Introduction

Prostate cancer is the most common cancer among men in the developed world [1,2] and radiotherapy is a curative treatment option. Conventional radiotherapy dose is limited by both acute and late side effects in organs at risk (OAR) located in close proximity to the target volume and conformal radiotherapy (3DCRT) gave the opportunity for dose escalation [3]. There is a clear relationship between increasing radiation dose and improved clinical outcome (biochemical progression-free survival) [4]. Intensity modulated radiotherapy (IMRT) has proven a powerful technique in terms of its dosimetric benefits for complex treatment sites, and has become widely adopted for the treatment of prostate cancer [5-8].

CHHiP (Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy In Prostate Cancer; CRUK/06/016) is a randomised phase III trial in men with localised prostate cancer which has demonstrated that hypofractionated radiotherapy (60 Gray (Gy) / 20 fractions (f)) is safe and non-inferior to conventionally fractionated (74Gy/37f) in terms of time to biochemical/clinical failure [9] . Radiotherapy treatment within CHHiP employed a complex target volume treated with IMRT. When the trial was initiated in 2002, IMRT was a relatively new technique in the UK, unavailable or restricted in clinical application at many centres [7]. Hence forward-planned (FP) techniques as well as inverse-planned (IP) IMRT were permitted. The FP technique used a multi-segment 3-field plan with optimal beam angles which had been compared with the 2 phase 3DCRT technique utilised in the previous Medical Research Council (MRC) RT01 trial [4,10]. All CHHiP FP plans produced lower mean irradiated rectal volumes at all measured dose levels compared with the RT01 plans and also gave lower mean irradiated bladder volumes at both 50 and 60Gy.

The study reported here compares dose-volume histogram (DVH) and rectum and bladder toxicity data for patients planned and treated using FP and IP techniques in the CHHiP trial. The aim was to determine if there were any systematic differences resulting from the two planning techniques. The analyses were planned and conducted in two stages. The first stage analysed dosimetry data to determine the relative merits of FP and IP on rectal and bladder DVHs; the second stage investigated whether any differences in the DVH data translated into clinically observable benefits in terms of a reduction in side effects.

Materials and Methods

Trial design

Full details of the CHHiP trial design, eligibility and treatment have been previously reported [9]. Briefly, men with histologically confirmed T1b-T3a,N0,M0 prostate cancer [11], suitable for radiotherapy were eligible. Patients were randomised (in a 1:1:1 ratio) to conventional fractionation (74Gy/37f over 7.4 weeks), or one of two hypofractionated schedules 60Gy/20fr/4.0weeks or 57Gy/19fr/3.8weeks). Randomisation was stratified by National Comprehensive Cancer Network (NCCN) risk-classification (low vs intermediate vs high) [12] and radiotherapy treatment centre. Treatment allocation was not masked.

Treatment details [13]

Target volumes and doses are summarised in Appendix 1, with the core high dose region receiving the target dose of 74Gy, 60Gy or 57Gy in accordance with allocated treatment.

Patients were CT scanned at ≤5mm intervals with comfortably full bladder and empty rectum, using approved immobilisation methods. Radiotherapy treatment employed either a single-phase FP method (field-in-field or segmented field arrangement with 3 beam angles) or 5 field IP IMRT, with “step and shoot” or “dynamic leaf” delivery. (Rotational arc delivery was permitted but was not widely used at the time of the trial).

OARs included bladder, rectum, bowel, and femoral heads. The entire bladder was outlined. The outer wall of the rectum was outlined from the anus (at the level of the ischial tuberosities or 1cm below the lower margin of the planning target volume (PTV), whichever was more inferior) to the recto-sigmoid junction. OAR dose constraints were applied for treatment plan (TP) optimisation, defined for the conventional fractionation arm and linearly scaled to the same percentage of prescribed dose for the hypofractionated schedules. The rectum dose constraints were V74Gy<3%, V70Gy<15%, V65Gy<30%, V60Gy<50%, V50Gy<60%. The bladder dose constraints were V74Gy<5%, V60Gy<25% and V50Gy<50%. A Plan Assessment Form (PAF) was completed by the treatment centre for each patient TP, which provided a synopsis of DVH data for PTVs and OARs.

Planning methods, treatment delivery and verification techniques used within each centre were identical for each fractionation regime and were reviewed and approved in advance by the national Radiotherapy Trials Quality Assurance (RTTQA) Group. Within a centre different planning techniques were permitted for low and intermediate/high risk groups.

Patients

CHHiP was conducted in three stages; this report utilises toxicity data from stages 1 and 2 (safety) which between October 18, 2002 and August 12, 2006 recruited 457 patients from 11 UK centres using 6 different treatment planning systems (TPS) [13]]. Radiotherapy planning data were available for 442/457 patients; 337 had intermediate risk and 105 low risk disease. The 105 low risk patients were excluded from all analyses due to small numbers of IP patients (15/105) (Figure 1).

Statistical considerations

Volume-matching procedure

To reduce the potential for bias in the non-randomised comparisons of planning technique, analysis sets balanced for key variables that might affect the relationship between planning method and radiation dose to the bladder/rectum were defined. In particular, the centre treating the majority of IP patients was unique in using daily rectal micro-enemas, and there was significant variability between centres in the drinking volumes recommended by their bladder preparation procedures (200-750ml). PTV volume differences resulting from the margin-growing algorithms of the various TPSs have also been reported [14]. IP and FP patients were matched (1:1) using two volume parameters, each divided into six volume bands. For rectum DVH analyses patients were matched according to PTV1 volume (including seminal vesicles (SV)) and rectal volume; for bladder DVH analyses PTV2 and bladder volumes were used for matching.

DVH Comparison

Dose-volume data recorded on the PAF for the rectum and bladder were compared. Although the three trial treatment groups differed in prescription dose and fractionation, the dose constraints, when scaled as a percentage of the prescribed dose, were identical, and each treatment group was planned and normalised in the same way within a treatment centre. DVH

data could thus be compared directly in this planning study using relative dose without regard for treatment group. Descriptive statistics and boxplots were used to summarise the DVH data. The Mann-Whitney test was used to compare the distribution of data at each dose level between planning methods.

Toxicity Comparison

The second stage was to investigate whether any observed differences in normal tissue dosimetry were associated with normal tissue toxicity. Dose and fractionation could potentially bias these results and so, for toxicity analysis, patients were additionally matched according to treatment dose schedule.

Acute side effects were assessed using the Radiation Therapy Oncology Group (RTOG) scoring system for acute toxicity [15] completed weekly during treatment and at weeks 10, 12 and 18 from radiotherapy start date. Late side effects were assessed at 6, 12, 18 and 24 months using RTOG, the Late Effects on Normal Tissues: Subjective: Objective/Management (LENT/SOM) and Royal Marsden Hospital (RMH) scoring systems [16-18]. Patient Reported Outcomes (PRO) were assessed prior to trial entry, pre-radiotherapy and at week 10, and 6, 12, 18, and 24 months post-radiotherapy using the UCLA Prostate Cancer Index (PCI) questionnaire [19]. The primary toxicity endpoint for this analysis was grade 2 or greater (G2+) RTOG bladder or bowel toxicity experienced two years from the start of radiotherapy.

Baseline characteristics were summarised using descriptive statistics and, as the two groups were not generated by random allocation, statistical comparisons were made between the groups using chi-squared or Mann-Whitney tests as appropriate. Patients were only included in toxicity analyses if they received at least one fraction of radiotherapy.

Toxicity and PRO data are presented as grade distributions at each time point and compared using Mann-Whitney tests. The proportion of patients with G2+ RTOG bladder or bowel toxicity at 2 years is presented together with exact binomial confidence intervals (CI). Time from radiotherapy start date to first occurrence of G1+ toxicity was analysed using Kaplan-Meier methods used to estimate the cumulative proportion with an event at 2 years. All data reported were used; patients with no event were censored on the date of last toxicity assessment. Cox proportional hazard models were used to estimate and test the effect of planning method (using the Wald test) with a hazard ratio (HR) of less than 1 favouring IP. The proportion hazards assumption was found to hold for all time-to-event analyses reported. Change in PRO scores between pre-radiotherapy assessment and two years were calculated and are presented graphically.

All analyses are exploratory in nature, however statistical analysis plans were written prior to conducting each of the pre-planned stages. A significance level of 1% was used to allow for multiple testing. Analyses were based on a database snapshot taken on 01/04/2010 and were conducted using Stata version 11.2.

Results

Volume-matching

There was considerable imbalance between the rectum, bladder, and PTV volumes in the FP and IP groups, with larger volumes for all four structures in the FP group. Following the volume-matching process there were no significant differences between FP and IP groups ($p>0.05$ for rectum, bladder, PTV1 and PTV2 volumes (Appendix 2). 78 FP-IP pairs of patients were

matched on rectum and PTV1 volume (i.e. 156/337 available patient datasets), and 86 pairs matched on bladder and PTV2 volume (172/337). Following additional matching on trial treatment allocation the number of pairs for toxicity analyses was reduced further to 53 for the rectum dataset (106/337) and 61 for the bladder (122/337) (Appendix 3). There was reasonable balance in the clinical baseline characteristics of the matched datasets (Appendix 4). Initial PSA levels were lower in the IP group for the bladder but not rectum subset. More patients in the FP group required a modification to the posterior target volume margins in both rectum (FP 4(8%): IP 0(0%)) and bladder (FP 6(10%): IP 1 (2%)) subsets. Derivation of the patients datasets for analysis are summarised in Figure 1.

DVH analysis

For the rectum (Figure 2A), IP patients had significantly smaller volumes of their rectum irradiated to doses of 50Gy (median: 43.7% FP, 27.2% IP), 60Gy (median: 34.3% FP, 16.0% IP), 65Gy (median: 22.1% FP, 9.5% IP) and 70Gy (median: 6.3% FP, 2.9% IP) compared to FP patients ($p<0.001$). No difference was apparent at 74Gy due to the small volumes receiving this dose. In contrast, IP patients had significantly larger volumes of bladder irradiated to 74Gy (median 1.7% FP, 3.2% IP) than FP patients ($p=0.001$) (Figure 2B). Differences between bladder volumes irradiated to 50Gy and 60Gy were not statistically significant, but IP tended to result in lower bladder DVH volumes at these doses.

Toxicity

There was a statistically significant difference in the worst acute bowel toxicity ($p=0.0002$) with 52% (27/52) FP compared to 21% (11/53) IP experiencing a G2+ toxicity during the first 18 weeks from start of radiotherapy (Figure 3A). Late toxicity was low with both planning methods with 0/49 (0%; 95%CI 0-7.2%) and 1/50 (2.0%; 95%CI 0.1-10.6%) RTOG bowel G2+ events in the FP and IP groups respectively at 2 years (Table 1). The RMH and LENT-SOM tools suggested benefits for IP at almost all time points from 6 to 24 months (Table 1) though the only statistically significant difference was for LENT-SOM assessment at 18 months ($p=0.008$). Time to first post-radiotherapy G1+ RMH and LENT-SOM bowel toxicity was reduced for FP patients compared to IP (RMH G1+: HR=0.40; 95%CI 0.21-0.73; $p=0.003$; LENTSOM G1+: HR=0.48; 95%CI 0.27-0.84; $p=0.01$) though this was not seen with RTOG assessment (Figure 4 and Appendix 5). However, there was no difference for G2+ or G3+ events using any scoring system (Appendix 5), but the number of events was very small. PROs showed an approximate doubling of “overall bowel problems”, “distress” and “rectal urgency” at week 10, in keeping with the physician based scores. However no consistent differences in PROs between planning methods remained from months 6 to 24 when outcomes appeared very favourable in both groups (Table 2). Change scores from pre-radiotherapy to 24 months confirmed the generally favourable bowel outcomes and similarities between planning methods (Appendix 6).

For the bladder dataset, there was no evidence of a difference in the worst acute bladder toxicity ($p=0.709$) with 45% (27/60) FP and 46% (28/61) IP patients experiencing G2+ toxicity during the first 18 weeks (Figure 3B). However, G1+ toxicity was higher at all timepoints from weeks 1-18 in the IP Group. There was no evidence of a difference for G2+ late bladder toxicity (Table 1) which was low in both groups. At 2 years, RTOG G2+ bladder toxicity was reported in 0/54 (0%; 95%CI 0-6.6%) and 1/57 (1.8%; 95%CI 0.1-9.4%) patients in the FP and IP groups respectively. Time-to-event analyses indicated no statistically significant differences in bladder toxicity but there was a trend for higher G1+ in the IP group for RTOG and LENTSOM scales (Figure 4 and Appendix 5). Patient reported urinary outcomes appeared slightly higher at baseline in the IP group. At 2 years, both groups had similarly favourable profiles (Table 2). Change scores

indicated that at 24 months an improvement in overall urinary function was evident for some patients in both planning method groups (Appendix 6).

Discussion

Careful matching of patients on rectum and bladder volumes was necessary because patients were not randomised to planning method and there were systematic differences in patient preparation techniques between the centre recruiting the majority of the IP patients and elsewhere (e.g. daily use of rectal enema). The procedural differences resulted in a significant difference in rectum and bladder volumes, which were both smaller in the IP group, and these were accounted for successfully by the matching process.

Both FP and IP techniques were successful in achieving the rectal and bladder dose constraints. The use of IP IMRT enabled the dose to be conformed more optimally to the shape of the PTV, in particular to the concavity formed by the SVs wrapping around the rectum. This largely explains the differences seen in the IP and FP dose-volume data for the rectum, where IP reduced the volume of rectum irradiated to doses of 50Gy and above. Both techniques were successful at limiting the rectal volume receiving the prescribed 74Gy dose, where the PTV excluded SVs, so no difference was apparent at this dose. These results are similar to those reported in previous studies [10, 20-23] where IMRT significantly reduced volumes of rectum exposed to doses >60Gy, with no significant difference near the prescription dose.

The higher volume of bladder irradiated to 74Gy by IP may be due to the 5 field beam geometry used, which resulted in an anterior peak in the dose distribution above the PTV and up into the bladder from the overlapping of the two anterior-oblique beams. This did not occur with FP as an orthogonal beam arrangement was used (anterior and two lateral beams) so, although the isodoses did not conform so well to the circular shape of the prostate PTVs when viewed on axial CT images, the anterior shape of the isodoses was generally flat across the top of the PTV for FPs. In contrast, past studies have reported a slight reduction in bladder volumes exposed to high doses with IMRT, with volumes exposed to intermediate and low doses often higher for IMRT. This may be due in part to the different beam configurations used in these studies for FP, with 3-9 coplanar beams, and the use of multi-phase plans instead of field-in-field techniques. It is well documented that the most favourable CFRT dose distributions are obtained using 3 orthogonal fields as used in the CHHiP trial [24].

Acute bowel toxicity was greater in the FP group with an approximate doubling in the proportion of patients with RTOG G2+ events (FP 50% and IP 21% respectively) mirrored by a similar increase of PRO moderate or worse symptoms of rectal urgency, distress and overall problems with bowels assessed at week 10. The main toxicity endpoint in the main CHHiP trial study was G2+ RTOG toxicity at two years [13]. However, the low level of G2+ toxicity observed across the whole trial, as well as in this analysis (only one case each of G2 bowel and bladder toxicity), make it an insensitive tool for dissecting differences between FP and IP groups. Although there was no consistent difference in late RTOG toxicity scores, both RMH and LENT-SOM tools demonstrated benefits for IP with less than half the recorded RMH G1+ toxicity (HR 0.40) and LENT-SOM documented symptoms (HR 0.48). It is well documented that there are different components to prostate radiotherapy side effects and proctopathy [25]. The RTOG scale reflects proctitis and bleeding whilst RMH/LENT-SOM instruments include bowel frequency and looseness. Our previous studies on the impact of different dose levels on bowel symptoms suggest that higher doses in the 60-70Gy range are associated with bleeding and "proctitis"

whereas a moderate dose "bath" of 50-60Gy is associated with frequency, looseness and sphincter control [26,27]. In the present study, IP produced both benefits, particularly in the 50-65Gy dose range for the RMH and LENT-SOM assessments. The favourable PRO in both FP and IP groups underlines the low level of late toxicity seen with both techniques. There were no obvious differences in either acute or late G2+ bladder toxicity between FP and IP groups, although the IP group appeared to have a slight increase in G1 acute and late side effects.

The lack of substantial differences in long term effects between FP and IP methods is in keeping with recent findings from the Radiation Therapy Oncology Group (RTOG) trial 0126 which showed similar dosimetric advantages of IMRT compared with carefully designed 3DCRT but with no difference in patient-reported bowel or bladder function [28]. One implication of the impact of the improvement in contemporary radiotherapy treatment is a need to use increasingly sensitive physician and patient reported outcome measures to dissect differences between alternative RT strategies.

Conclusions

Significant differences were found between the DVHs for FP and IP patients for rectum and bladder. There were some associations between DVH differences and normal tissue effects which were statistically significant for acute bowel toxicity and for minor levels of toxicity using LENT-SOM and RMH late side effect bowel subscales favouring IP techniques. Conversely, IP techniques were associated with a small excess of grade 1 bladder side effects. Both FP and IP planning techniques were associated with low levels of late normal tissue toxicity.

References

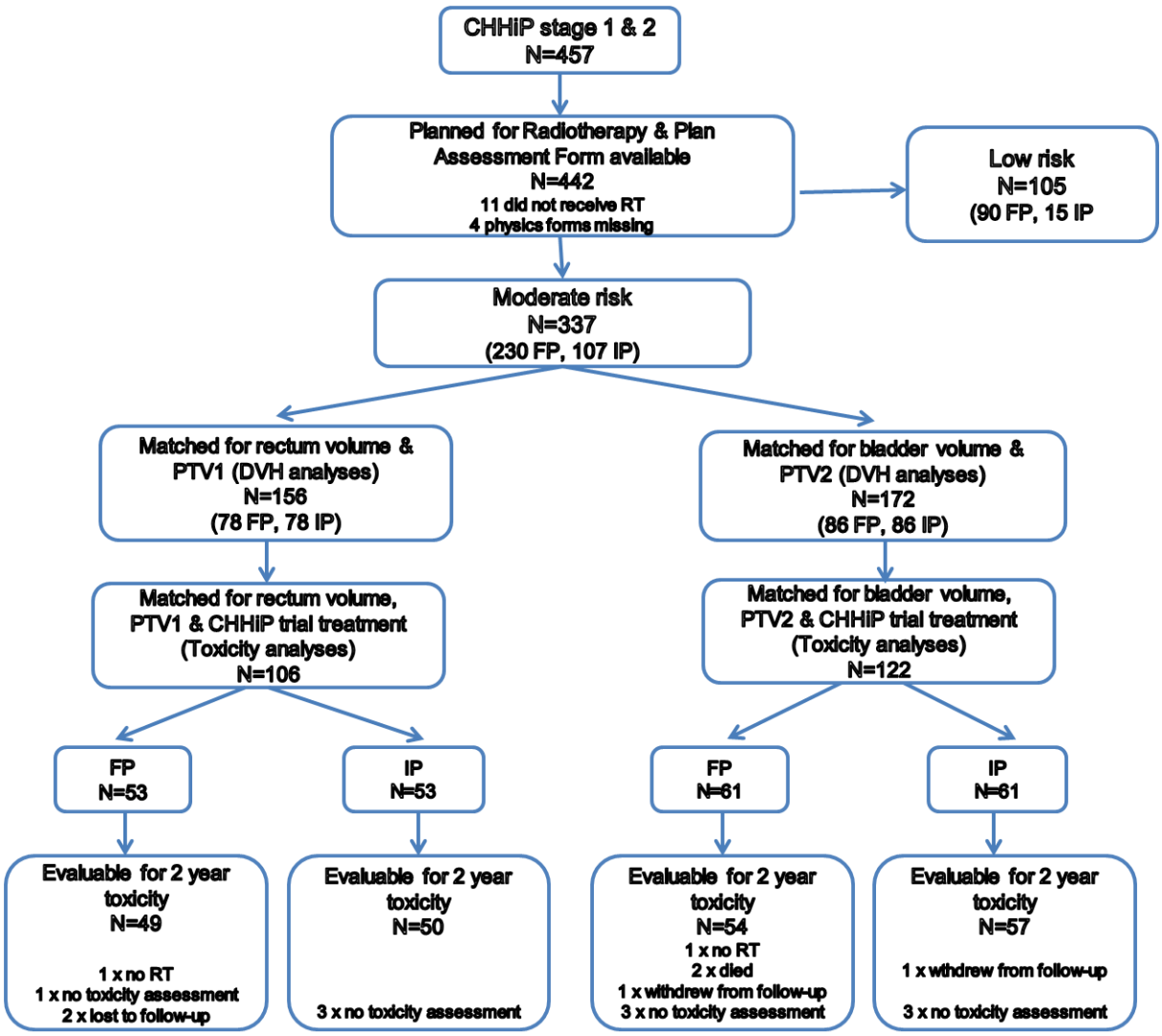
[1] Cancer Research UK. Prostate Cancer Statistics - Key Facts. http://infocancerresearchukorg/cancerstats/keyfacts/prostate-cancer/2015.
[2] International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. 2012.
[3] Dearnaley DP, Khoo VS, Norman AR, Meyer L, Nahum A, Tait D, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. Lancet. 1999;353:267-72.
[4] 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. 2014;15:464-73.
[5] Leibel SA, Fuks Z, Zelefsky MJ, Hunt M, Burman CM, Mageras GS, et al. Technological advances in external-beam radiation therapy for the treatment of localized prostate cancer. Semin Oncol. 2003;30:596-615.
[6] Mangar SA, Huddart RA, Parker CC, Dearnaley DP, Khoo VS, Horwich A. Technological advances in radiotherapy for the treatment of localised prostate cancer. Eur J Cancer. 2005;41:908-21.
[7] Mayles WP, Radiotherapy Development Board. Survey of the availability and use of advanced radiotherapy technology in the UK. Clin Oncol. 2010;22:636-42.
[8] Zelefsky MJ, Fuks Z, Leibel SA. Intensity-modulated radiation therapy for prostate cancer. Semin Radiat Oncol. 2002;12:229-37.
[9] Dearnaley D, Syndikus I, Mossop H, Khoo V, 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.

[10] 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. 2008;20:15-21.
[11] Diaz A, Roach M, 3rd, Marquez C, Coleman L, Pickett B, Wolfe JS, et al. Indications for and the significance of seminal vesicle irradiation during 3D conformal radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 1994;30:323-9.
[12] NCCN clinical practice guidelines in oncology (NCCN guidelines) for prostate cancer. 2011. http:\www.nccn.org (accessed Feb 1, 2016).
[13] 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;13:43-54.
[14] Pooler AM, Mayles HM, Naismith OF, Sage JP, Dearnaley DP. Evaluation of margining algorithms in commercial treatment planning systems. Radiother Oncol. 2008;86:43-7.
[15] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31:1341–1346.
[16] Pilepich MV, 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;13:1007-12.
[17] LENT SOMA tables. Radiother Oncol. 1995;35:17-60.
[18] Dearnaley DP, Hall E, Lawrence D, Huddart RA, Eeles R, Nutting CM, et al. Phase III pilot study of dose escalation using conformal radiotherapy in prostate cancer: PSA control and side effects. Br J Cancer. 2005;92:488-98.
[19] Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, Brook RH. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. Medical Care. 1998;36:1002-12.

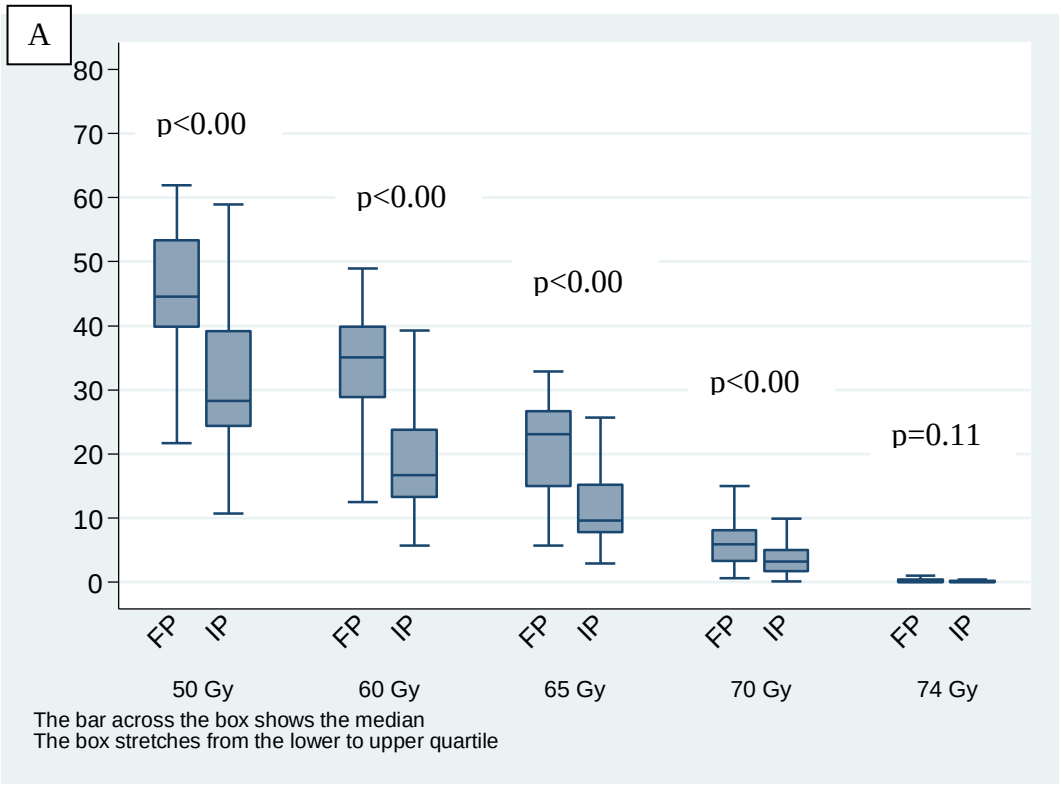
[20] Ailleres N, Azria D, Thezenas S, Barbier N, Fenoglietto P, Delard R, et al. Pilot study of conformal intensity modulated radiation therapy for localized prostate cancer. Cancer Radiotherapie. 2004;8:59-69.
[21] Corletto D, Iori M, Paiusco M, Brait L, Broggi S, Ceresoli G, et al. Inverse and forward optimization of one- and two-dimensional intensity-modulated radiation therapy-based treatment of concave-shaped planning target volumes: the case of prostate cancer. Radiother Oncol. 2003;66:185-95.
[22] Luxton G, Hancock SL, Boyer AL. Dosimetry and radiobiologic model comparison of IMRT and 3D conformal radiotherapy in treatment of carcinoma of the prostate. Int J Radiat Oncol Biol Phys. 2004;59:267-84.
[23] Webb S. Clinical IMRT - evidence-based medicine? Contemporary IMRT - Developing Physics and Clinical Implementation. London, UK: IOP Publishing Ltd; 2005. p.179-229.
[24] Khoo VS, Bedford JL, Webb S, Dearnaley DP. Class solutions for conformal external beam prostate radiotherapy. Int J Radiat Oncol Biol Phys. 2003;55:1109-20.
[25] Capp A, Inostroza-Ponta M, Bill D, Moscato P, Lai C, Christie D, et al. Is there more than one proctitis syndrome? A revisitation using data from the TROG 96.01 trial. Radiother Oncol. 2009;90:400-7.
[26] Ebert MA, Foo K, Haworth A, Gulliford SL, Kennedy A, Joseph DJ, et al. Gastrointestinal dose-histogram effects in the context of dose-volume-constrained prostate radiation therapy: analysis of data from the RADAR prostate radiation therapy trial. Int J Radiat Oncol Biol Phys. 2015;91:595-603.
[27] Gulliford SL, Foo K, Morgan RC, Aird EG, Bidmead AM, Critchley H, et al. Dose-volume constraints to reduce rectal side effects from prostate radiotherapy: evidence from MRC RT01 Trial ISRCTN 47772397. Int J Radiat Oncol Biol Phys. 2010;76:747-54.
[28] Bruner DW, Hunt D, Michalski JM, Bosch WR, Galvin JM, Amin M, et al. Preliminary patient-reported outcomes analysis of 3-dimensional radiation therapy versus intensity-modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group (RTOG) 0126 prostate cancer trial. Cancer. 2015;121:2422-30.

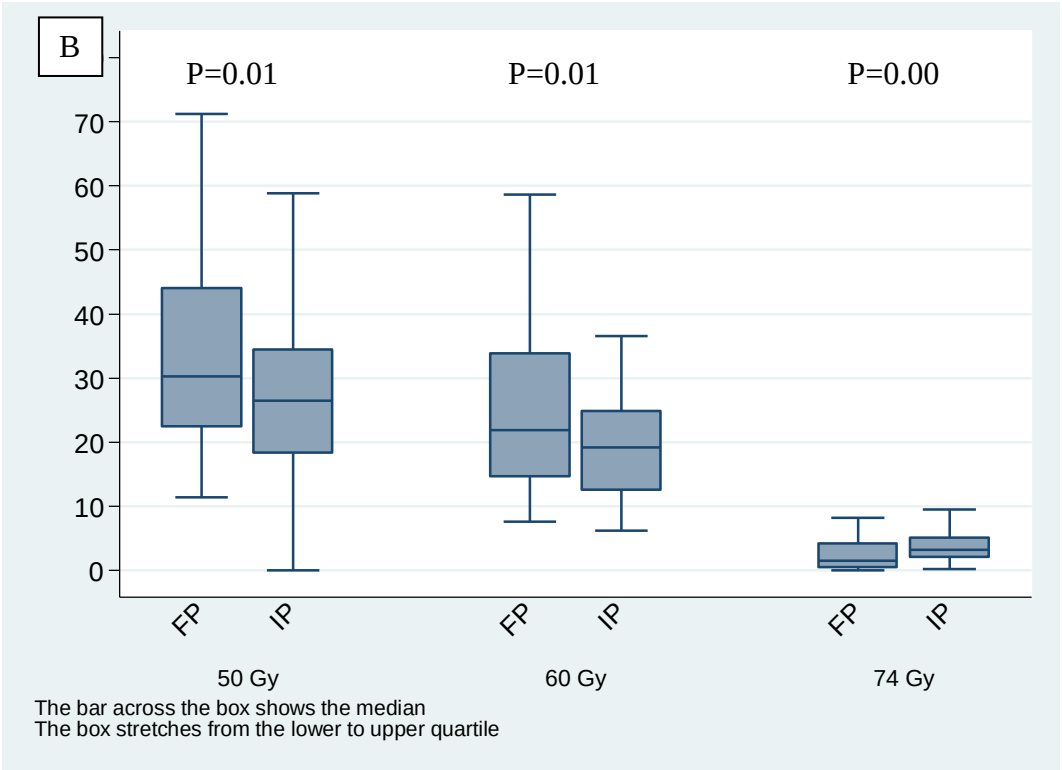
Figures

Figure 1 CONSORT flow diagram for CHHiP Forward (FP) and Inverse (IP) analyses



<u>Figure 2</u> Boxplots illustrating the distribution of (A) rectum volumes and (B) bladder volumes, for Forward (FP) and Inverse (IP) groups for each dose constraint

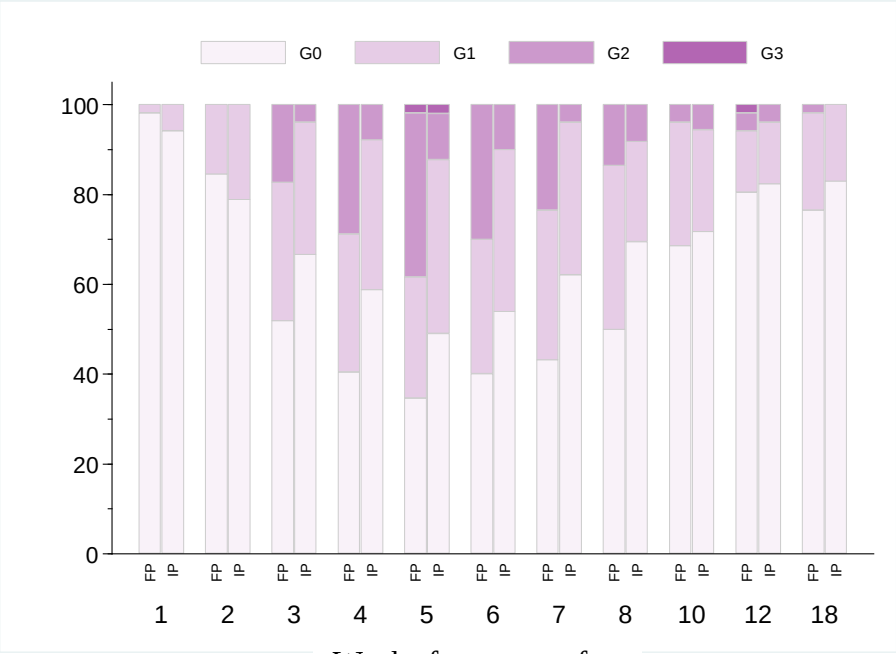




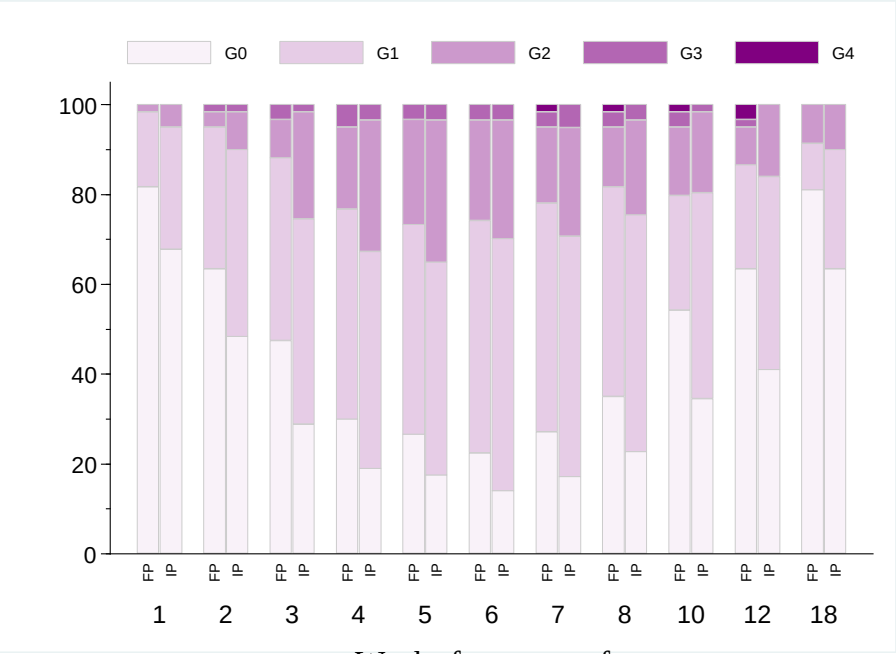
NB. Doses on x-axis are equivalent dose for the 2Gy fraction

<u>Figure 3</u> – Distribution of acute RTOG toxicity by planning method: (A) bowel toxicity (in rectum volume matched dataset) and (B) bladder toxicity (in bladder volume matched dataset)

A – RTOG bowel toxicity (rectum volume matched dataset)



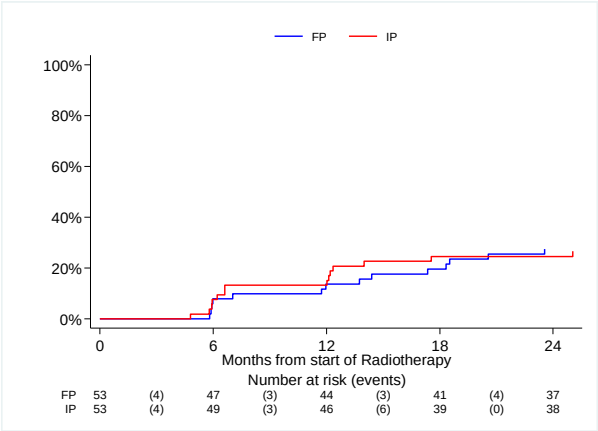
B – RTOG bladder toxicity (bladder volume matched dataset)



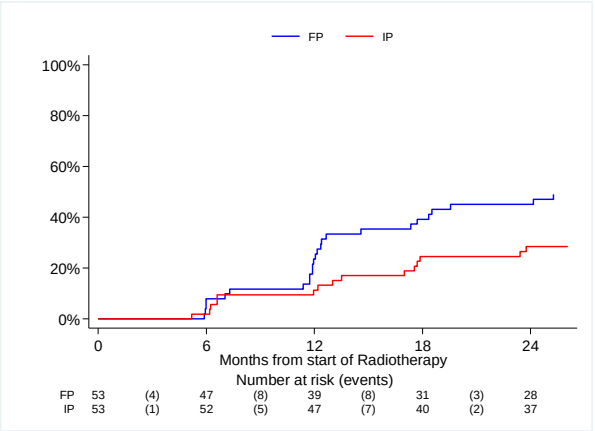
<u>Figure 4</u> – Cumulative proportion of grade 1+ toxicity assessed by RTOG, RMH and LENTSOM: Bowel toxicity for rectum-volume matched dataset (figures A, B & C) and bladder toxicity for bladder-volume matched dataset (figures D, E & F)

Rectum volume matched dataset

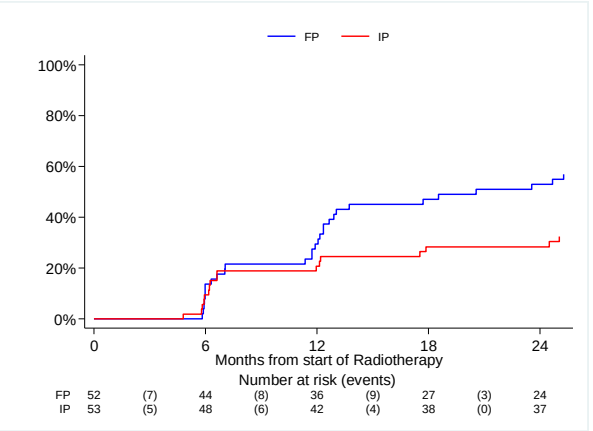
A – RTOG bowel grade 1+



B – RMH bowel grade 1+

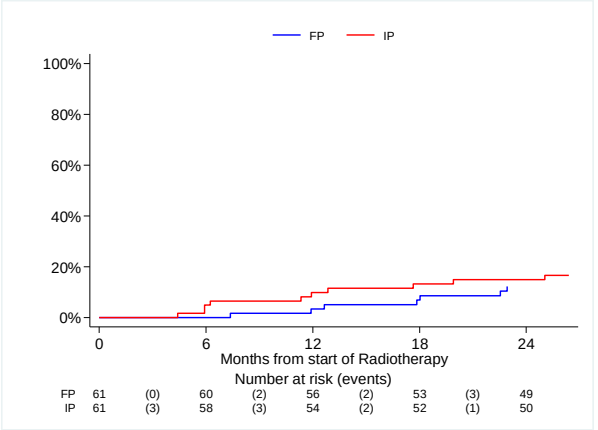


C – LENTSOM bowel grade 1+

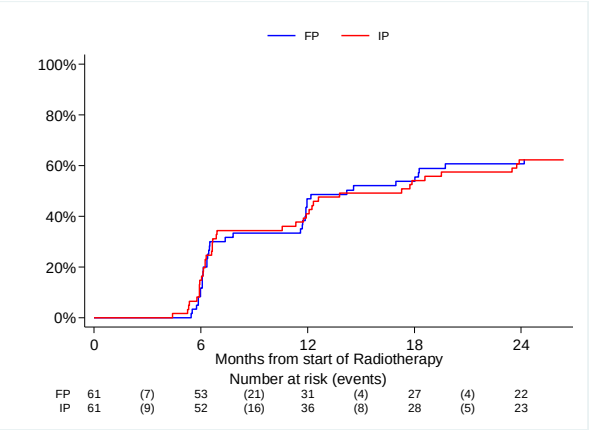


Bladder volume matched dataset

D – RTOG bladder grade 1+



E – RMH bladder grade 1+



F – LENTSOM bladder grade 1+

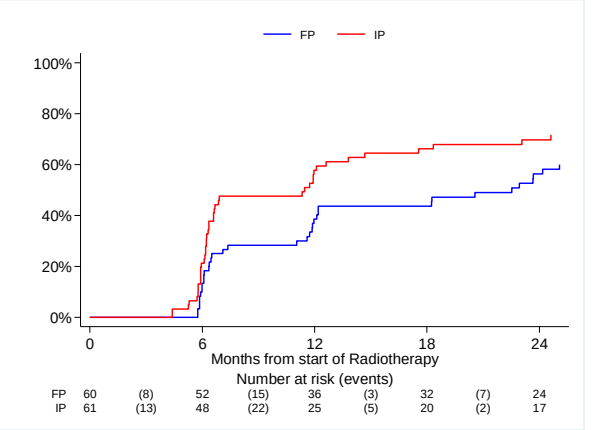


Table 1 Late toxicity assessed using RTOG, RMH and LENTSOM scoring systems: Bowel toxicity (in rectum volume matched dataset) & bladder toxicity (in bladder volume matched dataset)

		Rectum volume matched dataset						Bladder volume matched dataset					
		RTOG BOWEL		RMH BOWEL		LENTSOM BOWEL		RTOG BLADDER		RMH BLADDER		LENTSOM BLADDER	
		FP n=53 n (%)	IP n=53 n (%)	FP n=53 n (%)	IP n=53 n (%)	FP n=53 n (%)	IP n=53 n (%)	FP n=61 n (%)	IP n=61 n (%)	FP n=61 n (%)	IP n=61 n (%)	FP n=61 n (%)	IP n=61 n (%)
6 months	**0**	44 (90)	46 (87)	43 (88)	47 (90)	38 (78)	43 (81)	59 (98)	57 (93)	40 (67)	40 (66)	43 (72)	31 (51)
	1	3 (6)	7 (13)	4 (8)	5 (10)	9 (18)	7 (13)	0	4 (7)	16 (27)	19 (31)	10 (17)	21 (34)
	2	2 (4)	0	2 (4)	0	1 (2)	2 (4)	1 (2)	0	3 (5)	2 (3)	6 (10)	8 (13)
	3	0	0	0	0	1 (2)	1 (2)	0	0	1 (2)	0	1 (2)	1 (2)
	4	0	0	0	0	0	0	0	0	0	0	0	0
	not assessed	*4*	*0*	*4*	*1*	*4*	*0*	*1*	*0*	*1*	*0*	*1*	*0*
Mann-Whitney p-value		0.701		0.628		0.699		0.188		0.985		0.036	
12 months	**0**	44 (88)	45 (85)	35 (70)	46 (87)	33 (67)	40 (76)	56 (97)	58 (95)	36 (62)	41 (67)	42 (72)	29 (48)
	1	4 (8)	7 (13)	13 (26)	6 (9)	13 (27)	11 (21)	1 (2)	2 (3)	18 (31)	17 (28)	10 (17)	25 (41)
	2	2 (4)	1 (2)	1 (2)	1 (2)	2 (4)	2 (4)	1 (2)	1 (2)	1 (2)	2 (3)	4 (7)	6 (10)
	3	0	0	1 (2)	1 (2)	1 (2)	0	0	0	3 (5)	1 (2)	2 (4)	1 (2)
	4	0	0	0	0	0	0	0	0	0	0	0	0
	not assessed	*3*	*0*	*3*	*0*	*4*	*0*	*3*	*0*	*3*	*0*	*3*	*0*
Mann-Whitney p-value		0.690		0.047		0.350		0.697		0.524		0.016	
18 months	**0**	39 (81)	49 (94)	35 (73)	46 (89)	32 (67)	46 (89)	50 (93)	56 (93)	34 (62)	38 (63)	38 (72)	35 (59)
	1	7 (15)	2 (4)	11 (23)	5 (10)	10 (21)	4 (8)	3 (6)	3 (5)	19 (35)	20 (33)	4 (8)	18 (31)
	2	2 (4)	1 (2)	1 (2)	1 (2)	4 (8)	2 (4)	1 (2)	0	1 (2)	1 (2)	9 (17)	5 (9)
	3	0	0	1 (2)	0	2 (4)	0	0	1 (2)	1 (2)	0	2 (4)	0
	4	0	0	0	0	0	0	0	0	0	1 (2)	0	1 (2)
	not assessed	*5*	*1*	*5*	*1*	*5*	*1*	*7*	*1*	*6*	*1*	*8*	*2*
Mann-Whitney p-value		0.049		0.050		0.008		0.883		0.866		0.460	
24 months	**0**	44 (90)	48 (96)	33 (67)	44 (88)	32 (65)	42 (86)	51 (94)	56 (98)	37 (69)	39 (68)	34 (63)	34 (60)
	1	5 (10)	1 (2)	15 (31)	5 (10)	14 (19)	6 (12)	3 (6)	0	14 (26)	14 (25)	10 (19)	17 (30)
	2	0	1 (2)	1 (2)	1 (2)	2 (4)	1 (2)	0	1 (2)	2 (4)	3 (5)	9 (17)	4 (7)
	3	0	0	0	0	1 (2)	0	0	0	1 (2)	1 (2)	1 (2)	2 (4)
	4	0	0	0	0	0	0	0	0	0	0	0	0
	not assessed	*4*	*3*	*4*	*3*	*4*	*4*	*7*	*4*	*5*	*4*	*7*	*4*
Mann-Whitney p-value		0.247		0.016		0.019		0.298		0.954		0.984	

Table 2: Distribution of bowel and urinary symptoms from the UCLA Prostate Cancer Index questionnaire pre-radiotherapy and at week 10, and months 6, 12, 18 and 24 from the start of radiotherapy

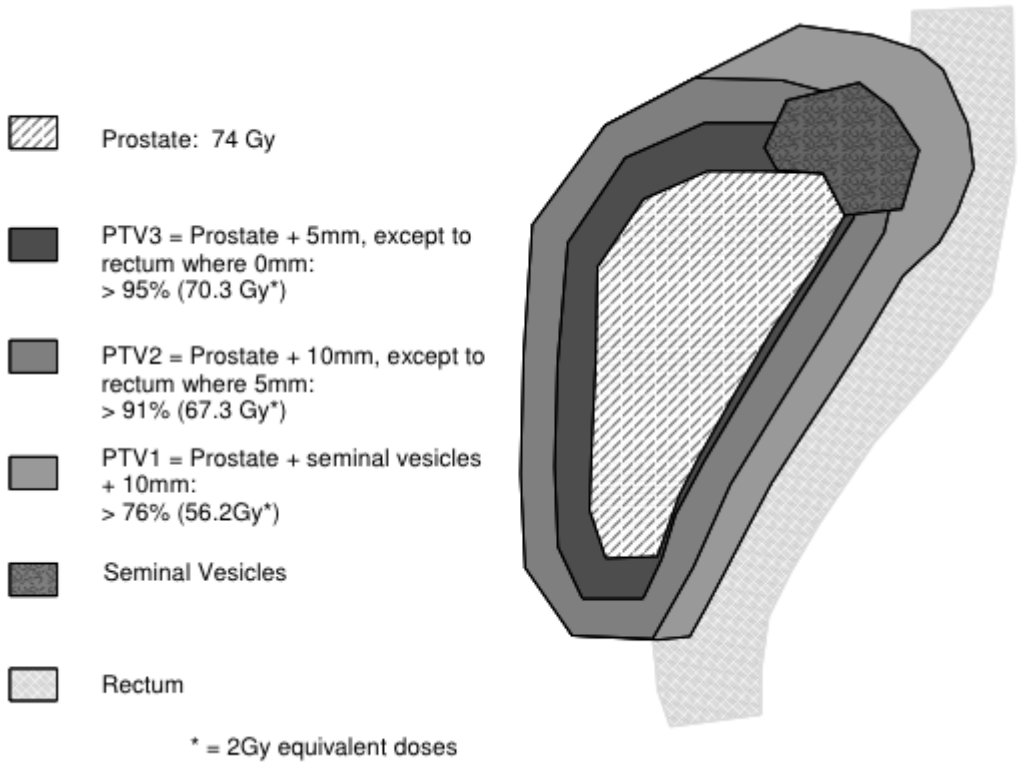
Bowel symptoms are presented in the rectum volume matched dataset and urinary symptoms in the bladder volume matched dataset

BOWEL HABITS (rectum volume matched dataset)	**Pre- radiotherapy**		**Week 10**		**6 months**		**12 months**		**18 months**		**24 months**	
	FP	**IP**	**FP**	**IP**	**FP**	**IP**	**FP**	**IP**	**FP**	**IP**	**FP**	**IP**
	N=42	**N=42**	**N=31**	**N=30**	**N=40**	**N=42**	**N=40**	**N=40**	**N=40**	**N=37**	**N=40**	**N=38**
Frequency of rectal urgency												
More than once a day	0	2 (5)	6 (19)	1 (3)	4 (10)	2 (5)	0	2 (5)	5 (13)	1 (3)	1 (2)	1 (3)
Once a day	6 (14)	3 (7)	4 (13)	4 (13)	1 (3)	4 (10)	4 (10)	5 (13)	3 (7)	1 (3)	1 (2)	1 (3)
More than once a week	0	1 (2)	3 (10)	2 (7)	5 (12)	5 (12)	0	2 (5)	1 (3)	0	2 (5)	2 (5)
Once a week	2 (5)	2 (5)	3 (10)	6 (20)	3 (7)	6 (14)	4 (10)	1 (3)	2 (5)	5 (14)	3 (8)	5 (13)
Rarely or never	34 (81)	34 (81)	15 (48)	17 (57)	27 (68)	25 (60)	32 (80)	30 (75)	29 (73)	30 (81)	33 (83)	29 (76)
Frequency loose/liquid stools												
Never	53 (55)	20 (48)	13 (42)	9 (30)	15 (37)	7 (17)	16 (39)	8 (20)	14 (35)	13 (35)	22 (55)	16 (42)
Rarely	14 (33)	17 (41)	10 (32)	10 (33)	18 (44)	27 (64)	20 (49)	21 (53)	16 (40)	17 (46)	13 (33)	11 (29)
About half the time	4 (10)	3 (7)	7 (23)	9 (30)	5 (12)	4 (10)	2 (5)	8 (20)	6 (15)	4 (11)	4 (10)	6 (16)
Usually	1 (2)	1 (2)	1 (3)	2 (7)	2 (5)	4 (10)	2 (5)	2 (5)	3 (8)	3 (8)	1 (2)	4 (11)
Always	0	1 (2)	0	0	1 (2)	0	1 (2)	1 (3)	1 (3)	0	0	1 (3)
Distress from bowel movements												
Severe	1 (2)	0	2 (7)	1 (3)	1 (2)	0	1 (2)	1 (3)	0	0	0	0
Moderate	0	3 (7)	4 (13)	2 (7)	1 (2)	4 (10)	3 (7)	1 (3)	2 (5)	1 (3)	2 (5)	1 (3)
A little	5 (12)	9 (21)	9 (29)	13 (43)	10 (24)	10 (24)	5 (12)	8 (20)	10 (25)	6 (16)	5 (13)	7 (18)
No distress	36 (86)	30 (71)	16 (52)	14 (47)	29 (71)	28 (67)	32 (78)	30 (75)	28 (70)	30 (81)	33 (83)	30 (79)
Crampy pain												0
Several times a day	0	0	2 (6)	1 (3)	2 (5)	1 (2)	0	2 (5)	1 (2)	0	0	0
Once a day	1 (2)	0	1 (3)	0	0	1 (2)	1 (2)	0	2 (5)	0	1 (2)	2 (5)
Several times a week	1 (2)	2 (5)	1 (3)	1 (3)	1 (2)	0	1 (2)	2 (5)	1 (2)	3 (8)	1 (2)	2 (5)
Once a week	5 (12)	2 (5)	1 (3)	1 (3)	1 (2)	2 (5)	0	3 (8)	0	1 (3)	1 (2)	1 (3)
Once this month	1 (2)	4 (10)	1 (3)	3 (10)	3 (7)	9 (21)	3 (7)	5 (13)	1 (2)	2 (5)	4 (10)	33 (87)
Rarely or never	33 (81)	34 (81)	2 (81)	23 (79)	34 (83)	29 (69)	36 (88)	28 (70)	35 (88)	31 (84)	33 (83)	
Overall problem of bowel habits Big	0	1 (2)	1 (3)	1 (3)	1 (2)	0	1 (2)	1 (3)	0	0	0	0
Moderate	1 (2)	1 (2)	4 (13)	1 (3)	1 (2)	3 (7)	3 (7)	3 (8)	2 (5)	1 (3)	1 (2)	0
Small	3 (7)	2 (5)	4 (13)	3 (10)	3 (7)	2 (5)	0	4 (10)	5 (13)	3 (8)	1 (2)	4 (11)
Very small	3 (7)	12 (29)	8 (26)	10 (33)	11 (27)	12 (29)	8 (20)	8 (20)	7 (18)	6 (16)	12 (30)	6 (16)
No problem	35 (83)	26 (62)	14 (45)	15 (50)	25 (61)	25 (60)	29 (71)	24 (60)	26 (65)	27 (73)	26 (65)	28 (74)

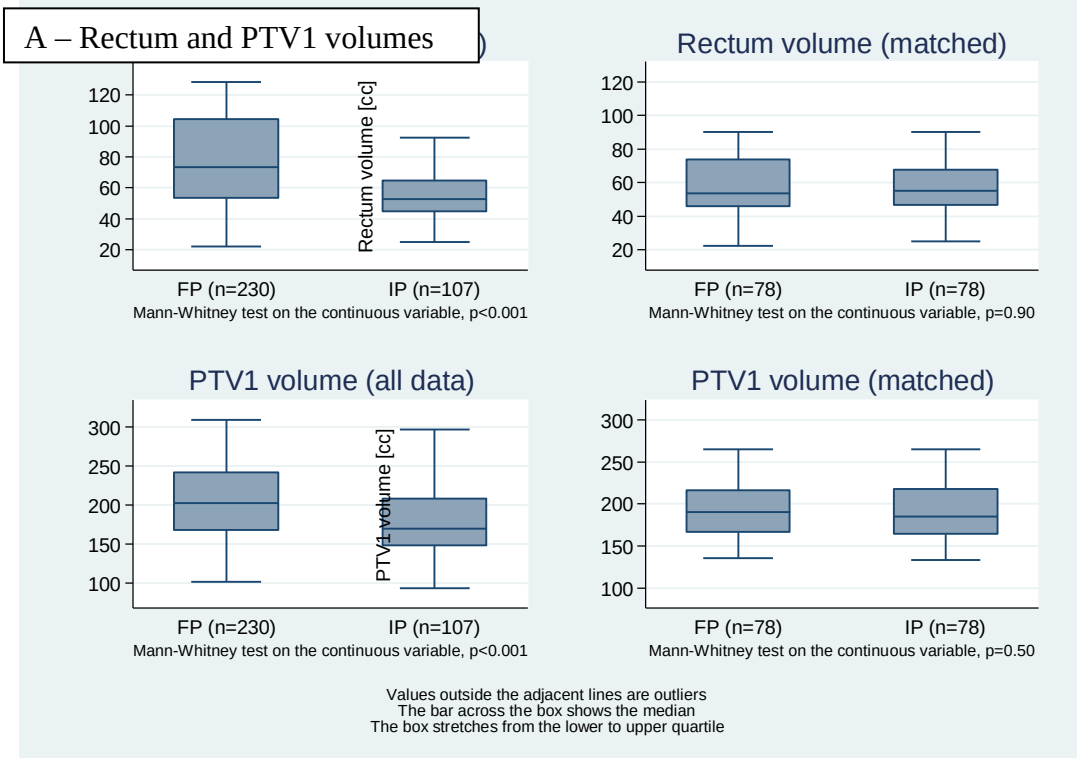
URINARY FUNCTION (bladder volume matched dataset)	Pre-radiotherapy		Week 10		6 months		12 months		18 months		24 months	
	FP	IP	FP	IP	FP	IP	FP	IP	FP	IP	FP	IP
	N=45	N=52	N=31	N=35	N=43	N=42	N=44	N=49	N=41	N=44	N=42	N=41
Frequency of leaking urine												
Everyday	2 (4)	3 (6)	1 (3)	1 (3)	0	2 (5)	2 (5)	5 (10)	1 (2)	2 (5)	0	1 (2)
About once a week	2 (4)	4 (8)	2 (6)	2 (6)	3 (7)	5 (12)	2 (5)	3 (6)	5 (12)	3 (7)	7 (17)	4 (10)
Less than once a week	3 (7)	7 (13)	3 (10)	9 (26)	3 (7)	9 (21)	2 (5)	7 (14)	5 (12)	9 (21)	2 (5)	4 (10)
Not at all	38 (84)	38 (73)	25 (81)	23 (66)	37 (86)	26 (62)	38 (86)	34 (69)	30 (73)	30 (68)	33 (79)	31 (78)
Urinary control												
No control whatsoever	0	1 (2)	0	0	1 (2)	0	0	0	0	0	0	0
Frequent dribbling	1 (2)	1 (2)	0	0	0	1 (2)	0	1 (2)	0	0	0	0
Occasional dribbling	8 (18)	16 (31)	7 (23)	10 (30)	6 (14)	13 (31)	5 (11)	13 (27)	10 (24)	14 (32)	10 (24)	12 (30)
Total control	36 (80)	34 (65)	24 (78)	23 (70)	36 (84)	28 (67)	39 (89)	35 (71)	31 (76)	30 (68)	32 (76)	28 (70)
Pads or diapers required per day												
3 or more pads	0	0	0	0	0	0	0	0	0	1 (2)	0	0
1-2 pads	2 (5)	0	1 (3)	0	0	1 (2)	0	2 (4)	0	0	1 (2)	0
No pads	42 (95)	52 (100)	30 (97)	33 (100)	40 (100)	42 (98)	43 (100)	47 (96)	41 (100)	43 (98)	41 (98)	41 (100)
Dripping urine/wetting pants												
No problem	40 (91)	39 (75)	22 (71)	25 (74)	34 (79)	30 (70)	33 (79)	35 (71)	33 (81)	36 (82)	33 (79)	33 (81)
Very small problem	2 (5)	8 (15)	6 (19)	7 (21)	7 (16)	10 (23)	7 (17)	9 (18)	4 (10)	5 (11)	8 (19)	7 (17)
Small problem	1 (2)	2 (4)	2 (6)	1 (3)	2 (5)	1 (2)	2 (5)	4 (8)	3 (7)	3 (7)	0	1 (2)
Moderate problem	1 (2)	0	1 (3)	1 (3)	0	1 (2)	0	1 (2)	1 (2)	0	1 (2)	0
Big problem	0	3 (6)	0	0	0	1 (2)	0	0	0	0	0	0
Urine leakage interfering with sexual activity												
No problem	39 (93)	41 (85)	26 (93)	28 (90)	38 (93)	35 (92)	41 (98)	35 (83)	38 (97)	38 (95)	37 (88)	34 (94)
Very small problem	0	2 (4)	1 (4)	3 (10)	1 (2)	0	0	4 (10)	0	0	3 (7)	1 (3)
Small problem	2 (5)	1 (2)	0	0	2 (5)	0	0	1 (2)	0	1 (2)	0	1 (3)
Moderate problem	0	0	1 (4)	0	0	1 (3)	0	2 (5)	0	1 (2)	2 (5)	0
Big problem	1 (2)	4 (8)	0	0	0	2 (5)	1 (2)	0	1 (3)	0	0	0
Overall problem urinary function												
No problem	30 (67)	23 (44)	10 (32)	15 (43)	28 (65)	26 (61)	33 (75)	29 (59)	29 (71)	31 (70)	31 (74)	29 (71)
Very small problem	7 (16)	15 (29)	11 (36)	11 (31)	11 (26)	13 (30)	8 (18)	12 (25)	7 (17)	8 (18)	6 (14)	8 (20)
Small problem	2 (4)	6 (12)	4 (13)	6 (17)	3 (7)	2 (5)	2 (5)	6 (12)	4 (10)	4 (9)	5 (12)	2 (5)
Moderate problem	4 (9)	6 (12)	6 (19)	2 (6)	0	2 (5)	1 (2)	2 (4)	1 (2)	1 (2)	0	2 (5)
Big problem	2 (4)	2 (4)	0	1 (3)	1 (2)	0	0	0	0	0	0	00

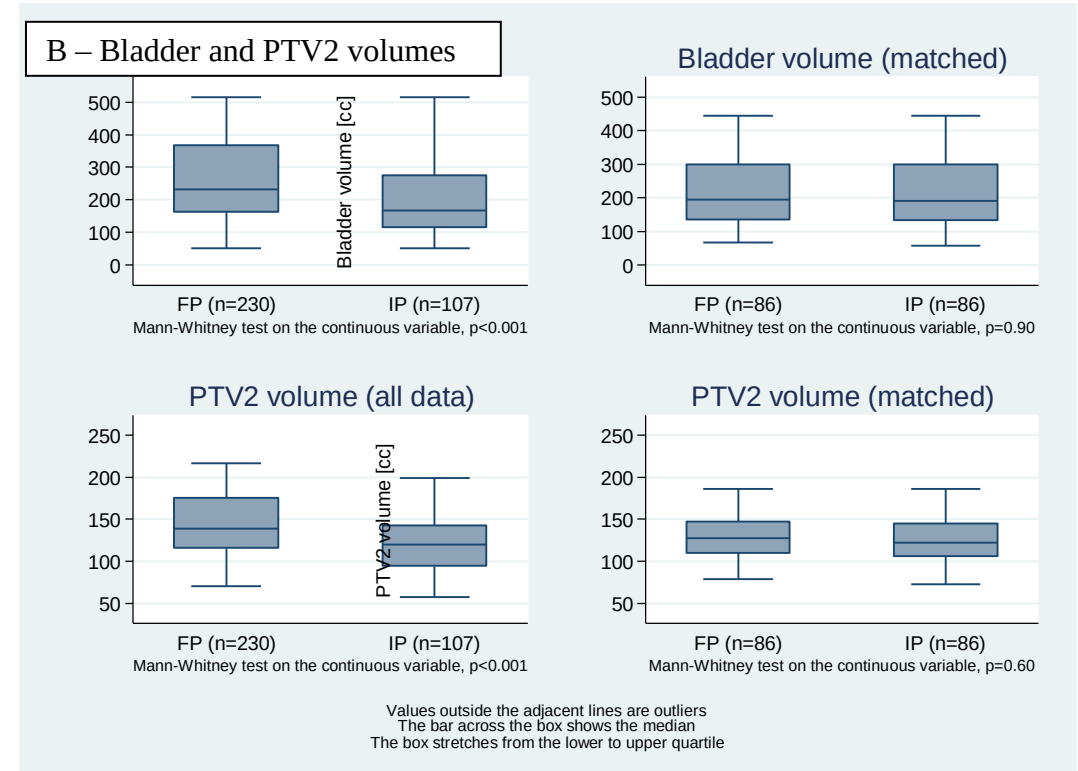
Forward and Inverse Planning: APPENDIX

Appendix 1: CHHiP PTVs and target doses



<u>Appendix 2:</u> Effect of matching process illustrated by (A) distribution of rectum and PTV1 volume for all patients (left column) and matched patients (right column) (B) distribution of bladder and PTV2 volume for all patients (left column) and matched patients (right column)





Appendix 3: Distribution of matched datasets

Distribution of dataset matched for rectum volume and PTV1 (n=156)

Rectal volume	PTV1						
	<120cc	120-160	160-200	200-240	240-280	>280cc	Total
<40cc	0	2	7	1	0	0	10
40-60	0	5	19	7	4	1	36
60-80	0	8	6	5	2	1	22
80-100	0	0	3	1	1	1	6
100-120	0	0	0	0	1	1	2
>120cc	0	0	0	2	0	0	2
Total	0	15	35	16	8	4	78

Distribution of dataset matched for bladder volume and PTV2 (n=172)

Bladder volume	PTV2						
	<70cc	70-100	100-130	130-160	160-190	>190cc	Total
<100cc	0	2	1	3	2	0	8
100-175	0	4	9	13	3	1	30
175-250	0	2	12	3	2	1	20
250-325	0	2	6	2	1	0	11
325-400	0	2	1	1	0	0	4
>400cc	0	2	3	4	2	2	13
Total	0	14	32	26	10	4	86

Distribution of dataset matched for rectum volume, PTV 1 and CHHiP dose schedule (n=106)

Rectal volume	PTV1						
	<120cc	120-160	160-200	200-240	240-280	>280cc	Total
<40cc	0	1	6	1	0	0	8
40-60	0	3	18	6	3	1	31
60-80	0	3	2	2	2	0	9
80-100	0	0	2	0	1	0	3
100-120	0	0	0	0	1	0	1
>120cc	0	0	0	1	0	0	1
Total	0	7	28	10	7	1	53

Distribution of dataset matched for bladder volume, PTV2 and CHHiP dose schedule (n=122)

Bladder volume	PTV2						
	<70cc	70-100	100-130	130-160	160-190	>190cc	Total
<100cc	0	1	1	0	1	0	3
100-175	0	4	7	12	1	1	25
175-250	0	1	12	1	1	1	16
250-325	0	1	5	1	1	0	8
325-400	0	0	1	0	0	0	1
>400cc	0	1	2	2	2	1	8
Total	0	8	28	16	6	3	61

Appendix 4 Baseline characteristics for rectum-volume matched dataset and bladder-volume matched datasets

	Rectum volume matched dataset			Bladder volume matched dataset		
	FP n=53 n (%)	IP n=53 n (%)	P value	FP N=61 n (%)	IP N=61 n (%)	P value
Age at registration (years)						
Median (quartiles)	68 (64-71)	67 (63-72)	0.4	68 (64-71)	66 (62-70)	0.13
Range	57-78	56-76		58-79	51-78	
Weeks from histological confirmation of prostate cancer to randomisation						
Median (quartiles)	26 (18-33)	22 (19-25)	0.19	22 (15-30)	22 (19-27)	0.97
Range	6-145	11-190		6-143	7-93	
T stage (clinical assessment)						
T1a/T1b/T1c/T1x	17 (32)	13 (25)		27 (44)	17 (28)	0.1
T2a/T2b/T2c/T2x	32 (60)	35 (66)	0.39	29 (48)	39 (64)	
T3a/T3x	4 (8)	5 (9)		5 (8)	5 (8)	
Gleason score						
≤4	3 (6)	1 (2)		2 (3)	1 (2)	
5-6	15 (28)	13 (25)		13 (21)	15 (25)	
7	33 (62)	35 (66)	0.29	44 (72)	43 (71)	0.89
8	2 (4)	4 (8)		2 (3)	2 (3)	
PSA (pre-hormone treatment) (ng/ml)						
Median (quartiles)	14.0 (9.8-17.8)	11.7 (7.3-17.1)		14.4 (10.4-19.0)	10.9 (7.3-18.1)	
Mean (SD)	14.6 (6.4)	13.1 (6.2)	0.22	15.4 (6.4)	13.0 (6.2)	0.04
PSA (ng/ml)						
0.0-4.99	2 (4)	1 (2)		1 (2)	2 (3)	
5.0-9.99	12 (23)	21 (40)		11 (18)	26 (43)	
10.0-19.99	29 (55)	23 (43)		35 (58)	22 (36)	
20.0-49.99	10 (19)	8 (15)		14 (23)	11 (18)	
Pre-treatment risk group						
Low	0	0	-	0	0	-
Medium	53 (100)	53 (100)		61 (100)	61 (100)	
Radiotherapy regimen						
74Gy/37f	19 (36)	19 (36)		23 (38)	23 (38)	
60Gy/20f	15 (28)	15 (28)	-	19 (31)	19 (31)	-
57Gy/19f	19 (36)	19 (36)		19 (31)	19 (31)	
Posterior margins modified						
Yes	4 (8)	0		6 (10)	1 (2)	
No	48 (92)	52 (100)		54 (90)	59 (98)	0.05
Missing	1	1	0.04	1	1	

<u>Appendix 5:</u> – Total number of events, hazard ratio and cumulative proportion with events by 2 years for bowel (population A) and bladder toxicity by planning method

		Total events	HR[1] (95% CI)	P-value[2]	2 year cumulative incidence (95% CI) FP	2 year cumulative incidence (95% CI) IP
BOWEL TOXICITY (rectum volume matched dataset)						
RTOG	Grade≥1	33	0.76 (0.38-1.51)	0.431	27.5 (17.3-41.9)	24.6 (15.1-38.5)
	Grade≥2	5	0.24 (0.03-2.16)	0.204	5.9 (1.9-17.1)	1.9 (0.3-12.6)
	Grade≥3	2	1.18 (0.07-18.9)	0.906	-	-
RMH	Grade≥1	48	0.40 (0.21-0.73)	0.003	45.1 (32.7-59.7)	28.4 (18.2-42.6)
	Grade≥2	10	0.43 (0.11-1.68)	0.226	7.8 (3.0-19.6)	3.8 (1.0-14.3)
	Grade≥3	4	0.35 (0.04-3.34)	0.360	1.9 (0.3-13.1)	1.9 (0.03-12.7)
LENTSOM	Grade≥1	54	0.48 (0.27-0.84)	0.010	52.9 (40.1-67.0)	28.3 (18.1-42.5)
	Grade≥2	18	0.39 (0.14-1.09)	0.074	15.7 (8.2-28.9)	7.6 (2.9-18.9)
	Grade≥3	5	0.28 (0.3-2.51)	0.255	3.9 (0.01-14.8)	1.9 (0.003-12.7)
BLADDER TOXICITY (bladder volume matched dataset)						
RTOG	Grade≥1	20	1.58 (0.65-3.87)	0.316	12.2 (6.0-24.0)	14.9 (8.1-26.7)
	Grade≥2	8	0.99 (0.25-3.98)	0.992	5.2 (1.7-15.2)	3.3 (0.1-12.7)
	Grade≥3	2	1.11 (0.07-18.0)	0.968	-	1.7 (0.2-11.3)
RMH	Grade≥1	87	1.04 (0.68-1.59)	0.850	60.7 (48.5-73.1)	62.3 (50.4-74.3)
	Grade≥2	19	0.95 (0.38-2.35)	0.910	10.1 (5.7-21.1)	8.3 (3.6-18.8)
	Grade≥3	8	0.35 (0.07-1.75)	0.203	5.1 (1.7-15.1)	3.3 (0.8-12.7)
LENTSOM	Grade≥1	89	1.58 (1.03-2.43)	0.037	56.3 (44.1-69.3)	69.6 (57.8-80.7)
	Grade≥2	51	1.21 (0.69-2.10)	0.506	32.8 (22.3-46.6)	33.2 (22.9-46.6)
	Grade≥3	14	0.84 (0.29-2.42)	0.743	6.8 (2.6-17.2)	5.0 (1.7-14.8)

[1] Hazard ratio (HR)<1 favours Inverse planning method

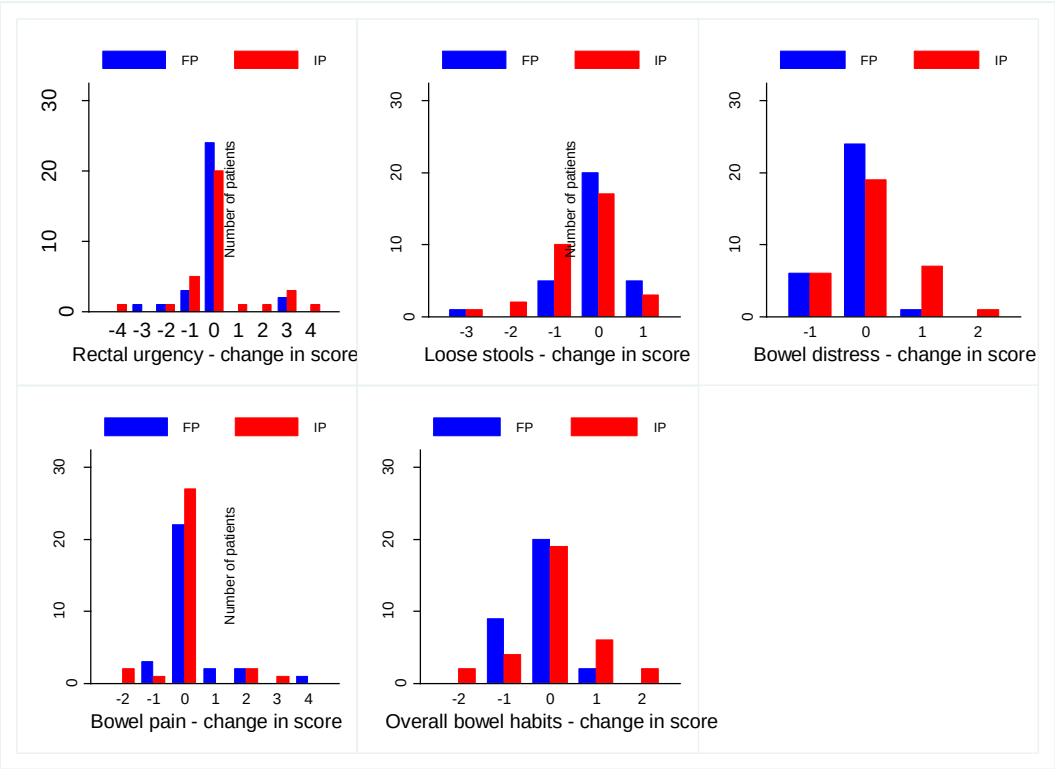
[2] P-value from Wald test

<u>Appendix 6</u>: Prostate Cancer Index change scores from pre-RT to 24 months

Positive change scores indicate better QL score at 24 months compared to pre-RT
Negative change scores indicate worse QL score at 24 months compared to pre-RT

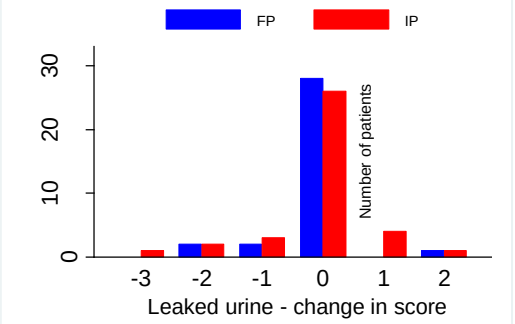
NB. Loose stools is scored in the opposite direction from the other bowel habits but the loose stools scoring has been reversed so it is the same direction as all the other bowel items, so all plots can be interpreted in the same way

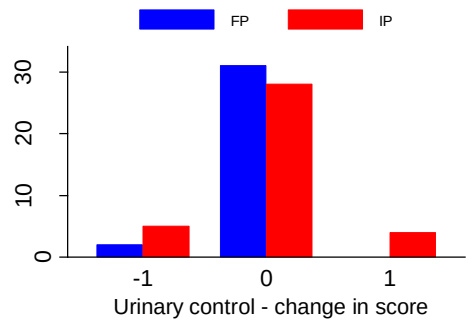
A – Bowel habits – change pre-radiotherapy to 24 months (rectum volume matched dataset)

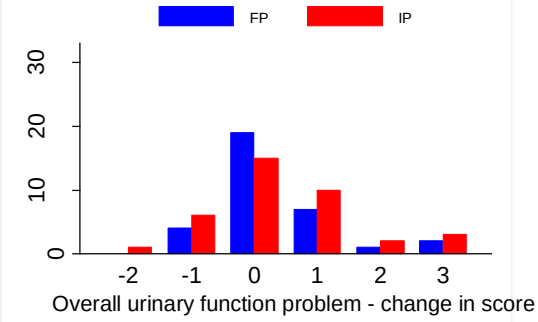


NB. Overall problem with urinary function is scored in the opposite direction from the other urinary items but the overall urinary problem scoring has been reversed so it is the same direction as all the other urinary items, so all plots can be interpreted in the same way

B – Urinary function change from pre-radiotherapy to 24 months (bladder volume matched dataset)


FP
IP
Number of patients
0
10
20
30
-3
-2
-1
0
1
2
Leaked urine - change in score


FP
IP
0
10
20
30
-1
0
1
Urinary control - change in score


FP
IP
0
10
20
30
-2
-1
0
1
2
3
Overall urinary function problem - change in score