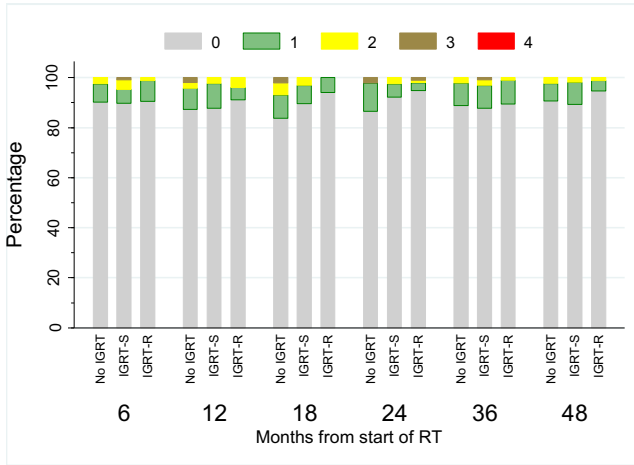


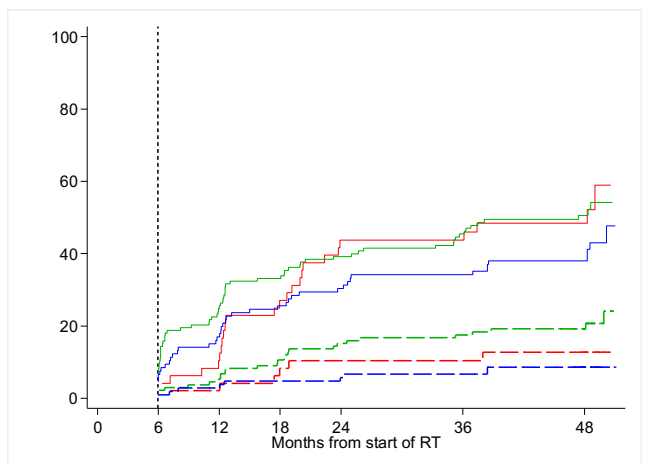
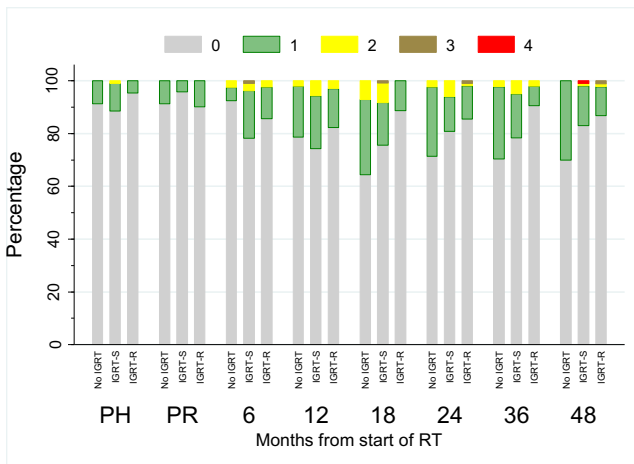
Figure 4

(A) BOWEL

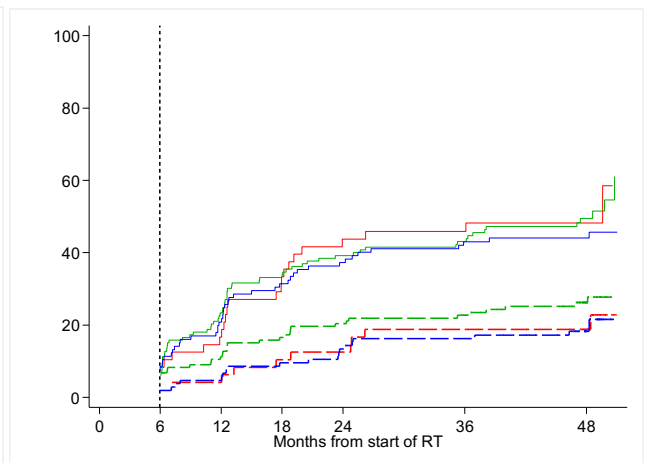
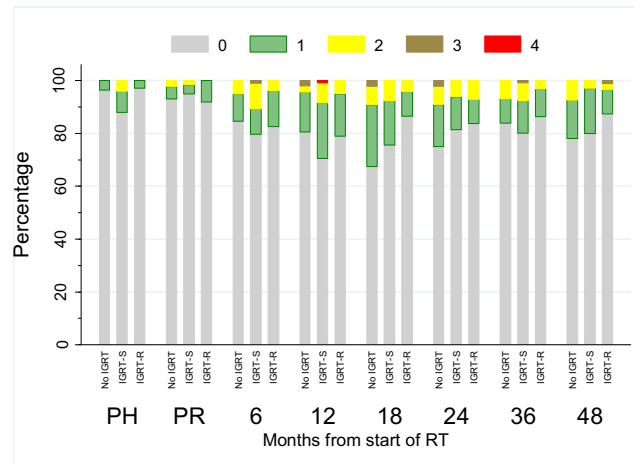
RTOG



RMH

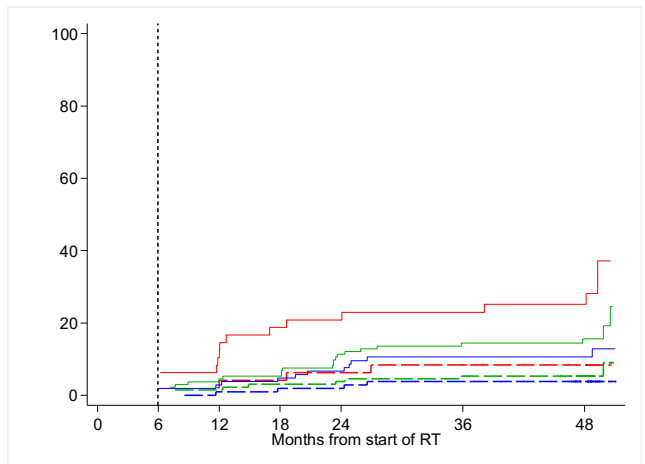
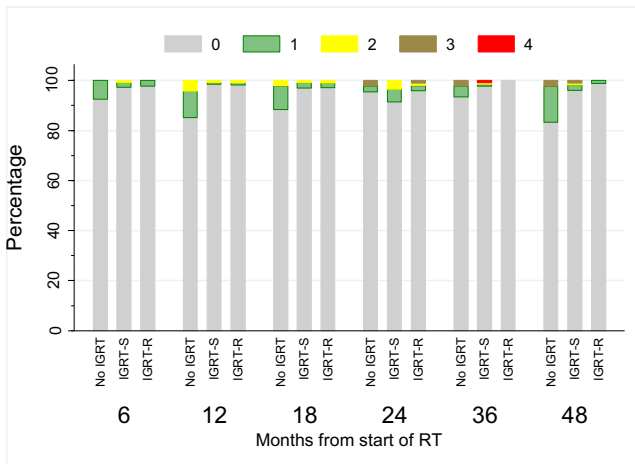


LENTSOM rectal toxicity

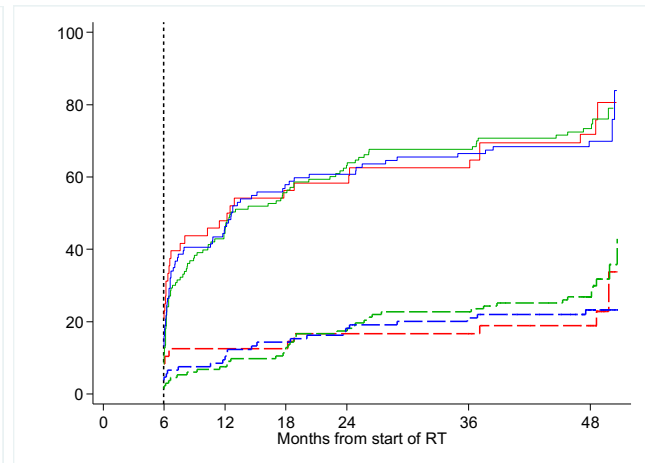
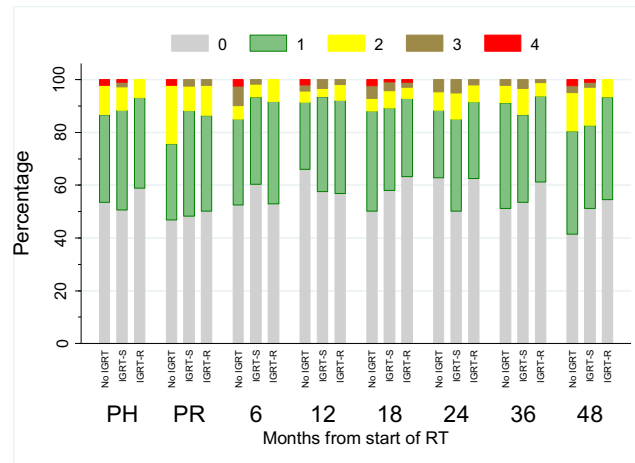


(B) BLADDER

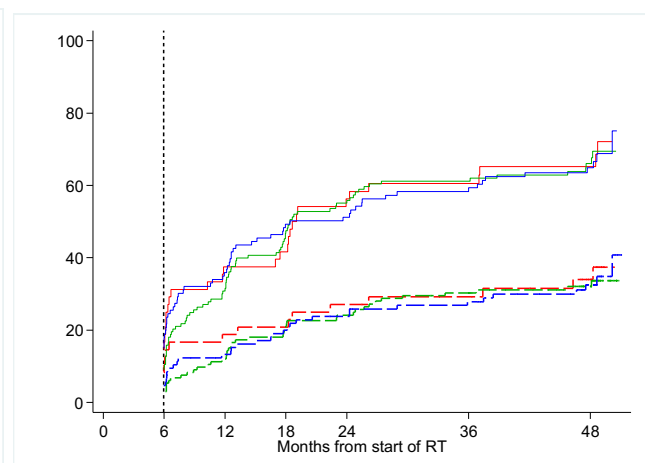
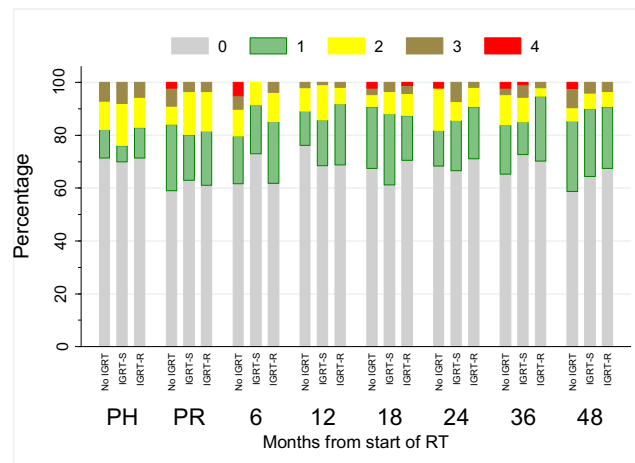
RTOG



RMH



LENTSOM



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