Title:

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

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Abstract (271 words)

Background

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

Methods

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

Findings

Between June 2010 to July 2011, 293 men were recruited from 16 centres (48 no-IGRT, 137 IGRT-S and 108 IGRT-R). Median follow-up is 56.9 months (IQR 54.3-60.9). Rectal and bladder dose-volume and surface percentages were significantly lower in IGRT-R compared to IGRT-S group ($p<0.0001$). The cumulative proportion with RTOG grade$\geq$2 toxicity reported to 2 years for bowel was 8.3(95% CI 3.2-20.7)%, 8.3(4.7-14.6)% and 5.8(2.6-12.4)% and for urinary 8.4(3.2-20.8)%, 4.6(2.1-9.9)% and 3.9(1.5-9.9)% in the no IGRT, IGRT-S and IGRT-R groups respectively. In an exploratory analysis, treatment efficacy appeared similar in all three groups.

Interpretation

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

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Introduction

Intensity-modulated radiotherapy (IMRT) enables dose escalation to the prostate target volume, with low gastrointestinal or genitourinary toxicity.[1–4] The success of radical prostate radiotherapy depends on accurate delivery of high dose conformal radiotherapy to a defined target volume. Image guided radiotherapy (IGRT) with daily online imaging has the potential to improve prostate localisation, consequently improving treatment accuracy and reducing the required clinical to planning target volume margin.[5] This may result in less normal tissue receiving target doses, and consequently less toxicity.[6]

However, to enable online daily IGRT, either an additional invasive procedure for insertion of fiducial markers into the prostate is required or availability of treatment equipment enabling soft tissue matching is needed. Intrafraction motion and outlining uncertainties necessitate a small margin around the target volume.[5]

In addition to optimising prostate radiotherapy techniques, there has been interest in the exploitation of fraction sensitivity of prostate cancer through hypofractionation.[7–9] This has been successfully examined within the UK multicentre randomised controlled trial (Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer; CHHiP) which aimed to compare the efficacy and toxicity of conventional and hypofractionated radiotherapy using high-quality radiation techniques. Within the trial, 3216 patients were enrolled from 71 centres within the UK between October 2002 and June 2011.[10]

During the latter stages of the CHHiP trial, IGRT became available in participating treatment centres. Rather than this technology being introduced into the CHHiP trial in a piecemeal fashion, the CHHiP IGRT phase 2 substudy was developed. We aimed to determine the feasibility and generalisability of IGRT in the context of a multicentre trial and assess acute

and late toxicity. A patient reported outcome (PRO) protocol was subsequently integrated into the substudy. To our knowledge, this is the only randomised study of prostate IGRT undertaken worldwide.

Methods

Study design and participants

CHHiP is a randomised phase 3, non-inferiority trial which recruited men with localised prostate cancer (pT1b-T3aN0M0).[10] Patients were randomly assigned (1:1:1) to conventional 74 Gray (Gy) in 2Gy/fraction (f) daily or one of two hypofractionated schedules giving 60Gy or 57Gy in 3Gy/f daily. Patients were all treated with intensity modulated radiotherapy.[11]

The IGRT substudy was implemented following a separate ethics application in June 2010 and approved by Central London REC1 Research Ethics Committee (10/H0718/31). Men who had entered the CHHiP trial were eligible for the IGRT substudy provided they had no contraindication to implanted fiducial markers or a hip prosthesis or fixation which would interfere with positional imaging. A separate consent was required for the IGRT substudy in addition to the main trial entry. Treatment allocation to the IGRT substudy occurred immediately following randomisation to the CHHiP trial. Minimisation was used to assign patients in a 1:1:1 ratio to either no-IGRT – using standard CHHiP planning margins, IGRT using standard CHHiP planning margins (IGRT-S), or IGRT with reduced planning margins (IGRT-R), with radiotherapy centre and dose/fractionation schedule as balancing factors. Neither patients nor clinicians were blinded to treatment allocation. Sixteen UK radiotherapy centres took part in this substudy. Centres could choose depending on previous IGRT experience to randomise among all three options or no IGRT versus IGRT-S or IGRT-S versus IGRT-R. In 2014, a patient reported outcomes (PRO) assessment was introduced to collect data at a single time point at least 3 years post randomisation. This separate protocol received ethical approval from the NRES Committee South West – Central Bristol (14/SW/1071).

Treatment

Patients randomised to treatment with IGRT, either had fiducial markers inserted into the prostate using trans-rectal ultrasound guidance or soft tissue matching if using the TomoTherapy® system. Fiducial markers were implanted with antibiotic cover approximately 2 weeks prior to the radiotherapy planning scan. Patient positioning was supine and target and treatment planning volumes have been previously described.[11] Treatment was planned and delivered using an integrated simultaneous boost technique (SIB) with three different target volumes and dose levels as previously detailed[12] and illustrated in Table S1. Mandatory dose constraints were defined for both target coverage and avoidance of normal tissues including rectum, bowel, bladder and femoral heads (Table S2). Treatment was delivered with 6-15 MV photons with multileaf collimators to shape beams.

Patients randomised to no-IGRT, had offline portal imaging to verify treatment accuracy, which was to be within 3mm. Patients receiving IGRT had daily pre-treatment imaging and any observed set-up error $\geq$2mm was corrected prior to treatment. No post-correction imaging was required. A quality-assurance programme previously detailed was designed as an integral part of the study.[12]

Trial assessments

Pre-trial staging investigations included PSA, lymph node assessment by MRI or CT, and bone scan. Histology was assessed from diagnostic TRUS guided biopsies (or TURP specimens) and reported using the Gleason system.

Toxicity experienced from fiducial marker insertion was recorded using CTCAE grading.[13]

Pre-hormone and pre-radiotherapy clinical assessments used Late Effects of Normal Tissues Subjective-Objective Management (LENT-SOM)[14] and the Royal Marsden Hospital (RMH) grading.[15] Clinical assessment of acute toxicity was made weekly during radiotherapy and at weeks 10, 12 and 18 from the start of radiotherapy using the Radiation Therapy Oncology (RTOG) scoring system.[16] Late toxicity was assessed at 6, 12, 18 and 24 months then annually to 5 years using RTOG, LENTSOM and RMH scoring systems.

In the PRO substudy, data was collected at a single time point using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire, (EPIC-50 used for bowel and urinary domains and EPIC-26 for sexual and hormonal domains) [17], the Vaizey Incontinence[18], Short Form 12 (SF-12)[19] and International Index of Erectile Function (IIEF-5)[20] questionnaires.

Questionnaires were sent directly from participating centres to patients (following confirmation of health status) who were ≥3 years from completing treatment. A single reminder letter was sent.

For each patient, the treatment planning data (planning CT, dose distribution and organ contours) were uploaded using dedicated analysis software (VODCA, MSS Medical Software Solutions, Hagendorn, Switzerland). Using in-house code, all radiotherapy plans were converted into equivalent dose in 2Gy per fraction, using Withers formula[21] with an α/β ratio of 3Gy for rectum and 5Gy for bladder. Dose volume (DVH) and dose-surface (DSH) histograms were generated for the rectum and bladder.

Statistical considerations

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

Analysis methods

All analyses have been presented according to randomly allocated IGRT group. Descriptive statistics and boxplots have been used to present treatment planning data. Analyses of side effects included all data available at each time point for patients who received at least one fraction of radiotherapy (unless otherwise stated). Acute and late toxicity have been presented as stacked bar charts and the prevalence of grade≥1, grade≥2 and grade≥3 at each time point. Worst acute bladder and bowel toxicity was calculated using the worst grade reported during the first 18 weeks from the start of radiotherapy. For the primary

endpoint, only patients with a 2 year RTOG toxicity assessment were included in the denominator, although a sensitivity analysis was conducted using all randomised patients. The proportion of patients with RTOG bladder or bowel toxicity of grade≥2 at 2 years were presented together with exact binomial 95% confidence intervals. Time to first occurrence of late radiation induced side effects of grade≥1 and grade≥2 were analysed using the Kaplan Meier method to calculate the cumulative proportion with events reported on the 2 year assessment form for each scoring system. Time was measured from the start of radiotherapy. Patients not experiencing an event were censored at date of last toxicity assessment or at date of death for deceased patients. The log-rank test was used to compare no IGRT versus IGRT-S and IGRT-S versus IGRT-R with a significance level of 1%, to account for multiple comparisons. Biochemical/clinical failure was defined as time to first PSA failure (PSA value greater than nadir +2ng/ml with a consecutive confirmatory PSA value) or prostate cancer recurrence (local, lymph node, pelvic or distant). Patients event free at the time of analysis were censored at their last know PSA assessment.

Statistical analyses were based on a data snapshot taken on 18th May 2016 (except for efficacy analyses which were based on a snapshot taken on 3rd April 2018 to maximise data maturity). All analyses were performed using STATA Version 13.1. Patient reported outcomes were scored in accordance with the recommended scoring manuals[22,23] and presented as descriptive statistics by treatment group. The Vaizey questionnaire is scored on a continuous scale, with minimum score, 0 representing perfect continence and a maximum score, 24 representing total incontinence.[18] Patients were divided into 3 categories for Vaizey total score according to tertiles and dose data presented. In health related quality of life, the clinically meaningful change is defined as a mean change score exceeding half the standard deviation of the baseline value.[24] As there was no baseline data available for this patient group, the mean and standard deviation values from the main CHHiP trial QoL substudy[25] (Table S3) were used to define a threshold score for a meaningful change for the EPIC bowel and urinary domain scores.

Results

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

Radiotherapy

Three patients received no radiotherapy (one withdrew consent, one died and one biochemically progressed prior to radiotherapy). Adherence to randomly allocated treatment was high (Figure 1): 3 no-IGRT patients received IGRT, 8 IGRT-S patients did not receive standard CHHiP planning margins and 4 IGRT-R patients did not have reduced margins.

Median (IQR) rectum volumes were 65 (59-77), 68 (56-86) and 67 (58-85) cm^3 for the no-IGRT, IGRT-S and IGRT-R groups respectively. Corresponding figures for bladder volumes were 277 (200-379), 249 (167-375) and 281 (180-386) cm^3 (Table S4). A summary of DVH and DSH for rectum and bladder by treatment group are shown in Figure 2. Both rectal and bladder dose volume and surface percentages were consistently statistically lower in the IGRT-R compared to IGRT-S group (Table S5).

Acute toxicity

Toxicity associated with fiducial marker insertion was minimal with 19/190 (10%) reporting grade 1 and one patient reporting grade 2 haemorrhage. Six (3%) patients had an infection, three grade 1, two grade 2 and one grade 3. Worst RTOG bowel toxicity reported during 18 weeks from starting radiotherapy was grade≥2 in 13/48 (27%), 38/135 (28%) and 26/107 (24%) of no-IGRT, IGRT-S and IGRT-R patients respectively. Corresponding figures for RTOG bladder grade≥2 were 21/48 (44%), 71/135 (53%) and 48/107 (45%). By week 18, the majority of toxicity had resolved with grade≥2 bowel toxicity reported in 0% no-IGRT, 5% IGRT-S and 2% IGRT-R patients and RTOG bladder grade≥2 reported in 3% no-IGRT, 8% IGRT-S and 4% IGRT-R patients (Figure 3).

Late toxicity

At two years, RTOG bowel and bladder toxicity was low across all groups (Table S6) with 13 out of 274 (4.7%) patients assessed reporting any RTOG grade≥2 toxicity, which was the primary endpoint of the substudy. The upper limits of 95% confidence intervals ruled out greater than 20% toxicity within each treatment group. Moderate to severe RTOG bowel toxicity was similar across treatment groups, with 1/46 (2%), 3/125 (2%) and 2/103 (2%) no-IGRT, IGRT-S and IGRT-R patients reporting grade≥2 at 2 years. The cumulative proportion with grade≥2 RTOG bowel toxicity reported to 2 years was 8.3% (95%CI 3.2-20.7), 8.3% (4.7-14.6%) and 5.8% (2.6-12.4%) for no-IGRT, IGRT-S and IGRT-R groups respectively (Figure 4A and Table S6). RMH and LENTSOM scales showed similar low levels of moderate to severe bowel/rectum toxicity. RMH bowel grade≥2 showed reduced toxicity in the IGRT-R group compared to IGRT-S with borderline statistical significance (HR=0.39, 95%CI 0.18-0.83, p=0.012).

Moderate to severe RTOG bladder toxicity was similar across treatment groups, with 1/46 (2%), 4/125 (3%) and 2/103 (2%) no-IGRT, IGRT-S and IGRT-R patients reporting grade≥2 at 2 years. The cumulative proportion of RTOG bladder grade≥2 toxicity by 2 years was low for all groups with the least toxicity reported in the IGRT-R group: 8.4 (3.2-20.8)%, 4.6 (2.1-9.9)% and 3.9 (1.5-9.9)% for no-IGRT, IGRT-S and IGRT-R groups respectively (Figure 4B and Table S7). The RMH and LENTSOM scales reported higher incidences of bladder toxicity compared to RTOG but with a similar trend across groups. There was no evidence of significant differences between treatment groups.

Patient reported outcomes

A total of 193/265 (72.8%) PRO booklets were completed at a median of 50.3 months (IQR 47.8-52.0) from randomisation. Baseline characteristics were balanced between treatment groups and there were no significant differences between patients who did and did not complete the PRO booklet (Table S8). There was no evidence of any differences between treatment groups for EPIC or Vaizey summary scores (Table 2). There was no suggestion of a worsening of Vaizey score with increased dose volume or dose surface at any dose level (Table S9). The median DVH and DSH values were calculated for patients whose EPIC bowel

and urinary scores were below and above the threshold level previously defined. There was a trend that patients whose score were below the cut-point had higher dose volume or surface levels (Figure S1).

Efficacy

Thirty-three patients had biochemical/clinical failure reported (4, 20 and 9 in the no IGRT, IGRT-S and IGRT-R groups respectively) (Table S10 and Figure S2). Five-year biochemical/clinical failure free survival was 91.1 (95% CI 77.9-96.6), 85.2 (95%CI 77.7-90.3) and 93.1 (95%CI 86.1-96.7) for no IGRT, IGRT-S and IGRT-R groups respectively. Fourteen patients had recommenced androgen deprivation therapy, nine had local recurrence, seven had lymph node/pelvic recurrence and seven had distant recurrence. Twenty-seven patients had died, three from prostate cancer, twenty-three from other reasons and one unknown.

Discussion

We have demonstrated that implementation of IGRT was feasible in a multi-centre trial in the UK. Recruitment of patients was swift, and completed within one year. Accrual peaked at 45 patient/month, with 16 radiotherapy centres participating. Subsequently IGRT has become part of the national guidelines recommended treatment pathway emphasising the potential of a clinical trial as a vehicle to introduce advanced radiotherapy technology. Limitations of this substudy include it's relatively small size, uneven randomisation between groups and PRO assessment at a single time point. Yet, to our knowledge, this is the only randomised prospective study evaluating no-IGRT, IGRT and treatment margins using the same planning techniques.

We found minimal toxicity associated with insertion of fiducial markers. Dosimetric assessments showed that reduced margins in the IGRT-R group resulted in rectal and bladder volumes receiving 5-65Gy being significantly lower (<0.0001) than using standard margins, this was also seen for surface dose. The mean dose to the rectal surface in the IGRT-S group was 33.9(±5.1) Gy and similar to that previously reported of 34.4(±7.2)Gy using IG-IMRT[26] despite differences in dose prescription and margining techniques. As

expected, the mean dose to the rectum in the IGRT-R group was significantly lower at 28.9(±4.2)Gy. Similarly, the mean dose to bladder surface was 26.6(±9.2)Gy / 20.5(±6.6)Gy for IGRT-S / IGRT-R groups respectively, both lower than previously reported (33.1 ± 10.9Gy) (26). Late GI toxicity was consistently reported less often using the three clinician based scores in the IGRT-R group. However, the improved rectal dosimetry did not translate into a statistically significant benefit in acute or late GI toxicity, with the possible exception of grade≥2 RMH GI side-effects. This perhaps unexpected result may relate to the low level of side-effects seen in all randomised groups in the main CHHiP trial which used strict normal tissue dose constraints and a SIB technique limiting dose to the seminal vesicles.[10] The lack of improvement in acute and late GU side effects may relate to similar doses to the urethra in all treatment groups. It maybe the combination of dose/volume/fractionation employed in the trial has reached a plateau for radiotherapy side effects and other patient[27], radiogenomic[28] or microbiota[29] related factors become more important in determining residual symptoms. We believe it imprudent to extrapolate to treatments using higher doses, treating larger target volumes or using more extreme forms of hypofractionation where the clinical benefits of IGRT-R might be more apparent. Previous studies comparing patient cohorts treated with IG-IMRT and 3D-CFRT[26,27] have suggested improvements in grade≥2 GU or GI side-effects using IGRT but are compromised by differences in planning and delivery techniques as well as differing dose constraints. It has also been suggested that high-dose IGRT improves disease control.[9] IGRT may increase accuracy and reduce the chance of underdosage in the target volume, alternatively however it is possible that the reduced margins might lower inadvertent dose outside the prostate which has been suggested as a cause of treatment failure.[30] However, we found no evidence to suggest that IGRT was associated with a reduction in disease control.

The IGRT experience gained within this study has facilitated development of a new national trial PIVOTALboost (CRUK/16/018) in which all patients receive IG-IMRT and are randomised to receive pelvic lymph node IMRT or MR-directed dominant lesion boosts using hypofractionated schedules as in the CHHiP study.

We have shown it is feasible to introduce prostate IGRT in a national randomised trial and that reduced margins translate into dosimetric benefits. Overall side effect profiles were low with/without IGRT in the CHHiP trial and this substudy.

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