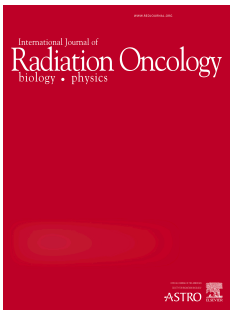

Standard and hypofractionated dose escalation to intraprostatic tumour nodules in localised prostate cancer: efficacy and toxicity in the DELINEATE trial

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19, outside the submitted work; 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.
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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 intra-prostatic 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[16].

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[17] 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[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)[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[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[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 [16]. 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 [31]; 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[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[16].

Whilst dose escalation to the whole prostate increases GI toxicity, this has not been clearly corroborated for GU toxicity[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[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 >80Gy[35] and increased maximal dose

to the trigone (>90.9Gy) [36] 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[37]. The largest published series is the FLAME trial[38] 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[39,40], and other Phase II studies exploring ultrahypofractionation with 2 fractions[41], 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[42], which is exceeded by standard SBRT doses of 40Gy in 5 fractions. A small Phase 1a/b study[43] 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.

References

1. Wolff RF, Ryder S, Bossi A, Briganti A, Crook J, Henry A, et al. A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer. Eur J Cancer. 2015;51(16):2345–67.
2. Dearnaley DP, Jovic G, Syndikus I, Khoo V, Cowan RA, Graham JD, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. Lancet Oncol [Internet]. 2014;15(4):464–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24581940
3. Michalski JM, Moughan J, Purdy J, Bosch W, Bahary J-P, Lau HY, et al. A randomized trial of 79.2Gy versus 70.2Gy radiation therapy (RT) for localized prostate cancer. J Clin Oncol [Internet]. 2015 Mar 1;33(7_suppl):4. Available from: http://dx.doi.org/10.1200/jco.2015.33.7_suppl.4
4. Heemsbergen WD, Al-Mamgani A, Slot A, Dielwart MFH, Lebesque J V. Long-term results of the Dutch randomized prostate cancer trial: Impact of dose-escalation on local, biochemical, clinical failure, and survival. Radiother Oncol. 2014;110(1):104–9.
5. Cellini N, Morganti AG, Mattiucci GC, Valentini V, Leone M, Luzi S, et al. Analysis of intraprostatic failures in patients treated with hormonal therapy and radiotherapy: implications for conformal therapy planning. Int J Radiat Oncol Biol Phys [Internet]. 2002/06/14. 2002;53(3):595–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12062602
6. Pucar D, Hricak H, Shukla-Dave A, Kuroiwa K, Drobnjak M, Eastham J, et al. Clinically significant prostate cancer local recurrence after radiation therapy occurs at the site of primary tumor: magnetic resonance imaging and step-section pathology evidence. Int J Radiat Oncol Biol Phys [Internet]. 2007/08/21. 2007;69(1):62–9. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/17707266

7. Arrayeh E, Westphalen AC, Kurhanewicz J, Roach 3rd M, Jung AJ, Carroll PR, et al. Does Local Recurrence of Prostate Cancer After Radiation Therapy Occur at the Site of Primary Tumor? Results of a Longitudinal MRI and MRSI Study. Int J Radiat Oncol Biol Phys [Internet]. 2012/02/15. 2012; Available from: http://www.ncbi.nlm.nih.gov/pubmed/22331003

8. Riches SF, Payne GS, Morgan VA, Dearnaley D, Morgan S, Partridge M, et al. Multivariate modelling of prostate cancer combining magnetic resonance derived T2, diffusion, dynamic contrast-enhanced and spectroscopic parameters. Eur Radiol. 2015;

9. Pathmanathan AU, Alexander EJ, Huddart RA, Tree AC. The delineation of intraprostatic boost regions for radiotherapy using multimodality imaging. Futur Oncol [Internet]. 2016 Nov;12(21):2495–511. Available from: https://www.futuremedicine.com/doi/10.2217/fon-2016-0129

10. Scheltema MJ, Chang JI, Stricker PD, van Leeuwen PJ, Nguyen QA, Ho B, et al. Diagnostic accuracy of (68) Ga-prostate-specific membrane antigen (PSMA) positron-emission tomography (PET) and multiparametric (mp)MRI to detect intermediate-grade intra-prostatic prostate cancer using whole-mount pathology: impact of the addition of (68) Ga-PSMA PET to mpMRI. BJU Int. 2019 Jul;

11. Zamboglou C, Sachpazidis I, Koubar K, Drendel V, Wiehle R, Kirste S, et al. Evaluation of intensity modulated radiation therapy dose painting for localized prostate cancer using (68)Ga-HBED-CC PSMA-PET/CT: A planning study based on histopathology reference. Radiother Oncol. 2017 Jun;123(3):472–7.

12. 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.

13. Catton CN, Lukka H, Gu CS, Martin JM, Supiot S, Chung PWM, et al. Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer. Int J Clin Oncol. 2017/03/16. 2017;35(17):1884–90.

14. Lee WR, Dignam JJ, Amin MB, Bruner DW, Low D, Swanson GP, et al. Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. J Clin Oncol. 2016;34(20):2325–32.

15. Incrocci L, Wortel RC, Alemayehu WG, Aluwini S, Schimmel E, Krol S, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol. 2016;17(8):1061–9.

16. 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 [Internet]. 2011/12/16. 2012;13(1):43–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22169269

17. Dickinson L, Ahmed HU, Allen C, Barentsz JO, Carey B, Futterer JJ, et al. Magnetic Resonance Imaging for the Detection, Localisation, and Characterisation of Prostate Cancer: Recommendations from a European Consensus Meeting. Eur Urol [Internet]. 2011/01/05. 2010; Available from: http://www.ncbi.nlm.nih.gov/pubmed/21195536

18. Alexander EJ, Murray JR, Morgan VA, Giles SL, Riches SF, Hazell S, et al. Validation of T2- and diffusion-weighted magnetic resonance imaging for mapping intra-prostatic

tumour prior to focal boost dose-escalation using intensity-modulated radiotherapy (IMRT). Radiother Oncol. 2019 Sep;

19. Dearnaley DP, Sydes MR, Graham JD, Aird EG, Bottomley D, Cowan RA, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. Lancet Oncol [Internet]. 2007/05/08. 2007;8(6):475–87. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17482880

20. Seppala J, Seppanen M, Arponen E, Lindholm P, Minn H. Carbon-11 acetate PET/CT based dose escalated IMRT in prostate cancer. Radiother Oncol [Internet]. 2009/09/22. 2009;93(2):234–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19766336

21. 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) [Internet]. 2008;20(1):15–21. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18054471

22. 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 [Internet]. 2003/08/07. 2003;13(3):176–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12903007

23. 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 [Internet]. 2007/03/30. 2007;83(1):31–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17391791

24. Gulliford SL, Partridge M, Sydes MR, Andreyev J, Dearnaley DP. A comparison of dose-volume constraints derived using peak and longitudinal definitions of late rectal toxicity. Radiother Oncol [Internet]. 2010/01/26. 2010;94(2):241–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20096945

25. 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):1007–12.

26. Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology [Internet]. 1989/03/01. 1989;96(3):804–10. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2644154

27. Vaizey CJ, Carapeti E, Cahill JA, Kamm MA. Prospective comparison of faecal incontinence grading systems. Gut [Internet]. 1998/12/24. 1999;44(1):77–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9862829

28. Barry MJ, Fowler Jr. FJ, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol [Internet]. 1992/11/11. 1992;148(5):1549–57; discussion 1564. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1279218

29. 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 [Internet]. 2010;76(5):1245–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20350762

30. Roach M, Hanks G, Thames H, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys. 2006;65(4):965–74.

31. Rees J. Patients not P values. 2015;678–9.

32. Dearnaley DP, Sydes MR, Graham JD, Aird EG, Bottomley D, Cowan RA, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. Lancet Oncol. 2007;8(6):475–87.

33. Michalski JM, Bae K, Roach M, Markoe AM, Sandler HM, Ryu J, et al. Long-term toxicity following 3D conformal radiation therapy for prostate cancer from the RTOG 9406 phase I/II dose escalation study. Int J Radiat Oncol Biol Phys [Internet]. 2009/07/07. 2010;76(1):14–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19577865

34. 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 [Internet]. 2012/02/15. 2012;84(1):125–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22330997

35. Heemsbergen WD, Al-Mamgani A, Witte MG, van Herk M, Pos FJ, Lebesque J V. Urinary obstruction in prostate cancer patients from the Dutch trial (68 Gy vs. 78 Gy): relationships with local dose, acute effects, and baseline characteristics. Int J Radiat Oncol Biol Phys [Internet]. 2010/01/09. 2010;78(1):19–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20056354

36. Ghadjar P, Zelefsky MJ, Spratt DE, Munck Af Rosenschöld P, Oh JH, Hunt M, et al. Impact of dose to the bladder trigone on long-term urinary function after high-dose intensity modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2014;88(2):339–44.

37. Onjukka E, Uzan J, Baker C, Howard L, Nahum A, Syndikus I. Twenty Fraction Prostate Radiotherapy with Intra-prostatic Boost: Results of a Pilot Study. Clin Oncol. 2017;29(1):6–14.

38. Monninkhof EM, van Loon JWL, van Vulpen M, Kerkmeijer LGW, Pos FJ, Haustermans K, et al. Standard whole prostate gland radiotherapy with and without lesion boost in prostate cancer: Toxicity in the FLAME randomized controlled trial. Radiother Oncol. 2018;

39. Widmark A, Gunnlaugsson A, Beckman L, Thellenberg-Karlsson C, Hoyer M, Lagerlund M, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet (London, England). 2019 Aug;394(10196):385–95.

40. Brand DH, Tree AC, Ostler P, van der Voet H, Loblaw A, Chu W, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. Lancet Oncol. 2019 Nov;20(11):1531–43.

41. Alayed Y, Cheung P, Chu W, Chung H, Davidson M, Ravi A, et al. Two StereoTactic ablative radiotherapy treatments for localized prostate cancer (2STAR): Results from a prospective clinical trial. Radiother Oncol. 2019 Jun;135:86–90.

42. Tree AC, Khoo VS, van As NJ, Partridge M. Is Biochemical Relapse-free Survival After Profoundly Hypofractionated Radiotherapy Consistent with Current Radiobiological Models? Clin Oncol. 2014;

43. Herrera FG, Valerio M, Berthold D, Tawadros T, Meuwly JY, Vallet V, et al. 50-Gy Stereotactic Body Radiation Therapy to the Dominant Intraprostatic Nodule: Results From a Phase 1a/b Trial. Int J Radiat Oncol Biol Phys. 2019;

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.

		Cohort A (n=55)	Cohort B (n=50)
Age at registration	Median (range)	70 (57 – 80)	71.5 (61 – 79)
Risk group	Intermediate n (%)	40 (73%)	30 (60%)
	High n(%)	15 (27%)	20 (40%)
Gleason score	<=6	13 (24%)	13 (26%)
	7	40 (73%)	34 (68%)
	8	2 (4%)	3 (6%)
Clinical T-stage*	T1	20 (36%)	24 (48%)
	T2a	6 (11%)	14 (28%)
	T2b	18 (33%)	0 (0%)
	T2c	5 (9%)	2 (4%)
	T3a	6 (11%)	10 (20%)
Pre-hormone PSA (ng/ml)	Median (IQR)	11 (7.4 – 17)	11.8 (7.9 – 17)
Co-morbidities	Diabetes	2 (4%)	15 (30%)
	Hypertension	21 (38%)	27 (54%)
	IBD/Diverticular	2 (4%)	8 (16%)
	Pelvic surgery	4 (7%)	12 (24%)
	Haemorrhoids	11 (20%)	2 (4%)
	Previous TURP	5 (9%)	4 (8%)
	Statins	20 (36%)	24 (48%)
	Current smoker	5 (9%)	4 (8%)
Intended ADT	150mg bicalutamide	3 (5.5%)	1 (2%)
	long term LHRHa + short term AA	3 (5.5%)	13 (26%)
	Short term LHRHa + temporary AA	49 (89%)	36 (72%)
Weeks from hormone start to radiotherapy	Median (IQR)	17 (16 – 19)	17 (15 – 20)
Weeks from trial registration to radiotherapy	Median (IQR)	20 (17 – 22)	16.5 (14 – 18)
Days of radiotherapy	Median (IQR)	52 (50 – 55)	27 (27 – 28)
Prostate volume pre-ADT (cm^3)	Median (IQR)	45 (32-59)	43 (32-55)
DIL volume (cm^3) at baseline MRI	Median (IQR)	2.4 (1.3-4.0)	1.7 (0.9-2.9)
Worst CTCAE GI grade pre-RT	Grade 0 Grade 1 Grade 2	43 (78%) 11 (20%) 1 (2)	38 (81%) 8 (17%) 1 (2%)
Worst CTCAE GU grade pre-RT	Grade 0 Grade 1 Grade 2	41 (75%) 14 (25%) 0	38 (81%) 8 (17%) 1 (2%)

Table 1: Patient and tumour characteristics of patients treated within Cohort A and B (* by digital rectal examination)

	Cumulative RTOG rectal toxicity			Cumulative RTOG urinary toxicity		
	Grade 1+	**Grade 2+**	**Grade 3+**	**Grade 1+**	**Grade 2+**	**Grade 3+**
1 year proportion (%; 95% CI)	20.0 (11.6, 33.2)	3.6 (0.9, 13.8)	0	9.1 (3.9, 20.5)	0	0
2 year proportion (%; 95% CI)	40.0 (28.5, 54.1)	9.1 (3.9, 20.5)	0	20.0 (11.6, 33.2)	7.3 (2.8, 18.2)	1.8 (0.3, 12.2)
3 year proportion (%; 95% CI)	41.8 (30.1, 55.9)	12.8 (6.3, 25.1)	0	25.6 (16.0, 39.4)	9.1 (3.9, 20.6)	1.8 (0.3, 12.2)

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

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

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

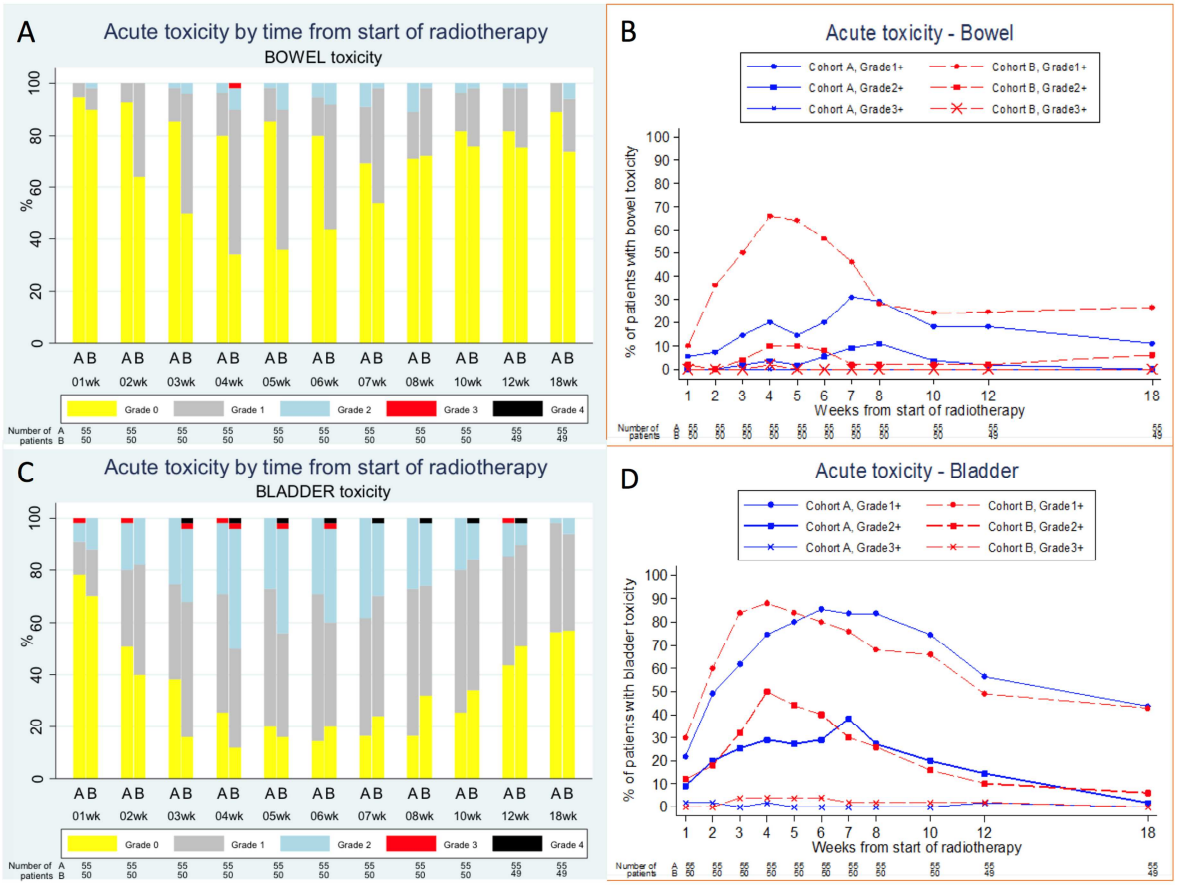

Figure 1: Acute RTOG toxicity by timepoint and cohort. Grade distribution (%) of (A) rectal adverse events and (C) urinary adverse events measured with RTOG and (B) prevalence (%) of rectal toxicity, (D) prevalence (%) of urinary toxicity.

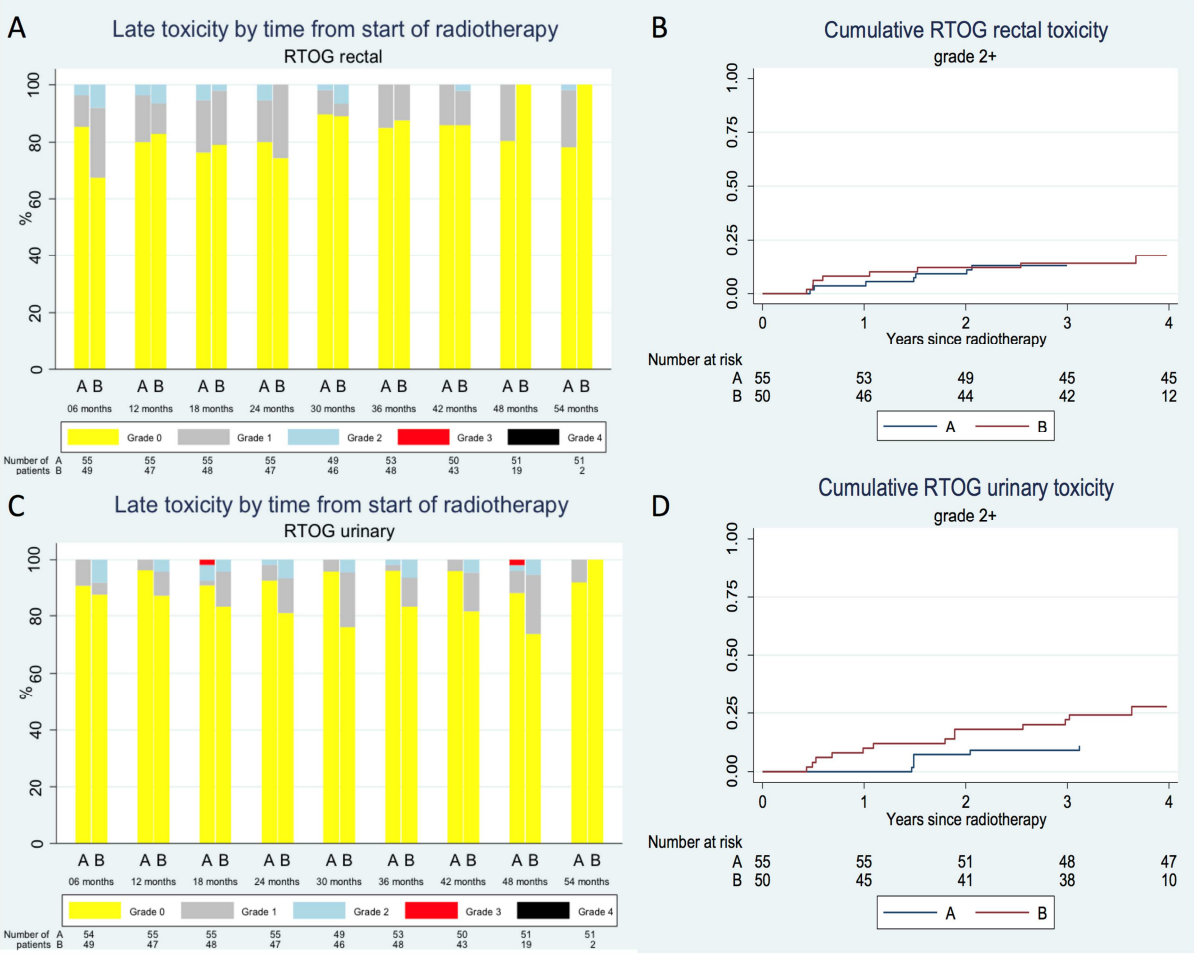

Figure 2: Late RTOG toxicity by timepoint and cohort. Grade distribution (%) of (A) rectal adverse events and (C) urinary adverse events measured with RTOG and cumulative incidence of (B) rectal toxicity and (D) urinary toxicity.

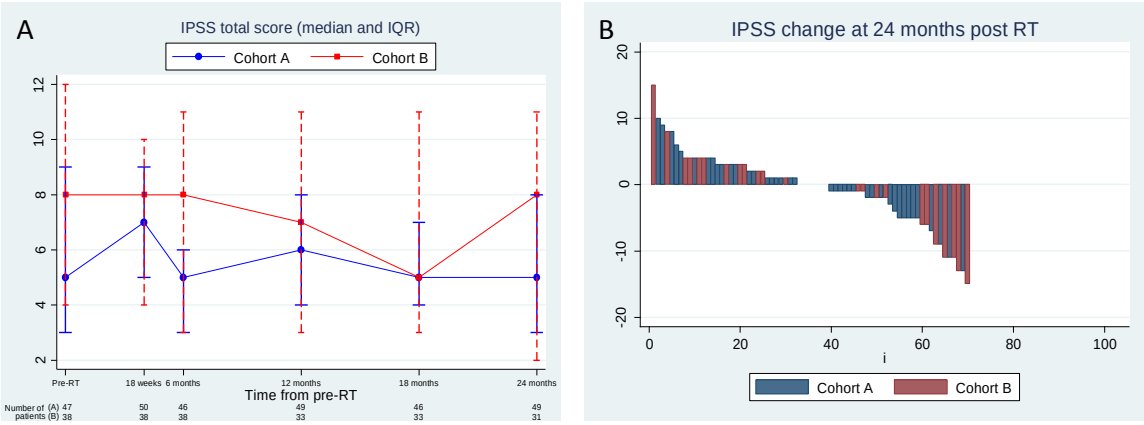

Figure 3: (A) IPSS total score median and IQR at all time points for cohort A and B and (B) waterfall plot showing change from pre-radiotherapy total IPSS score to 24 months post radiotherapy by cohort.