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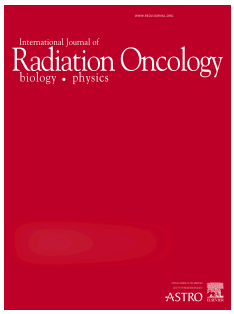


A phase I/II dose escalation study of the use of intensity modulated radiotherapy (IMRT) to treat the prostate and pelvic nodes in patients with prostate cancer

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• **Title:** A phase I/II dose escalation study of the use of intensity modulated radiotherapy (IMRT) to treat the prostate and pelvic nodes in patients with prostate cancer

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• **Contributors:** MRF and AK contributed equally and were involved in data collection and interpretation, literature search, manuscript design, manuscript writing and design of figures and tables. KT did the statistical analyses, and contributed to design of figures and tables, data interpretation and manuscript writing. DD, MRF, AK, KT, LT, HMN and BJ are members of the Trial Management Group responsible for the design and day-to-day oversight of the study and contributed to data interpretation. LT was responsible for data collection and study management at the Bob Champion Unit. MB and VH contributed to radiotherapy planning and quality assurance. MRF, AK, CP, RH, RE, VK, NvA and DD were involved in patient recruitment and data collection. DD, CP, RH, RE, VK, NvA were involved in the study the design. DD is the Chief Investigator and was involved with study design, recruiting patients, data interpretation, literature search and manuscript writing. All authors reviewed the manuscript.

**Summary**

Elective pelvic lymph node (PLN) radiotherapy and hypofractionation for advanced localised prostate cancer remains controversial. We report a single-centre sequential cohort study using IMRT to deliver conventionally-fractionated 50Gy, 55Gy, and 60Gy to the PLN and 70-74Gy (2Gy/fraction) to the prostate. Additionally we studied modest hypofractionation delivering 60Gy (3Gy/fraction) to the prostate with 47Gy to the PLN over 4-5 weeks. Our findings highlight the safety of dose-escalation and hypofractionation in PLN-IMRT.

**Title:** A phase I/II dose escalation study of the use of intensity modulated radiotherapy (IMRT) to treat the prostate and pelvic nodes in patients with prostate cancer


## Abstract:

**Background**

The role of pelvic lymph node (PLN) radiotherapy in advanced localised prostate cancer (PCa) remains controversial. In order to minimise toxicity, past studies limited the dose delivered to the PLN. We used Intensity Modulated Radiotherapy (IMRT) to investigate the feasibility of dose-escalation and hypofractionation of PLN-IMRT in PCa.

**Methods**

In a phase I/II study, patients with advanced localised PCa were sequentially treated with 70-74Gy to the prostate and dose-escalating PLN-IMRT at doses of 50Gy (Cohort 1), 55Gy (Cohort 2) and 60Gy (Cohort 3) in 35-37 fractions. Two hypofractionated cohorts received 60Gy to the prostate and 47Gy to PLN in 20 fractions over 4 weeks (Cohort 4) and 5 weeks (Cohort 5). All patients received long-course androgen deprivation therapy. Primary outcome was late RTOG toxicity at 2 years post-radiotherapy for all cohorts. Secondary outcomes were acute and late toxicity using other clinician/patient-reported instruments and treatment efficacy.

**Findings**

Between Aug 9, 2000 and June 9, 2010, 447 patients were enrolled. Median follow-up was 90 months. The 2-year rates of grade 2+ bowel/bladder toxicity were: Cohort 1 - 8.3%/4.2% (95%CI 2.2-29.4/0.6-26.1); Cohort 2 - 8.9%/5.9% (4.1-18.7/2.3-15.0); Cohort 3 - 13.2%/2.9% (8.6-20.2/1.1-7.7); Cohort 4 - 16.4%/4.8% (9.2-28.4/1.6-14.3); Cohort 5 - 12.2%/7.3% (7.6-19.5/3.9-13.6). Prevalence of bowel and bladder toxicity appeared stable over time. Other scales mirrored these results. The biochemical/clinical failure-free rate was 71% (66-75%) at 5 years for the whole group with pelvic lymph node control in 94% of patients.

**Interpretation**

The study shows the safety and tolerability of PLN-IMRT. Ongoing and planned phase III studies will need to demonstrate an increase in efficacy using PLN-IMRT to offset the small increase in bowel side-effects compared with prostate-only IMRT.

## 1 – Introduction

Prostate cancer is the most common cancer in men, accounting for 27% of new cancer cases in 2014 and more than 307,000 men died from prostate cancer in 2012 worldwide.[1,2] In the UK 46,690 new cases were diagnosed in 2014.[2] Most men are now diagnosed with localised disease but high-risk prostate cancer remains life-threatening. Treatment with external-beam radiotherapy (EBRT), androgen-deprivation therapy (ADT) and, in selected cases, high-dose rate brachytherapy have been used in this patient group.[3] About 15,800 men receive radical prostate radiotherapy every year in the UK.[4] However, the merit of elective pelvic lymph node radiotherapy (PLNRT) compared with treatment of prostate and seminal vesicles alone remains controversial and present guidelines suggest that PLNRT should be considered but not mandated for high-risk disease.[1,5] This uncertainty may relate to the modest doses of radiotherapy which are usually given with PLNRT so as to avoid bowel toxicity.

Intensity-modulated radiotherapy (IMRT) makes it possible to increase bowel sparing, which is the dose-limiting normal tissue when treating the pelvis.[6,7] IMRT brings the opportunity to dose escalate which has been linked with increased disease control in prostate cancer.[8–11] The low α/β ratio of prostate cancer makes hypofractionation an attractive option for treatment, with recent data demonstrating equivalent outcomes to standard dose schedules treating the prostate alone.[4] Dose escalation and hypofractionation have not been adequately evaluated for pelvic LNRT, with limited data available from small case series.[8–10,12]

The aim of this study was to test the feasibility of using IMRT to deliver LNRT to patients with high risk prostate cancer, using dose escalated conventional and hypofractionated schedules.

## 2 – Methods

### 2.a - Study design and participants

We performed a single-centre phase I/II study of IMRT to irradiate the prostate and pelvic lymph nodes (PLN) in patients with advanced localized prostate cancer. Eligible patients had prostate cancer with very high risk (T3b/T4) or node positive disease, high risk disease with Gleason score ≥8 or ≥ 2 risk factors, or an estimated risk of nodal metastases of >30% based on the Roach formula.[1,13] Post-prostatectomy patients (T2-T3a, N0) with extensive Gleason score ≥8 disease, seminal vesicle or lymph node involvement were also eligible. Patients unsuitable for radical radiotherapy, or with a history of pelvic surgery, or inflammatory bowel disease were excluded.

Patients were sequentially assigned to receive three different dose-schedules to the PLN of 50, 55, or 60Gy (cohorts 1, 2, 3 respectively) giving 70-74Gy in 2Gy fractions over 7 weeks to the prostate. An integrated boost of 5Gy was given to radiologically suspicious PLN. Two hypofractionated cohorts (cohorts 4 and 5) were then studied, based on equivalent doses to the conventional schedule calculated assuming an α/β ratio of 2·5Gy.

They received 60Gy to the prostate in 3Gy fractions over 4-5 weeks and 47Gy to the PLN. An integrated boost of 4Gy was given to radiologically suspicious PLN. Patients were initially treated in a 4-week schedule (cohort 4), which was later modified to a 5-week schedule (cohort 5) because of acute GI toxicity. Patients irradiated post-prostatectomy received 64Gy in 32 fractions in cohorts 1 and 2, 65Gy in 35 fractions in cohort 3, or 55Gy in 20 fractions in cohorts 4 and 5 (Appendix table SUPP-1).

2.b - Procedures

Patients received long course (2-3years) androgen deprivation therapy (ADT) with at least 6 months treatment before radiotherapy commenced.

Patients underwent planning CT-scans with a comfortably full bladder and empty rectum. From 2011, sodium citrate enemas were used for patients with rectal dilatation. Inverse radiotherapy planning was performed for all patients using mandatory normal tissue dose-constraints (Appendix table SUPP-2) as previously described.[14,15] CTV1 included the prostate and any radiologically involved seminal vesicle, with a margin of 8mm posteriorly and 10mm in all other directions to create PTV1. CTV2 included PLN and uninvolved seminal vesicles (Appendix 2). A uniform margin of 5mm was applied to create PTV2. CTV3 included any radiologically involved lymph nodes and uniform margin of 5mm was applied to create PTV3. All organs-at-risk were contoured as solid organs, by defining the outer wall of rectum, bowel and bladder. The rectum was contoured from the anus (usually at the level of the ischial tuberosities or 1cm below the lower margin of the PTV whichever was more inferior) to the recto-sigmoid junction. Bowel was outlined separately, excluding rectum and extending 2cm above the superior extent of PTV2. Bladder was outlined from base to dome. Treatment verification was performed offline using bony anatomy for registration (Appendix text SUPP-1).

Staging investigations included PSA, histological diagnosis, radiological or surgical lymph node assessment and staging MRI, CT, or bone scan.

Acute side-effects were recorded weekly using the RTOG scoring system up to 18 weeks after initiating radiotherapy. Late toxicity was scored according to the EORTC/RTOG and LENT/SOM late toxicity scales, and UCLA-PCI patient-reported outcomes.[16–18] Data was collected at baseline, 6-monthly up to five years post radiotherapy and yearly thereafter.

PSA was measured 6-monthly for 8 years after the start of ADT and annually thereafter. The nadir PSA was the lowest level recorded post radiotherapy. Biochemical failure was defined according to the Phoenix consensus guidelines as a PSA value greater than the nadir plus 2ng/ml. Local recurrence was confirmed on MRI pelvis or biopsy and post-prostatectomy patients (n=34) were excluded from this endpoint. Distant relapse was confirmed on MRI, CT scan, bone scan, or choline PET-CT scan.

2.c – Statistical considerations

The primary endpoint was late RTOG toxicity assessed 2 years after radiotherapy. Secondary endpoints included assessment of all toxicity scales during follow-up and disease recurrence. Patients were stratified by total bowel volume outlined (<450cc vs. ≥450cc). For each dose level stratified by bowel volume, at least 15 men were treated and followed up for at least 1 year. If 0 of 15 men had a grade ≥3 RTOG complication, then a ≥20% grade ≥3 toxicity rate was excluded with one sided significance level 0.05. As the dose to the initial cohort was modest, patients in the low bowel volume group were recruited to the second dose level after seven men had ≥12 months of follow-up, provided none of these had recorded a grade 3 or higher complication. For other cohorts and bowel volume groups, recruitment continued at that level until such time as fifteen men had been treated and followed up for at least one year. This strategy ensured that the low bowel volume group moved to the higher dose cohorts in advance of the high bowel volume group. Because recruitment continued in each cohort and bowel volume group until such time as the required total of men had reached ≥12 months of follow-up, in all cases the eventual sample size in each group exceeded the required total to an extent which varied according to the recruitment rate over time.

In cohorts 3 and 4, a further dose expansion phase was planned, with a target sample size of 103 patients (of any bowel volume) evaluable at 2 years in order to rule out a late grade 2 or over (grade 2+) bowel toxicity rate of >=25%, using a one-sided alpha 0·05 and power of 80% with an assumed true rate of toxicity not more than 15%. The sample size was expanded to a total of 123 in each of cohort 3 and 4 to allow for an expected drop-out rate of 16% by 2 years. However, due to high levels of acute bowel toxicity observed in cohort 4 (4-weekly schedule), the treatment schedule was amended to 5 weeks (cohort 5) with a target of 123 patients.

Late toxicity rates were calculated using Kaplan-Meier methods with time measured from start of radiotherapy. Rates by 1 and 2 years were calculated with 95% confidence intervals (CI). One-sided 95% CI were constructed for rate of RTOG grade 3+ bowel toxicity at 1 year (cohort 1 and 2) and for rate of RTOG grade 2+ bowel toxicity at 2 years (cohorts 3 and 4) in order to assess safety of the primary endpoint. In addition, the number of men experiencing defined toxicity grades at each timepoint was reported as a percentage of all men assessed. Efficacy was assessed using Kaplan-Meier methods to calculate length of disease control (defined as a composite endpoint of biochemical progression, local or lymph node/pelvic recurrence, or distant metastasis, or recommencement of androgen deprivation therapy), length of local disease control, length of distant disease control, disease specific, and overall survival from start of radiotherapy. For disease specific and overall survival, patients were censored at the date they were last known to be alive. Rates at 2 and 5 years were calculated with 95% CI. Data was extracted in September 2015 and analysed using STATA v13.1.

Univariable Cox regression on length of disease control was performed using factors of dose cohort, N-stage (N0 vs. N1-3), baseline PSA (log transformed), clinical T-stage (grouped as T1/T2; T3a; T3b+) and Gleason score (grouped as ≤6; 7; ≥8). Forward and backward stepwise selection methods were used to combine significant

factors (p<0·05 on univariable analysis) into a multivariable model and produce adjusted hazard ratios with 95% CI.

### 2.d – Trial setup

Institutional clinical research and ethics committees approved the study which was included in the National Cancer Research Network (NCRN) portfolio in December 2003. The trial was performed in accordance with the principles of good clinical practice and overseen by a trial management group. All patients provided written informed consent.

## 3 –Outcomes

Between Aug 9, 2000 and June 9, 2010, 447 male patients were recruited to cohorts 1-5, 426 were treated according to protocol and 421 were available for late toxicity assessment (Figure 1). Median age was 65 years (IQR: 60-70yrs) with median presenting PSA of 21·4ng/ml (10·2-42·8). 46% of patients had clinical T3/T4 disease, 54% had Gleason 8 or over scores, and 17% PLN involvement. Cohort 1 had a higher proportion of patients with adverse features than cohorts 2-5. Median duration of adjuvant hormone therapy was 35 months (33-37 months) and median follow-up was 90 months (Table 1), with 398 patients out of 426 followed-up for toxicity for at least 2 years and 327 followed up for at least 5 years. Thirty-four patients (8%) were treated adjuvantly after undergoing a radical prostatectomy prior to entering the trial (table SUPP-6).

Acute bowel toxicity peaked at 6-8 weeks in the conventionally-fractionated (CFRT) cohorts 1-3, compared with 4-5 and 5-6 weeks in the hypofractionated (HFRT) cohorts 4-5 respectively. Peak grade 2+ toxicity was recorded in 40%, 56%, and 54% of cohorts 1-3 respectively. Patients in cohort 4 developed the highest acute bowel toxicity rates, with 66% reporting grade 2+ bowel toxicity compared with 48% in cohort 5. However, by 18 weeks post-treatment the incidence of grade 2+ RTOG bowel toxicity was similar in all cohorts (Figure 2 and Appendix table SUPP-3). Acute grade 3+ peak toxicity occurred in 0 (0%), 1 (1%), 5 (4%), 3 (5%), and 9 (7%) patients in cohorts 1-5 respectively. One patient in each of cohorts 4 and 5 developed grade 4 acute toxicity and there was one death (recorded as Grade 5 toxicity), determined at autopsy to have resulted from perforation of an undiagnosed caecal carcinoma.

Acute bladder toxicity was related to dose in the CFRT cohorts, with peak grade 2+ toxicity recorded in 28%, 44%, and 53% patients in cohorts 1-3 respectively. Patients in cohort 4 experienced higher rates of bladder toxicity of grade 2+ (61%) than patients in cohort 5 (53%). However, rates of grade 2+ bladder toxicity at 18 weeks were low and similar in all cohorts (Figure 2).

The 2-year cumulative rate of RTOG grade 2+/grade 3+ bowel toxicity was 8·3% (95% CI 2·7-24·3)/0%, 8·9% (4·1-18·7)/1·5% (0·2-10.4), and 13·2% (8·6-20·2)/2·2% (0·7-6·7) in cohorts 1-3 (CFRT) respectively. In the HFRT cohorts 4-5, the 2 year rate of grade 2+/grade 3+ bowel toxicity was 16·4% (9·2-28·4)/6·6% (2·5-16·7), and

12·2% (7·6-19·5)/0·8% (0·1%-5·7%) respectively (Figure 3 and Appendix tables SUPP-4 and SUPP-5). A comparable 12·2% (4·7-29·3) of post-prostatectomy patients experienced grade 2+ bowel toxicity, with no clear difference between the cohorts in view of the small numbers included (table SUPP-6).

The 2-year cumulative rates of grade 2+/grade 3+ bladder toxicity were 4·2% (0·6-26·1)/4·2% (0·6-26·1), 5·9% (2·3- 15·0)/2·9% (0·7-11·3), and 2·9% (1·1-7·7)/ 2·2% (0·7-6·8) in cohorts 1-3 (CFRT) respectively. In cohorts 4-5 (HFRT), rates were 4·8% (1·6-14·3)/1·6% (0·2-10·9), and 7·3% (3·9-13·6)/1·2% (0·4-6·4) respectively (Figure 3 and Appendix tables SUPP-4, SUPP-5 and SUPP-6). Post-prostatectomy patients had a higher rate of urinary symptoms at 9·0%, albeit with a large CI (3·0-25·4), with no clear differences between cohorts (table SUPP-6).

The prevalence of bowel and bladder toxicity appeared stable over time (Figure 3 and Appendix tables SUPP-4 and SUPP-5). At 5 years follow-up, 0/0 (0%/0%), 1/0 (2%/0%), 5/1 (5%/1%), 3/0 (6%/0%), and 2/0 (2%/0%) men had grade 2+/3+ RTOG bowel toxicity in cohorts 1-5 respectively. The 5-year prevalence of grade 2+ bladder toxicity was 0/0 (0%/0%), 2/0 (4%/0%), 1/0 (1%/0%), 2/2 (4%/4%), and 3/1 (3%/1%) in cohorts 1-5 respectively.

All estimates of late toxicity met predefined safety criteria. Results using the RMH and LENT/SOM assessments are given in Appendix tables SUPP-4 and SUPP-5. Table SUPP-6 details rates of late symptoms in patients treated post-prostatectomy.

Patient-reported outcomes (PRO) were obtained with the UCLA-PCI instrument (Appendix tables SUPP-4 and SUPP-5). The cumulative 5-year rate of small or worse bowel/bladder bother was 26% (95% CI 13-50)/ 37% (19-63), 49%(37-63)/ 35%(24-49), 38% (30-48)/ 35% (27-45), 56% (43-69)/ 45% (32-59), and 54% (44-64)/ 46% 37-57) in cohorts 1-5 respectively. Prevalence of moderate/severe bowel problems at 2 years was 1/22 (5%), 4/47 (9%), 6/84 (7%) , 4/45 (9%), and 10/85 (12%) in cohorts 1-5 respectively. Moderate/severe urinary problems at 2 years were reported by 1/22 (5%), 5/47 (10%), 6/85 (7%), 6/47 (13%), and 10/85 (12%) in cohorts 1-5 respectively. At 5 years, prevalence rates for moderate/severe bowel problems were 0/12 (0%), 1/42 (2%), 1/76 (1%), 2/35 (6%), and 2/54 (4%) in cohorts 1-5 respectively. No severe bowel problems were reported at 5 years. Prevalence of moderate/severe urinary problems at 5 years was 0/12 (0%), 2/42 (4%), 6/78 (7%), 2/35 (6%), and 3/57 (5%) in cohorts 1-5 respectively. No men in the HFRT cohorts had severe urinary problems at 5 years.

Biochemical or clinical progression occurred in 169/426,(39·7%) of patients. At first-relapse, biochemical failure alone occurred in 141/169 (59%), local recurrence in 11/169 (7%), distant metastases in 7/169 (4%), and 3/169 (2%) patients commenced salvage hormone therapy in the absence of radiological confirmation of sites of disease. On subsequent follow-up there were 41/426 (10%) confirmed relapses within the prostate, 26/426 (6%) PLN recurrences, 39/426 (9%) relapses in distant nodal groups, and 99/426 (23%) relapses at other metastatic sites. The biochemical/clinical failure-free rate was 71% (95% CI 66-75%) at 5 years for the whole group, with 38%, 61%, 70%, 80%, and 78% remaining recurrence free in cohorts 1-5 respectively.

Disease specific survival at 5 years was 92% (95% CI 89-94%) for the whole cohort and 79%, 88%, 92%, 97%, and 95% in cohorts 1-5 respectively . The 5-year overall survival was 87% (95%CI 84-90%) and 76%, 87%, 86%, 89%, and 91% in cohorts 1-5 respectively (Figure 4).

Multivariate analysis identified pre-treatment PSA level (p=0·004), PLN involvement (p=0·02), T stage (p=0·05), and dose cohort (p=0·05) as factors associated with length of disease control. Patients treated in cohorts 4 and 5 had similar outcomes (Table 2).

## 4 – Discussion

We found acceptable acute and late GI/GU toxicity measured using both CRO and PRO in all patient cohorts. To assess the impact of PLNRT, we compared these results with a large contemporaneous group of patients treated in the CHHiP phase III trial, which used IMRT to treat the prostate alone using similar CFRT/HFRT schedules and scored side-effects with the same compendium of CRO and PRO.[4] We also used comparable data reported in a recent systematic review (Holch et al.), which included no studies with PLNRT.[19] We found that acute grade 2+ GI toxicity occurred in 40-56% of CFRT patients in cohorts 1-3 compared to 25% in CHHiP and 21-60% in Holch et al., with a rate of 66% in cohort 4 (four-week HFRT) compared to 30% in the CHHiP HFRT group and 36% in Holch et al. Increasing the overall treatment-time to five weeks reduced the rate to 48% in cohort 5. However, these side-effects settled rapidly in all groups. There were no differences in grade 2+ toxicity by 18 weeks, although some increase in mild grade 1+ side effect rates persisted with PLNRT (25-36% compared with 21% in CHHiP). There were no clear differences between grade 2+ peak/week 18 or grade 1+ week 18 GU toxicities between cohorts 1-5 or when comparing with the CHHiP or Holch et al. GU toxicity rates (Appendix table SUPP-3).

Late GI side-effects appeared highest in cohort 4 using clinician-reported outcomes (CRO) scales, both two and five years after treatment. For example, two-year estimated cumulative proportions with grade 2+ (CRO) or small or worse bowel problems (PRO) were 16%, 16%, 34%, and 53% using the RTOG, RMH, LENT-SOM and UCLA-PCI scales, respectively, compared with 8-13%, 8-15%, 13-25%, and 21-43% for the other cohorts. The rates for the comparator CHHiP group were 8-9%, 10-11%, 16-18%, and 25-27% respectively. Applicable results in the Holch et al. systematic review were similar to CHHiP. The increased acute and late GI toxicity seen in Cohort 4 would be consistent with a consequential late side-effect.[20,21] Extending treatment duration to five weeks by treating four times per week appears to reduce any impact of hypofractionation (Appendix tables SUPP-4 and SUPP-5).

Late GU side-effects, assessed using RTOG and RMH CRO scales, were similar between all groups with no obvious impact from dose, fractionation schedule or use of PLNRT. However, the cumulative proportion of patients with grade 2+ toxicity (LENT-SOM, CRO) or small or worse bladder bother (UCLA-PCI, PRO) at 2 years was somewhat higher than in the CHHiP groups, suggesting these scales are more sensitive. Any differences

had disappeared by five years, when the prevalence of small or worse bladder bother was 8-20% in cohorts 1-5 and 17% in the CHHiP comparator group (Appendix tables SUPP-4 and SUPP-5).

Late bowel and bladder side-effects did not show consistent differences when the sub-group of patients treated post-prostatectomy were analysed, either with CRO or PRO data (table supp-6). However, these results should be interpreted with caution given that only 34 patients were treated adjuvantly in this trial and limited conclusions can be drawn.

The low level of side-effects seen in the present series probably relates to the use of a strict IMRT protocol and the mandating of dose-constraints for both bowel and bladder. However the doses delivered in cohorts 3-5 are at least 10% higher than used in past and contemporary practice (Appendix figure 1). Similar dose increments have been shown to improve disease outcome in trials treating the prostate alone.[22,23]

The 5-year OS in this series (87%; 95% CI 84-90%) is at least comparable to a recent retrospective series from the National Cancer Database in which 7606 patients were treated with PLNRT with 5-year overall survival of 81.6%.[24] In the group randomised to PLNRT in the RTOG 94-13 trial, a 4-year OS of 84% was reported. The 5-year biochemical/clinical failure free rate of 71% for our entire series is similar to the control group treated with radiotherapy in the contemporaneous MRC STAMPEDE trial which showed an estimated 75%/50% 5-year control in patients with N0/N1 disease respectively.[25]

The low pelvic lymph node recurrence rate of 6% is reassuring, but further efforts to improve local control in the prostate for patients with aggressive bulky disease appear warranted (hazard ratio for local disease control in T3b+: 1·70, 95% CI 1·11-2·60; Table 2). Approaches using high dose focal radiotherapy boosts, prostatectomy or additional ablative focal therapies using, for example, high intensity focussed ultrasound or cryotherapy can be considered.[26] Avoidance of toxicity, however, is important, as a considerable majority of patients have disease controlled by IMRT and androgen-deprivation therapy or, alternatively, relapse with metastatic disease outside the pelvis, making additional measures to improve local control futile. The development of biomarkers to predict the response to radiotherapy and define patient groups destined to develop metastatic disease would therefore be invaluable in guiding treatment individualisation.[27] Treatment intensification with additional systemic treatments, such as docetaxel or the new generation of hormonal therapies, can be considered.[28] Additionally, radiogenomic and dosimetric studies are aiming to refine estimates of an individual's risk of developing side-effects.[29,30]

## 5 – Conclusion

This study has provided the safety data to encourage further investigation of high dose LNRT. The treatment techniques described have been generalised in a UK national phase II randomised pilot study, PIVOTAL (ISRCTN48709247) which compares prostate and pelvis with prostate alone IMRT. Hypofractionated RT will

become the UK standard of care following the CHHiP trial.[4] The safety data of hypofractionated schedules in the present study are encouraging and the use of HFRT in a new trial, PIVOTALboost, is planned. It will assess the value of pelvic IMRT as well as the effects of a focal high-dose intraprostatic boosts to dominant lesions. These studies will complement other ongoing phase III studies, RTOG 09-24 (NCT01368588) and PEACE 2 (NCT01952223), which should finally determine the role of PLNRT in prostate cancer. An increase in efficacy will need to be demonstrated to offset the small but expected adverse effects of pelvic IMRT.

## 6 – Figure legends

**Figure 1**

**Title:** Trial profile

**Legend:** RT = radiotherapy. LN = lymph node. CFRT = Conventionally-fractionated radiotherapy. HFRT = Hypofractionated radiotherapy.

**Figure 2**

**Title:** Acute RTOG grade 2+ toxicity by timepoint and treatment group.

**Legend:** A: Prevalence of acute RTOG grade 2+ bowel toxicity (A) and of acute RTOG grade 2+ bladder toxicity (B). RTOG = Radiation Therapy Oncology Group scale. Grade 2+=score of grade 2 or worse.

**Figure 3**

**Title:** Late bowel and bladder toxicity by timepoint, assessment, and treatment group.

**Legend:** Grade distribution of (A) bowel adverse events and (B) bladder adverse events measured with RTOG. Cumulative incidence of (C) grade 2+ bowel adverse events measured with RTOG and (E) small or worse bowel symptom scores measured with UCLA-PCI. Cumulative incidence of (D) grade 2+ bladder adverse events measured with RTOG and (F) small or worse bladder symptom scores measured with UCLA-PCI. RTOG=Radiation Therapy Oncology Group scale. UCLA-PCI=UCLA Prostate Cancer Index. Grade 2+=grade 2 or worse adverse event.

**Figure 4**

**Title:** Biochemical failure-free survival (A), disease-specific survival (B) and overall survival (C).

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**Table 1**

**Title:** Patient Demographics.

**Legend:** Data are n (%) or median (IQR) unless otherwise stated. NCCN=National Comprehensive Cancer Network. PSA = prostate-specific antigen. ADT = androgen deprivation therapy. CT = Computed Tomography. MR = magnetic resonance.

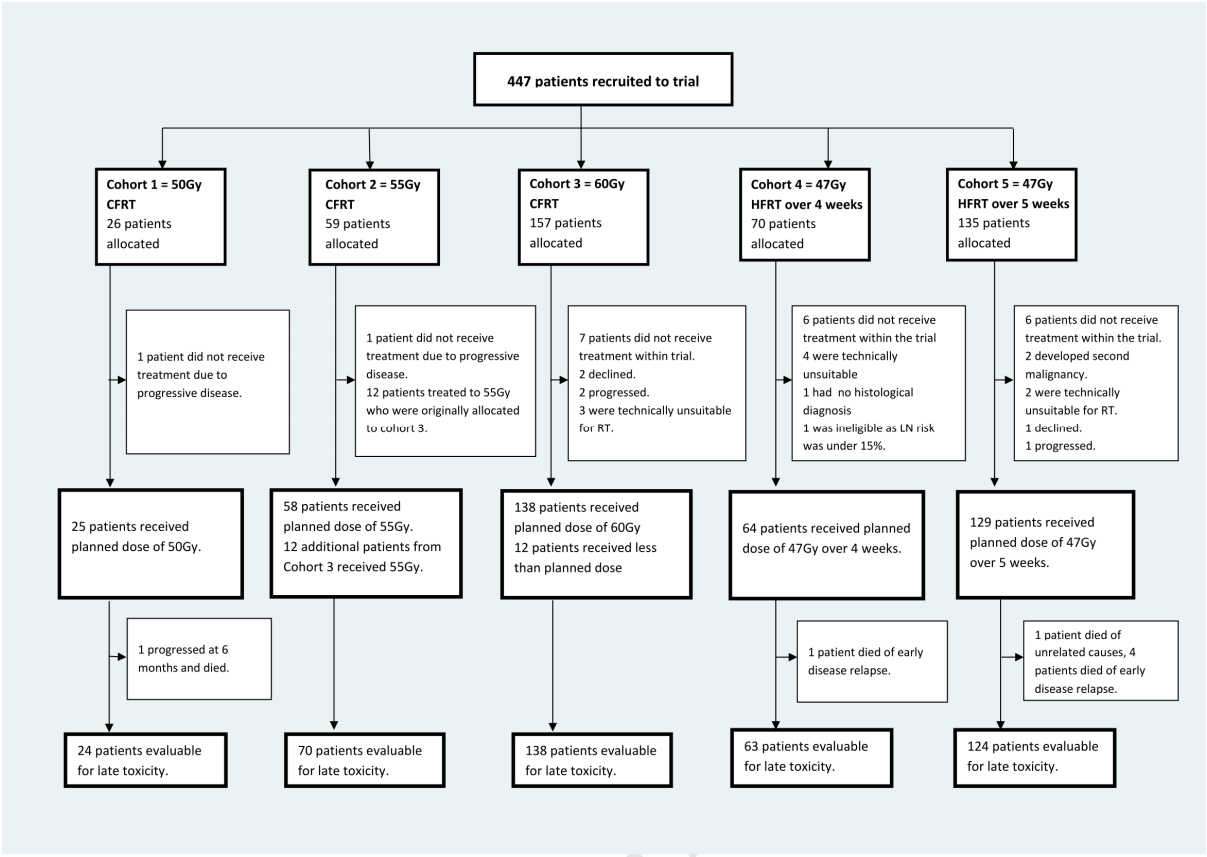
| | **Cohort 1 50Gy (n=25)** | **Cohort 2 55Gy (n=70)** | **Cohort 3 60Gy (n=138)** | **Cohort 4 47Gy/4wks (n=64)** | **Cohort 5 47Gy/5wks (n=129)** | **Cohorts 1-5 n=426** |
|---|---|---|---|---|---|---|
| **Age at Diagnosis (years)** | 63 (56-67) | 62 (57-67) | 65 (59-69) | 66 (62-72) | 67 (62-71) | 65 (60-70) |
| **PSA at Diagnosis (ng/mL)** | 39.1 (24.7-78.0) | 25.4 (12.4-44.7) | 24.5 (10.2-47.1) | 15.4 (8.5-31.4) | 18 (8.1-37.9) | 21.4 (10.2 – 42.8) |
| **Gleason Score** | | | | | | |
| Gleason ≤7 | 13 (52%) | 34 (48%) | 60 (43%) | 22 (35%) | 56 (44%) | 185 (44%) |
| Gleason 8 | 4 (16%) | 17 (24%) | 29 (21%) | 13 (20%) | 11 (9%) | 74 (17%) |
| Gleason ≥9 | 6 (24%) | 16 (22%) | 48 (35%) | 28 (44%) | 60 (47%) | 158 (37%) |
| Unknown | 2 (8%) | 3 (4%) | 1 (1%) | 1 (2%) | 2 (2%) | 9 (2%) |
| **CT/MR N Stage** | | | | | | |
| N0 | 16 (64%) | 49 (70%) | 115 (83%) | 51 (80%) | 110 (85%) | 341 (80%) |
| N1 | 9 (36%) | 14 (20%) | 22 (16%) | 11 (17%) | 18 (14%) | 74 (17%) |
| Unknown | 0 (0%) | 7 (10%) | 1 (1%) | 2 (3%) | 1 (1%) | 11 (3%) |
| **Clinical T Stage** | | | | | | |
| cT1/T2 | 18 (32%) | 23 (33%) | 60 (43%) | 6 (9%) | 42 (32%) | 156 (37%) |
| cT3 | 17 (68%) | 34 (49%) | 57 (41%) | 17 (27%) | 56 (43%) | 192 (45%) |
| cT4 | 0 (0%) | 2 (3%) | 3 (2%) | 28 (44%) | 1 (1%) | 6 (1%) |
| Unknown | 0 (0%) | 11 (16%) | 18 (13%) | 13 (20%) | 30 (23%) | 72 (17%) |
| **Duration of ADT (months)** | 36 (32-36) | 35 (33-37) | 36 (33-40) | 34 (33-36) | 35 (34-37) | 35 (33-37) |
| **Median length of follow-up (years)** | 13.9 | 11.2 | 9.0 | 7.1 | 5.7 | 7.6 |

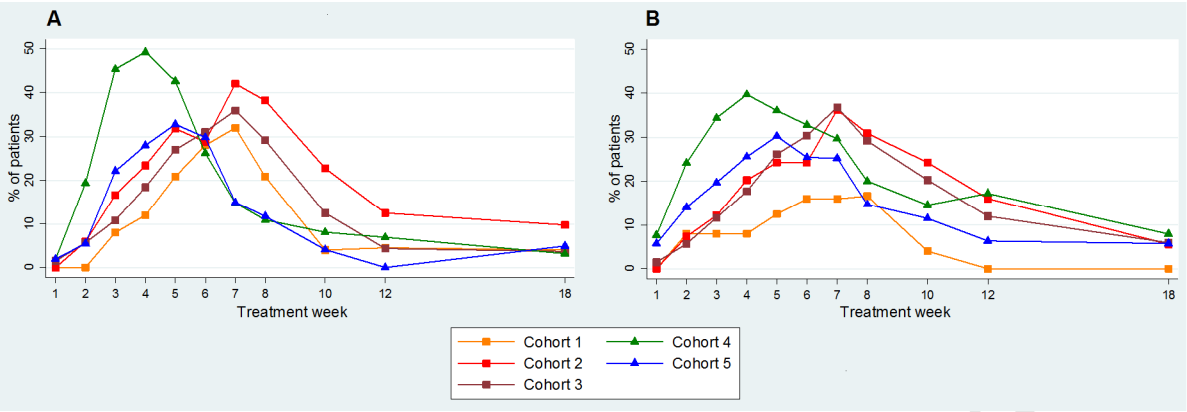
**Table 2**

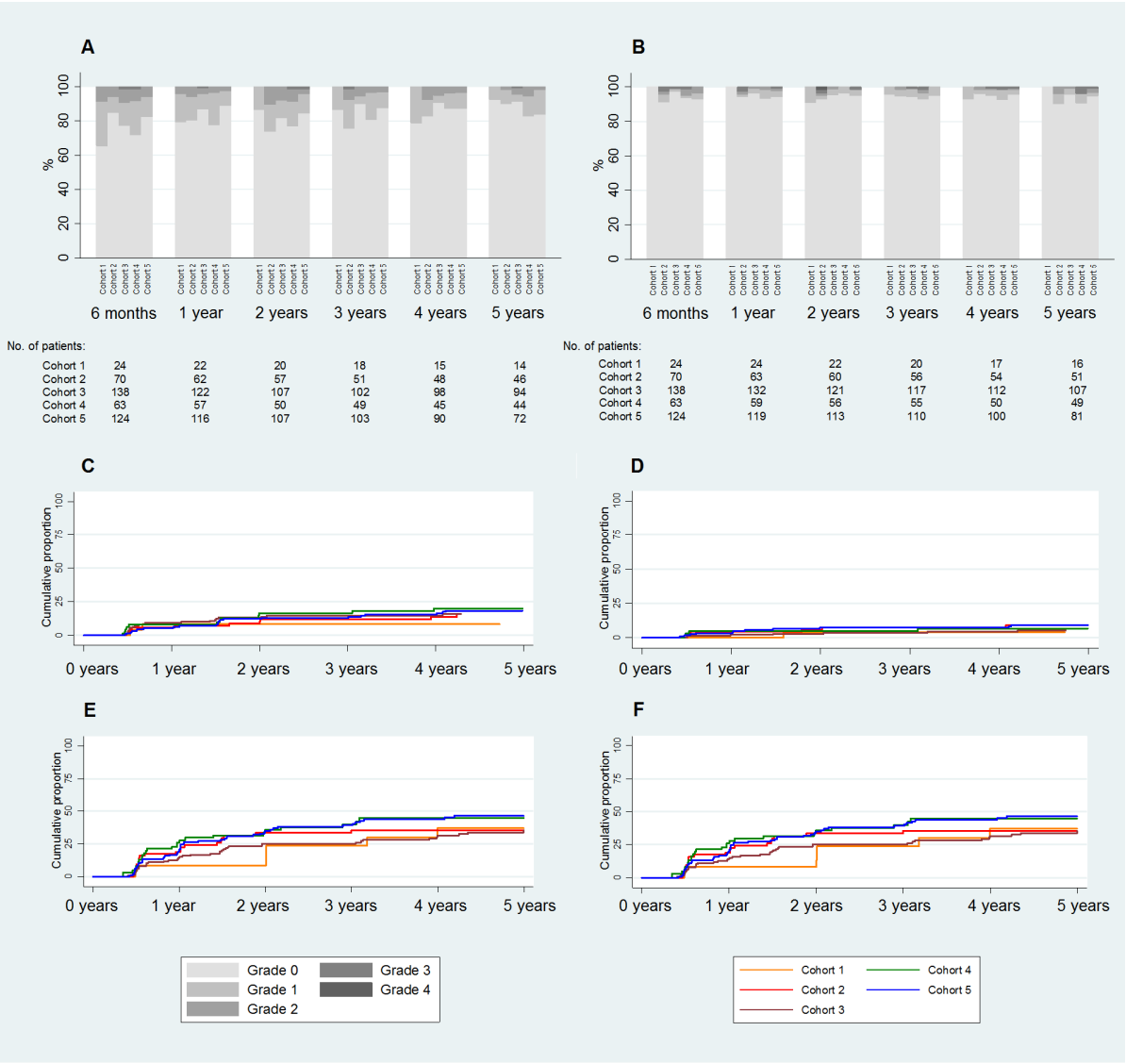
**Title:** Multivariate cox regression analysis, for length of disease control (n=326).

**Legend:** Hyp.=Hypofractionated.

| Factor | Levels | Hazard Ratio (95% CI) | p-value |
|---|---|---|---|
| **Dose Cohort** | Cohort 1 - 50Gy<br>Cohort 2 - 55Gy<br>Cohort 3 - 60Gy<br>Cohort 4 - Hyp. 4 wk<br>Cohort 5 - Hyp. 5 wk | 1 (NA)<br>0.71 (0.40, 1.26)<br>0.45 (0.26, 0.80)<br>0.50 (0.25, 1.01)<br>0.45 (0.24, 0.84) | 0.05 |
| **Log max pre-treatment PSA** | Continuous. ng/ml | 1.30 (1.08, 1.57) | <0.01 |
| **Clinical T-stage** | T1/T2<br>T3a<br>T3b+ | 1 (NA)<br>1.22 (0.78, 1.91)<br>1.70 (1.11, 2.60) | 0.05 |
| **Radiological N stage** | N0<br>N+ | 1 (NA)<br>1.65 (1.09, 2.48) | 0.02 |






A
B
%
0
20
40
60
80
100
6 months
1 year
2 years
3 years
4 years
5 years
No. of patients:
Cohort 1 24 22 20 18 15 14
Cohort 2 70 62 57 51 48 46
Cohort 3 138 122 107 102 98 94
Cohort 4 63 57 50 49 45 44
Cohort 5 124 116 107 103 90 72
No. of patients:
Cohort 1 24 24 22 20 17 16
Cohort 2 70 63 60 56 54 51
Cohort 3 138 132 121 117 112 107
Cohort 4 63 59 56 55 50 49
Cohort 5 124 119 113 110 100 81
C
D
E
F
Cumulative proportion
0
25
50
75
100
0 years
1 year
2 years
3 years
4 years
5 years
Grade 0
Grade 1
Grade 2
Grade 3
Grade 4
Cohort 1
Cohort 2
Cohort 3
Cohort 4
Cohort 5