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PII: S0360-3016(19)34461-X
DOI: https://doi.org/10.1016/j.ijrobp.2019.11.402
Reference: ROB 26081

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

Received Date: 18 July 2019
Revised Date: 11 November 2019
Accepted Date: 25 November 2019


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Standard and hypofractionated dose escalation to intraprostatic tumour nodules in localised prostate cancer: efficacy and toxicity in the DELINEATE trial

Julia R Murray, FRCR\textsuperscript{1,*} and Alison C Tree, FRCR\textsuperscript{1,2,*}, Emma Alexander, FRCR\textsuperscript{1}, Aslam Sohaib, FRCR\textsuperscript{1}, Steve Hazell, FRCPATH\textsuperscript{1}, Karen Thomas, MSc\textsuperscript{1}, Ranga Gunapala, MSc\textsuperscript{1}, Chris Parker, FRCR\textsuperscript{1,2}, Robert Huddart, FRCR\textsuperscript{2,1}, Annie Gao, MSc \textsuperscript{2,1}, Lesley Truelove, BSc\textsuperscript{2,1}, Helen McNair, PhD\textsuperscript{1,2}, Irena Blasiak-Wal, MSc\textsuperscript{1,2}, Nandita M deSouza, FRCR\textsuperscript{2,1,**}, David Dearnaley, FRCR\textsuperscript{2,1**}

*joint first authors; contributed equally to this paper
**joint senior authors

\textsuperscript{1} The Royal Marsden NHS Foundation Trust, London UK
\textsuperscript{2} The Institute of Cancer Research, London, UK

K Thomas, R Gunapala responsible for statistical analyses

Corresponding author:
Dr Julia Murray
Academic Uro-oncology Unit
Royal Marsden NHS Foundation Trust and Institute of Cancer Research
Downs Road, Sutton, SM2 5PT
0044 20 8661 3271
julia.murray@icr.ac.uk

Running title:
Intraprostatic tumour nodule dose escalation

Acknowledgements

This paper represents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and The Institute of Cancer Research. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The project is supported by CRUK Programme Grants C46/A10588 (2009-2014), C33589/A19727 (2014-2019) and C1060/A10334 (2009-2013), C1060/A16464 (2014-2019).

We would like to acknowledge the funding of the JP Moulton Foundation for the DELINEATE HYPO cohort.

Conflict of interest statements:
Prof Dearnaley reports grants and personal fees from The Institute of Cancer Research, during the conduct of the study; grants and personal fees from Takeda, personal fees from Janseen, grants from CRUK C46/A10588 2009-14, grants from CRUK C33589/A19727 2015-
In addition, Prof Dearnaley has a patent EP1933709B1 pending.

Dr. Murray reports other from Janssen, personal fees from Astellas, personal fees from Ferring, personal fees from Elekta, outside the submitted work.

Dr. Tree reports grants and personal fees from Elekta, grants from Accuray, grants from MSD, personal fees from Janssen, personal fees from Astellas, personal fees from Genesis Healthcare, personal fees from Ferring, outside the submitted work.

Prof Huddart reports non-financial support from Janssen, grants and personal fees from MSD, personal fees from Bristol Myers Squibb, grants from CRUK, other from Nektar, personal fees and non-financial support from Roche, outside the submitted work.
Standard and hypofractionated dose escalation to intraprostatic tumour nodules in localised prostate cancer: efficacy and toxicity in the XXX trial

Abstract

Purpose

To report a planned analysis of the efficacy and toxicity of dose escalation to the intraprostatic dominant nodule identified on multiparametric MRI (mp-MRI) using standard and hypofractionated external beam radiotherapy.

Methods and Materials

XXX is a single centre prospective phase 2 multi-cohort study including standard (Cohort A: 74Gy/37F) and moderately hypofractionated (Cohort B: 60Gy/20F) prostate image-guided IMRT in patients with NCCN intermediate and high-risk disease. Patients received an integrated boost of 82Gy (Cohort A) and 67Gy (Cohort B) to mp-MRI-visible lesions. 55 patients were treated within Cohort A and 158 patients treated in Cohort B; the first 50 sequentially treated patients in Cohort B were included in this planned analysis. The primary endpoint was late RTOG rectal toxicity at 1 year. Secondary endpoints included acute and late toxicity measured with clinician and patient reported outcomes at other timepoints as well as biochemical relapse (BCR) free survival for Cohort A. Median follow up for Cohort A was 74.5 months and 52.0 months for Cohort B.

Results

In Cohort A and B, there were 27% and 40% of patients respectively classified with NCCN high risk disease. The cumulative 1-year incidence of Radiation Therapy Oncology Group
(RTOG) grade 2 or worse rectal and urinary toxicity was 3.6% and 0% in Cohort A and 8% and 10% in Cohort B respectively. There was no reported late grade 3 rectal toxicity in either cohort. At a median follow up of 74.5 months (Cohort A) and 52 months (Cohort B) four patients, all from cohort A, had BCR.

Conclusions
Delivery of a simultaneous integrated boost to intraprostatic dominant nodules is feasible in prostate radiotherapy using standard and moderately hypofractionated regimens, with rectal and genitourinary toxicity comparable to contemporary series without an intraprostatic boost.

Introduction
External beam radiotherapy (EBRT) is a recommended treatment for prostate cancer patients with intermediate or high-risk disease\(^1\). Dose-escalation has been shown to improve biochemical disease-free survival with results continuing to show a benefit 8-10 years after EBRT\(^2-4\). The benefits of dose escalation are gained at the expense of increased rectal toxicity. Treatment strategies that exploit likely sites of local failure within the prostate, as well as the radiobiology of prostate cancer, should be investigated to mitigate these risks.

The most common site for local recurrence is the dominant intra-prostatic tumour lesion (DIL) suggesting that focal radiation boosts to the DIL may improve the therapeutic ratio of prostate radiotherapy\(^5-7\). Delivery of a focal radiation boost requires accurate identification
of the DIL. This can be achieved with multiparametric (mp)-MRI, which includes diffusion-weighted magnetic imaging (DWI) and dynamic contrast enhancement (DCE) \(^8\,^9\). Current advances in PET imaging, with the use of PSMA-PET/CT have been shown to be accurate in detecting segments containing intermediate-grade intra-prostatic prostate cancer (ISUP grade \( \geq 2 \))\(^10\). Studies have shown the feasibility for these techniques in DIL identification\(^11\), with ongoing studies investigating whether this additional information for radiotherapy planning is clinically meaningful.

Within the last 3 years, the evidence base for hypofractionation has been strengthened by the reported results of four randomised controlled trials\(^12\,^15\). The largest of these, the CHHiP trial, which included 3216 patients, showed that after a median follow-up of 62 months, 60Gy in 20 fractions was non-inferior to 74Gy in 37 fractions, with no differences in long term side effects\(^12\).

The aim of this study was to assess toxicity and feasibility of dose-escalated intensity-modulated image-guided radiotherapy boost to tumour nodule(s) within the prostate using anatomical and functional mp-MRI to identify the DIL. We report a planned analysis of toxicity and efficacy in the first two dose cohorts using both standard fractionation and moderate hypofractionation.

**Methods and Materials**

**Study design and patient population**
XXX (XXX) is a single institution prospective phase 2 multi-cohort study, evaluating the role of an integrated boost to the dominant nodule visible on mp-MRI. The trial was carried out at XXX and sponsored by XXX. The trial was approved by the local institutional review board and Regional Ethics Committee and was conducted in accordance with the principles of Good Clinical Practice. The trial is registered on the ISRCTN database (XXXXXXXX).

Patients with intermediate- or high-risk prostate adenocarcinoma, defined according to National Comprehensive Cancer Network (NCCN) criteria, were eligible to participate if they had a dominant lesion visible on MRI. Patient’s with a medical contraindication to MRI scanning and/or implantation of fiducial markers were excluded. All patients gave written informed consent.

The XXX trial opened to recruitment for Cohort A in July 2011. Once Cohort A had completed recruitment, Cohort B opened to recruitment in October 2013, following the preliminary safety reports from the CHHiP trial.

**Protocol intervention**

All patients had standard diagnostic and staging investigations prior to recruitment, which included prostate MRI (both 1.5T and 3.0T permitted). Staging mp-MRI was performed before commencing androgen deprivation therapy (ADT). The DIL was identified as per PI-RADS 1 criteria initially by two observers (for 26 patients within cohort A) who individually have more than 20 years’ experience of prostate MRI and then by a single radiologist thereafter. A PIRADS score of at least 3 with a corroborative biopsy was required for the
lesion to be considered suitable for boosting. The accuracy of mp-MRI against a template biopsy gold-standard has been reported in a subset of these patients\textsuperscript{18}. All patients were commenced on hormone therapy after the mpMRI; ADT was prescribed in accordance with local guidelines, giving short or long course ADT with initial bicalutamide for prevention of testosterone flare.

All patients had three gold seeds placed in the prostate under transrectal or transperineal ultrasound guidance about 1 week before radiotherapy planning imaging. MRI was performed with an external array coil alone on the same day as the planning CT scan. Patients were scanned with a moderately full bladder and rectal preparation. This included use of a microlette enema prior to emptying their bladder an hour before and drinking around 300ml. All scans were carried out with patients in the radiotherapy position (on a flat table top with knee and ankle immobilisation (CombiFix, Oncology Systems Ltd, UK)).

Patients treated within Cohort A had a urinary catheter inserted for the planning CT to aid contouring of urethra. For Cohort B, the urethra was outlined using fused planning CT-MRI scan. The DIL boost region was contoured using “cognitive fusion” of diagnostic mpMRI and planning scans which were displayed side by side to aid contouring. All contours were reviewed by the chief investigator (XX).

**Radiation therapy**

All patients within the XXX trial received radiotherapy to the whole prostate, to a dose of 74Gy in 37 fractions and 60Gy in 20 fractions in cohort A and B respectively. A simultaneous
integrated boost to dominant nodule(s) was planned to a total dose of 82Gy in 37 fractions and 67Gy in 20 fractions in cohort A and B respectively. The rationale for this dose was founded on the 11% improvement in biochemical progression free survival within the MRC RT01 trial of a dose escalation to the whole prostate of 115% (64Gy to 74Gy)\textsuperscript{19}. This translated into a dose of 86Gy, which in 2Gy per fraction has a similar biologically equivalent dose of 82Gy in 37 fractions (BED = 143Gy using an alpha/beta of 3Gy).

Additionally, Seppala et al. debated that although tumour control probability (TCP) continued to increase up to a maximum of 99-100% with doses up to 90Gy, the highest mean dose associated with the probability of uncomplicated control was 82.1Gy and the increase in TCPs plateaued at 84Gy\textsuperscript{20}. The choice of dose for the moderately hypofractionated cohort was derived for equivalence of normal tissue toxicity to achieve a similar EQD2 with an alpha/beta of 3Gy as in the conventionally fractionated cohort.

Treatment was planned and delivered using an simultaneous integrated boost technique (SIB) with four different target volumes and dose levels, based on CHHiP trial technique as previously detailed\textsuperscript{21} and illustrated in Table S1. No more than three separate nodules were permitted to be boosted, and no maximum boost volume was stipulated. Mandatory dose constraints were defined for both target coverage and avoidance of normal tissues including rectum, anal canal, bowel, bladder, urethra and femoral heads (Table S2).

All patients were treated with inverse planned IMRT either with 5- to 7-field static step and shoot IMRT. Daily online image-guidance registering to gold fiducial markers was performed, with rectal and bladder filling assessed. Bladder filling protocol was adhered to during the radiotherapy and microlette enemas were used prior to the first 10 fractions.
**Trial assessments**

Pre-trial staging investigations included PSA, lymph node assessment by MRI or CT and, if indicated, a bone or choline PET/CT scan. Histology was assessed from diagnostic TRUS guided biopsies (or TURP specimens) and reported using the Gleason system. Toxicity experienced from the insertion of fiducial markers was recorded.

Clinician reported outcomes (CRO) were assessed pre-hormone and pre-radiotherapy using NCI CTCAE v4 grading\(^{22}\), XXX grading\(^{23}\) and Gulliford Rectal\(^{24}\) scores. Clinical assessment of acute toxicity was made weekly until week 8, then at weeks 10, 12 and 18 from the start of radiotherapy using the Radiation Therapy Oncology (RTOG) scoring system\(^{25}\). At week 18 from start of radiotherapy NCI CTCAE v4, XXX, Gulliford Rectal and RTOG were evaluated. CRO for late toxicity was assessed at 6 months from the start of radiotherapy, then 6-monthly to 5 years using RTOG, NCI CTCAE v4, Gulliford Rectal and XXX scoring systems.

Patient reported outcomes (PRO) were collected in both cohorts. Patients recruited to Cohort A and B completed modified IBDQ\(^{26}\), Vaizey\(^{27}\) and IPSS\(^{28}\) questionnaires at enrolment, pre-radiotherapy, week 18 from start of radiotherapy and then at 6, 12, 18, 24 months from start of radiotherapy. Patients within Cohort B also completed EPIC-26\(^{29}\) questionnaires at these timepoints.

PSA was evaluated at week 10 and 18 from the start of radiotherapy and then at 6 months and then 6-monthly to 5 years. Biochemical progression was defined as an increase in serum PSA of at least 2ng/ml greater than post-radiotherapy nadir confirmed by a second consecutive reading also of at least 2ng/ml greater than post-treatment nadir\(^{30}\).
**Statistical analysis**

The primary endpoint was cumulative RTOG late rectal toxicity of grade 2+ at 1 year, calculated using Kaplan-Meier methods from start date of radiotherapy and presented with an exact one-sided 95% confidence interval (calculated as the upper limit of a 2-sided 90% CI). The sample size (n=50) for the cohorts was calculated to rule out a 10% increase in cumulative RTOG ≥ G2 rectal toxicity at 1 year using an Ahern single stage design (with p0=0.87, p1=0.97, alpha of 0.034 and 81% power), assuming a cumulative incidence of 3%, which was an estimate based on the early CHHiP trial data. Secondary endpoints include acute and late toxicity measured with both CRO and PRO, time to biochemical progression, time to distant progression, time to local progression, patterns of local progression and are reported using summary statistics and using Kaplan-Meier method for time-to-event analyses. The rates of missing follow-up data are reported (Table S3), with no imputation methods used in the analysis.

**Results**

Between July 13th 2011 and January 19th 2015, 105 patients were recruited within Cohorts A & B. In cohort A, a total of 56 patients were recruited. Of these, one withdrew from the trial prior to treatment through patient choice (unable to attend scheduled clinic visits) and is excluded from analysis. In cohort B, 50 patients were initially recruited and are reported here, with a subsequent cohort expansion to a total of 158 patients. Median follow up for reported patients is 74.5 months for Cohort A and 52.0 months for Cohort B.
Baseline characteristics

Baseline characteristics of the two cohorts are shown in Table 1. NCCN intermediate risk disease was recorded in 40/55 (73%) patients in Cohort A and 30/50 (60%) in Cohort B. Cohort B contains more patients with high risk disease and a higher proportion of patients with comorbidities. More patients were planned to receive long term ADT (2-3 years of LHRHa) in Cohort B 13/50 (26%) than Cohort A 3/55 (5%).

The median volume (IQR) of the contoured DIL GTV for planning was 4.4 (2.8-6.4) cm$^3$ in cohort A and 3.6 (2.2-5.6) cm$^3$ in cohort B. This was larger than the DIL contoured on the baseline MRI by the radiologist (see Table 1). The mean (SD) dose delivered to the mp-MRI defined DIL PTV was 82.1Gy ± 0.12Gy in cohort A and 67.0 Gy ± 0.02Gy. All dose objectives for the DIL PTV were achieved in both cohorts, with all mandatory organ at risk doses accomplished (Table S4a and b).

The median (IQR) mean dose to the rectum was 38.0 (35.8-39.2) Gy in cohort A and 31.1 (29.6-31.7) Gy in cohort B and to bladder 21.5 (16.9-31.8) Gy and 23.2 (15.8-28.3) Gy respectively. Penile bulb median (IQR) volume was 3.5 (2.4-5.1) cm$^3$ in cohort A and 5.1 (3.6-6.2) cm$^3$ in cohort B, with a median (IQR) mean dose of 9.4 (7-18.5) Gy in cohort A and 11.9 (8.0-15.9) Gy in cohort B (Figure S1).

Primary endpoint

The cumulative 1-year incidence of Radiation Therapy Oncology Group (RTOG) grade 2 or worse rectal toxicity was 3.6% in Cohort A and 8.0 % in Cohort B. The calculated upper limit
for RTOG ≥ Grade 2 of a two-sided 90% confidence interval for Cohort A was 11% and for Cohort B 17%. There was no reported late grade 3 rectal toxicity in either cohorts by one year.

Acute RTOG toxicity

The acute toxicity seen within XXX was low with acute bowel and bladder RTOG grade ≥3 toxicity both ≤2% throughout weeks 0-18 (Figure S2). Rates of acute Grade 2 GI toxicity peaked at 11% in Cohort A and 10% in Cohort B in weeks 8 and 5 respectively (Figure 1). The wave of acute ≥ Grade 1 GI toxicity occurred sooner (peak week 4) and was more pronounced (64% max) in cohort B than Cohort A (peak week 7) (31%). Grade ≥ 1 and ≥2 acute GU toxicity were similar in Cohorts A and B but with peak reactions appearing earlier in cohort B (peak Grade 1+ at week 4) compared to Cohort A (peak Grade 1+ at week 6). One patient in Cohort B had Grade 4 GU toxicity (urinary catheter). No patient had acute GI toxicity ≥ Grade 4.

Late RTOG toxicity

Cumulative rates of late GI and GU toxicity are documented in Table 2. Cumulative late Grade 2+ RTOG GI toxicity was seen in 3.6% of Cohort A and 8% of Cohort B at one year. The prevalence of Grade ≥1 and Grade ≥2 RTOG GI toxicity was most different between the two cohorts at 6 months and similar by 12 months and thereafter (Figures 2A, S3A). No patients had ≥Grade 3 late GI toxicity. Figure 2B displays the cumulative risk of Grade ≥2 GI toxicity in
Cohorts A and B. Cumulative 2 and 3 year rates were 9.1% /12.0% and 12.8/14.0% respectively.

Cumulative late RTOG Grade ≥2 GU toxicity was seen in 0% of Cohort A and 10% of Cohort B at one year (Figure 2D). Prevalence of toxicity is shown in Figure 2C. There were similar and low rates of Grade ≥2 toxicity but Grade 1 side-effects appeared to persist in Cohort B. No Grade 3+ late toxicity was seen in either group at 1 year, but one patient had Grade 3 late GU toxicity at 18 months.

**Late toxicity - CTCAE**

There was no Grade 3+ late CTCAE GI toxicity recorded at any point during follow up (Figure S3). Two patients in Cohort A had Grade 3 late CTCAE GU toxicity (haematuria and urinary incontinence). There was no Grade 3+ late CTCAE GU toxicity in Cohort B, and no Grade 4+ late CTCAE GU toxicity in Cohort A.

**Erectile dysfunction (ED)**

Rates of ED increased after treatment. In Cohort A, at baseline (pre-ADT) 0% had Grade 3 CTCAE ED, but at 2 years 15% (8/55) had Grade 3 CTCAE ED. In Cohort B, at baseline (pre-ADT), 2% (1/50) had Grade 3 CTCAE ED but at 2 years, 26% (12/47) had Grade 3 ED.

**Patient reported outcomes**

There was no obvious effect of neoadjuvant ADT on IPSS, with pre-ADT median(IQR) IPSS total score being 6(4-10) and 5(4-13) in Cohort A and B respectively, and 5(3-9) and 8(4-12)
pre-radiotherapy respectively. There was no clear deterioration in IPSS after radiotherapy (Figure 3) with similar proportions showing improving or deteriorating scores. At one point the IPSS meets the criteria for a mild change in score (3 points \(^3\); at 18 months in Cohort B) but otherwise no significant changes are seen. Median (IQR) Vaizey score pre-ADT was 9 (9-10) in cohort A and 9 (9-11) in Cohort B, with the median score at 24 months of 10 (9-11) in Cohort A and 10 (9-12) in Cohort B, showing no substantial changes with treatment.

The EPIC questionnaire was only completed by patients in Cohort B, with no substantial change in median EPIC values for urinary incontinence, irritative or obstructive symptoms. Bowel symptoms were more pronounced post-RT particularly at month 12 but had returned to baseline by month 24. Sexual or hormonal domains showed deterioration from baseline at all time-points. (Figure S4).

**Biochemical recurrence**

Within Cohort A, four (8%) patients had BCR. Three of these patients had radiological evidence of disease recurrence; sites of recurrence were pelvic lymph nodes (1), solitary rib metastasis (1) and local recurrence (1).

**Discussion**

In this pre-planned interim analysis, we found that significant late toxicity was rarely seen in both standard and hypofractionated radiotherapy arms. In keeping with many other prostate radiotherapy contemporary series, urinary symptoms affected more patients than rectal symptoms, with patient reported outcomes having shown low levels of bowel and
urinary bother. Patient numbers were too small for definitive conclusions regarding efficacy, but rates of biochemical control appeared encouraging.

Toxicity rates appeared similar to those seen in other contemporary series (Table S5), including comparison with both boost and non-boost trials. We have focussed on 2 year cumulative RTOG GI Grade 2 toxicity to enable comparison with other contemporary trials and to enable conclusions to be drawn on relative toxicity. The CHHiP trial\textsuperscript{12} recorded a 2 year cumulative RTOG GI Grade 2 toxicity rate of 8.0\%(6.5-9.9\%) for 74Gy and 8.6\%(7.1-10.5\%) for 60Gy, compared to 9.1\%(3.9-20.5\%) and 12.0\%(5.6-24.8\%) seen here in Cohorts A and B respectively. Cumulative 2 year RTOG Grade 2 GU toxicity was 3.9\%(2.9-5.3\%) (74Gy) and 5.7\%(4.5-7.3\%) (60Gy) in CHHiP, compared to 7.3\% and 18\% in Cohorts A and B respectively. CHHiP Grade 3+ GU toxicity was 1.4\% and 4.2\% for 74 Gy and 60 Gy, compared to 1.8\% and 0\% for Cohorts A and B\textsuperscript{16}.

Whilst dose escalation to the whole prostate increases GI toxicity, this has not been clearly corroborated for GU toxicity\textsuperscript{32,33}. Rectal toxicity can be mitigated by increasing accuracy of delivery with image guidance, and by reducing margins posteriorly. The reduction in rectal toxicity observed over successive large phase III prostate radiotherapy trials is likely due to this increase in accuracy combined with the development and strict application of dose constraints. It has also been suggested that image guided radiotherapy may reduce urinary symptoms\textsuperscript{34}, however, the determinants of genitourinary toxicity remain an enigma. Various structures have been proposed to be responsible, including bladder (whole or trigone) and the urethra. As yet no dose constraint has been reproducibly shown to predict toxicity, although some correlation with bladder surface doses \textgtr 80Gy\textsuperscript{35} and increased maximal dose
to the trigone (>90.9Gy) has been reported. The maximum planned dose to the bladder in these patients treated within XXX was 83.6Gy and 66.9Gy in cohorts A and B respectively.

Concept of boosting the dominant intra-prostatic lesion is gaining momentum, as other centres prove feasibility and tolerability. The largest published series is the FLAME trial which dose-escalated the DIL to 95Gy and showed no difference in toxicity compared to a no-boost technique (77Gy in 35 fractions). They reported late cumulative Grade 2+ GI and GU toxicity by 2 years after treatment as 10.2% and 27.1% respectively in the boost arm and 11.2% and 22.6% respectively in the standard arm; efficacy data is awaited.

With several studies now seeking to test if profoundly hypofractionated radiotherapy (5-7 fractions) is equivalent to 20+ fractions, and other Phase II studies exploring ultrahypofractionation with 2 fractions, there is a need to test similar boost techniques with stereotactic body radiotherapy (SBRT). The optimal boost dose and schedule is not known, although previous work suggests that 95% tumour control probability requires doses in excess of 95Gy EQD2, which is exceeded by standard SBRT doses of 40Gy in 5 fractions. A small Phase 1a/b study of 9 patients has recently been published, delivering a boost dose of up to 50 Gy in 5 fractions (delivered twice per week) using a biodegradable spacer device. No dose-limiting toxicity, defined as Grade 3+ GU or GI toxicity within 90 days, was seen. They also excluded patients with tumours located within 3mm of the urethra. No grade 3 or worse toxicity was reported, with median follow up of 24 months.

Larger trials that address the questions around optimal SBRT boost dose and schedule are in progress (XXX-HYPO, alternate day treatment delivering 36.25Gy to prostate PTV, 40Gy to
prostate CTV with an isotoxic DIL boost to 45Gy; HYPO-FLAME, delivering 35Gy to the prostate and up to 50Gy (isotoxic) to the DIL in 5 weekly fractions).

We recognise the limitations of our study. Significant toxicity after prostate radiotherapy is now rare, so this study is underpowered to demonstrate equivalence to standard techniques. Concordant with this, the rate of events is low, limiting our ability to draw conclusions about preferred fractionation or predictive dosimetry. As a single centre trial, the toxicity results seen here may not be generalisable to a wider variety of centres.

The efficacy of a DIL boost using the same technique as Cohort B is also under investigation in a UK randomised phase III trial. Men with intermediate and high-risk prostate cancer are being randomised to a boost versus no boost, and also to a second randomisation to prophylactic pelvic nodal irradiation or prostate alone radiotherapy. The optimal method for delivering a boost (IMRT or HDR brachytherapy) is also being evaluated in the PIVOTAL boost (ISRCTN80146950) trial.

In conclusion, we have shown that delivery of a simultaneous integrated boost to DILs is feasible, with GI and GU toxicity comparable to contemporary series without a boost. Further analysis of this trial and others will interrogate whether biochemical relapse-free survival is impacted by a boost technique.

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**Figure Captions**

Figure 1: Acute RTOG toxicity by timepoint and cohort. Grade distribution (%) of (A) rectal adverse events and (C) urinary adverse events measured with RTOG and (B) prevalence (%) of rectal toxicity, (D) prevalence (%) of urinary toxicity.

Figure 2: Late RTOG toxicity by timepoint and cohort. Grade distribution (%) of (A) rectal adverse events and (C) urinary adverse events measured with RTOG and cumulative incidence of (B) rectal toxicity and (D) urinary toxicity.
Figure 3: (A) IPSS total score median and IQR at all time points for cohort A and B and (B) waterfall plot showing change from pre-radiotherapy total IPSS score to 24 months post radiotherapy by cohort.
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<td></td>
<td>7 40 (73%)</td>
<td>34 (68%)</td>
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<tr>
<td></td>
<td>8 2 (4%)</td>
<td>3 (6%)</td>
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<td>Current smoker 5 (9%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td><strong>Intended ADT</strong></td>
<td>150mg bicalutamide 3 (5.5%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td></td>
<td>long term LHRHa + short term AA 3 (5.5%)</td>
<td>13 (26%)</td>
</tr>
<tr>
<td></td>
<td>Short term LHRHa + temporary AA 49 (89%)</td>
<td>36 (72%)</td>
</tr>
<tr>
<td><strong>Weeks from hormone start to radiotherapy</strong></td>
<td>Median (IQR) 17 (16 – 19)</td>
<td>17 (15 – 20)</td>
</tr>
<tr>
<td><strong>Weeks from trial registration to radiotherapy</strong></td>
<td>Median (IQR) 20 (17 – 22)</td>
<td>16.5 (14 – 18)</td>
</tr>
<tr>
<td><strong>Days of radiotherapy</strong></td>
<td>Median (IQR) 52 (50 – 55)</td>
<td>27 (27 – 28)</td>
</tr>
<tr>
<td><strong>Prostate volume pre-ADT (cm³)</strong></td>
<td>Median (IQR) 45 (32-59)</td>
<td>43 (32-55)</td>
</tr>
<tr>
<td><strong>DIL volume (cm³) at baseline MRI</strong></td>
<td>Median (IQR) 2.4 (1.3-4.0)</td>
<td>1.7 (0.9-2.9)</td>
</tr>
<tr>
<td><strong>Worst CTCAE GI grade pre-RT</strong></td>
<td>Grade 0 43 (78%)</td>
<td>38 (81%)</td>
</tr>
<tr>
<td></td>
<td>Grade 1 11 (20%)</td>
<td>8 (17%)</td>
</tr>
<tr>
<td></td>
<td>Grade 2 1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Worst CTCAE GU grade pre-RT</strong></td>
<td>Grade 0 41 (75%)</td>
<td>38 (81%)</td>
</tr>
<tr>
<td></td>
<td>Grade 1 14 (25%)</td>
<td>8 (17%)</td>
</tr>
<tr>
<td></td>
<td>Grade 2 0</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

Table 1: Patient and tumour characteristics of patients treated within Cohort A and B (* by digital rectal examination)
<table>
<thead>
<tr>
<th></th>
<th>Cumulative RTOG rectal toxicity</th>
<th>Cumulative RTOG urinary toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1+ Grade 2+ Grade 3+</td>
<td>Grade 1+ Grade 2+ Grade 3+</td>
</tr>
<tr>
<td>1 year proportion (%; 95% CI)</td>
<td>20.0 (11.6, 33.2) 3.6 (0.9, 13.8) 0</td>
<td>9.1 (3.9, 20.5) 0 0</td>
</tr>
<tr>
<td>2 year proportion (%; 95% CI)</td>
<td>40.0 (28.5, 54.1) 9.1 (3.9, 20.5) 0</td>
<td>20.0 (11.6, 33.2) 7.3 (2.8, 18.2) 1.8 (0.3, 12.2)</td>
</tr>
<tr>
<td>3 year proportion (%; 95% CI)</td>
<td>41.8 (30.1, 55.9) 12.8 (6.3, 25.1) 0</td>
<td>25.6 (16.0, 39.4) 9.1 (3.9, 20.6) 1.8 (0.3, 12.2)</td>
</tr>
</tbody>
</table>

Table 2a: Cumulative RTOG rectal and urinary toxicity for Cohort A. RTOG = Radiation Therapy Oncology Group.

<table>
<thead>
<tr>
<th></th>
<th>Cumulative RTOG rectal toxicity</th>
<th>Cumulative RTOG urinary toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1+ Grade 2+ Grade 3+</td>
<td>Grade 1+ Grade 2+ Grade 3+</td>
</tr>
<tr>
<td>1 year proportion (%; 95% CI)</td>
<td>34.0 (22.7, 48.9) 8.0 (3.1, 19.9) 0</td>
<td>16.0 (8.3, 29.5) 10.0 (4.3, 22.4) 0</td>
</tr>
<tr>
<td>2 year proportion (%; 95% CI)</td>
<td>42.0 (29.8, 56.8) 12.0 (5.6, 24.8) 0</td>
<td>32.0 (21.0, 46.8) 18.0 (9.8, 31.7) 0</td>
</tr>
<tr>
<td>3 year proportion (%; 95% CI)</td>
<td>56.1 (43.0, 70.0) 14.0 (6.9, 27.1) 0</td>
<td>50.1 (37.2, 64.5) 22.1 (12.9, 36.3) 0</td>
</tr>
</tbody>
</table>

Table 2b: Cumulative RTOG rectal and urinary toxicity for Cohort B. RTOG = Radiation Therapy Oncology Group.
Figure 1: Acute RTOG toxicity by timepoint and cohort. Grade distribution (%) of (A) rectal adverse events and (C) urinary adverse events measured with RTOG and (B) prevalence (%) of rectal toxicity, (D) prevalence (%) of urinary toxicity.
Figure 2: Late RTOG toxicity by timepoint and cohort. Grade distribution (%) of (A) rectal adverse events and (C) urinary adverse events measured with RTOG and cumulative incidence of (B) rectal toxicity and (D) urinary toxicity.
Figure 3: (A) IPSS total score median and IQR at all time points for cohort A and B and (B) waterfall plot showing change from pre-radiotherapy total IPSS score to 24 months post radiotherapy by cohort.