Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial

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Summary

Background Prostate cancer might have high radiation-fraction sensitivity, implying a therapeutic advantage of hypofractionated treatment. We present a pre-planned preliminary safety analysis of side-effects in stages 1 and 2 of a randomised trial comparing standard and hypofractionated radiotherapy.

Methods We did a multicentre, randomised study and recruited men with localised prostate cancer between Oct 18, 2002, and Aug 12, 2006, at 11 UK centres. Patients were randomly assigned in a 1:1:1 ratio to receive conventional or hypofractionated high-dose intensity-modulated radiotherapy, and all were given with 3–6 months of neoadjuvant androgen suppression. Computer-generated random permuted blocks were used, with risk of seminal vesicle involvement and radiotherapy-treatment centre as stratification factors. The conventional schedule was 37 fractions of 2 Gy to a total of 74 Gy. The two hypofractionated schedules involved 3 Gy treatments given in either 20 fractions to a total of 60 Gy, or 19 fractions to a total of 57 Gy. The primary endpoint was proportion of patients with grade 2 or worse toxicity at 2 years on the Radiation Therapy Oncology Group (RTOG) scale. The primary analysis included all patients who had received at least one fraction of radiotherapy and completed a 2 year assessment. Treatment allocation was not masked and clinicians were not blinded. Stage 3 of this trial completed the planned recruitment in June, 2011. This study is registered, number ISRCTN97182923.

Findings 153 men recruited to stages 1 and 2 were randomly assigned to receive conventional treatment of 74 Gy, 153 to receive 60 Gy, and 151 to receive 57 Gy. With 50·5 months median follow-up (IQR 43·5–61·3), six (4·3%; 95% CI 1·6–9·2) of 138 men in the 74 Gy group had bowel toxicity of grade 2 or worse on the RTOG scale at 2 years, as did five (3·6%; 1·2–8·3) of 137 men in the 60 Gy group, and two (1·4%; 0·2–5·0) of 143 men in the 57 Gy group. For bladder toxicities, three (2·2%; 0·5–6·2) of 138 men, three (2·2%; 0·5–6·3) of 137, and none (0·0%; 97·5% CI 0·0–2·6) of 143 had scores of grade 2 or worse on the RTOG scale at 2 years.

Interpretation Hypofractionated high-dose radiotherapy seems equally well tolerated as conventionally fractionated treatment at 2 years.

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Introduction Prostate cancer is the most common cancer in men in the UK, USA, and western Europe, with 37 000 men diagnosed in the UK and an estimated 913 000 cases worldwide in 2008.1 After the introduction of prostate-specific antigen (PSA) testing, most men diagnosed have localised disease. Management options include external-beam radiotherapy, brachytherapy, radical prostatectomy, active surveillance (for men with low-risk disease), and watchful waiting (for those unsuitable for radical curative treatment). External-beam radiotherapy might be most appropriate for men with disease features of intermediate or high risk,2,3 and is associated with long-term disease control in most patients.4 About 10 000 men receive radical prostate radiotherapy in the UK every year.5

Substantial technological advances over the past decade have improved both the ability to adjust dose distributions to the prostate target and treatment accuracy. Several phase 3 randomised control trials have shown the benefit of dose escalation,6 and high-dose conformal radiotherapy with conventional 2 Gy daily fractions to a total dose of 74 Gy has become the standard of care in the UK.7

Additionally, there has been interest in the fraction sensitivity of prostate cancer.8–10 The α-β ratio for most cancers is believed to be about 10 Gy, but for prostate cancer values as low as 1·5 Gy have been suggested, which is smaller than the roughly 3 Gy reported for the late reactions of most normal tissues (including rectum).10 These findings have potentially important therapeutic implications. Hypofractionated radiotherapy with fewer high-fraction-size treatments would be beneficial for prostate cancer because it would deliver a larger biological-equivalent dose to the tumour than would conventional treatment in 1·8–2·0 Gy fractions, while...
maintaining a similar or lower incidence of late normal tissue reactions. Furthermore, improved resource use and patient convenience because of short treatment duration would be important gains.

Maintenance of few treatment-related side-effects is of paramount importance, because they increase with dose escalation. In previous dose-escalation randomised controlled trials (with differences of 8–10 Gy between groups), variations in side-effects of 10–15% have been reported. Meta-analysis showed an odds ratio of 1.58 for late gastrointestinal toxicity of grade 2 or more, in favour of conventional rather than high-dose radiotherapy. We therefore aimed to compare a conventional radiotherapy schedule with hypofractionated schedules in prostate cancer.

Methods

Trial design

We undertook a multistage, multicentre randomised controlled trial (Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer; CHHiP). We used a three-arm design to ensure that we would be able to extrapolate an isoeffective dose for a specific rate of complications (in a similar way to the large UK breast fractionation trials). Biological doses in the experimental schedules were calculated to be equivalent to those in the conventional schedule; equivalence was achieved with the assumptions that \( \alpha/\beta \) ratios were 2.5 Gy for the 60 Gy group and 1.5 Gy for the 57 Gy group. All treatment groups received conformal and intensity-modulated radiation techniques. This report is a pre-planned analysis of stages 1 and 2 of this trial, with the objective of establishing the safety of experimental hypofractionated radiotherapy schedules.

Patients

Patients were recruited to stage 1 between Oct 18, 2002 and April 27, 2005, at the Royal Marsden NHS Trust (London, UK) and Clatterbridge Centre for Oncology NHS Foundation Trust (Wirral, UK); and to stage 2 between May 4, 2005, and Aug 12, 2006, at 11 UK centres (see appendix). Men with histologically confirmed T1B–T3A N0 M0 prostate cancer; prostate-specific antigen (PSA) concentrations of less than 30 ng/mL, estimated risk of lymph-node involvement less than 30%, and WHO performance status 0 or 1 were eligible. Patients were excluded if they had T3 tumours and a Gleason score of 8 or more, a life expectancy of less than 10 years, previous pelvic radiotherapy, previous androgen suppression, another active malignancy in the past 5 years (other than cutaneous basal-cell carcinoma), comorbid conditions precluding radical radiotherapy, full antiagulation treatment, or hip prosthesis.

CHHiP (CRUK/06/016) was approved by the London Multi-centre Research Ethics Committee (04/MRE02/10) and the local ethics committees of all participating centres. It was sponsored by the Institute of Cancer Research and was done in accordance with the principles of good clinical practice. All patients provided written informed consent. The trial was coordinated by the Royal Marsden Hospital Bob Champion Unit (Sutton, UK) and the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU; Sutton, UK), in which central statistical monitoring and all analyses were done. The trial management group was overseen by an independent trial steering committee. Emerging safety and efficacy data were reviewed regularly in confidence by the independent data monitoring committee. Both committees approved reporting of this pre-planned analysis of side-effect data to 2 years from patients recruited in stages 1 and 2.

Randomisation and masking

Men were registered in the trial before or after starting initial hormone therapy. Patients were randomly assigned (in a 1:1:1 ratio) 4–6 weeks before radiotherapy. Independent randomisation was via telephone to the ICR-CTSU. Computer-generated random permuted blocks were used; stratification was by risk of seminal vesicle involvement and radiotherapy treatment centre. Treatment allocation was not masked and, because of the trial’s size, assessors could not be blinded to toxicity or clinical assessments.

Treatment

As part of standard treatment, men received short-course androgen suppression for 3–6 months before and during radiotherapy, although it was optional for men with low-risk disease. Injections of a luteinising-hormone-releasing hormone (LHRH) analogue every month, combined with initial antiandrogen to reduce testosterone flare, or an antiandrogen alone, were allowed.

Individuals in the control group received prostate radiotherapy with standard 2 Gy daily fractions (Monday to Friday treatment) for 7.4 weeks to give a total dose of 74 Gy in 37 fractions. Patients in the experimental groups were given hypofractionated treatment with 3 Gy daily fractions to a total dose of either 60 Gy in 20 fractions in 4–0 weeks or 57 Gy in 19 fractions in 3–8 weeks. Planning of radiotherapy treatment for all three groups was done with forward or inverse three-dimensional methods about 12 weeks after start of hormonal treatment. A complex forward-planned multisegment technique was developed for the trial. Target and treatment planning volumes have been previously described. Treatment was planned and delivered using an integrated simultaneous-boost technique with target volumes designed to include the conventional 74 Gy group: a dose of 59 Gy (80%) to the prostate and base or all seminal vesicles, with a uniform 1.0 cm margin; a dose of 71 Gy (96%) to the prostate with a 1.0 cm margin, except posteriorly where the margin was reduced to 0.5 cm; and 74 Gy (100%) to the prostate with a margin of 0.5 cm (0.0 cm posteriorly).

Target volumes had to be covered by the 95% isodose. Pelvic lymph nodes were not included in the target volumes.

For the hypofractionated groups, similar proportions of the prescribed dose (ie, 60 Gy or 57 Gy) were given to
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outer target volumes. Mandatory dose constraints were defined for both target coverage and avoidance of normal tissues including rectum, bowel, bladder, and femoral heads. Treatment was delivered with 6–15 MV photons with multileaf collimators to shape beams. Portal imaging was used to verify treatment accuracy, which was to be within 3 mm.

A quality-assurance programme was designed as an integral part of the study. Before trial entry began, every centre completed a process document that defined the methods to be used for CT simulation, treatment planning, and verified treatment accuracy and dosimetry. This document was reviewed and refined as necessary by the trial’s quality-assurance physicist. The chief investigator and quality-assurance physicist reviewed target and normal tissue outlining for the first two or three patients entered by each centre. They gave detailed individual feedback and outlines were modified when necessary before patients were treated. During the trial, on-site quality-assurance visits measured the accuracy of treatment delivery and dosimetry with a trial-specific phantom. Details of target volumes, dose parameters, constraints, and the proforma used to record each patient’s dose distribution are given in the appendix.

Assessments

Staging investigations included PSA measurement, standard haematology and biochemistry, lymph-node assessment by pelvic MRI or CT, and bone scan for patients at intermediate or high risk. Histology was locally assessed with diagnostic transrectal ultrasound-guided biopsies (or specimens from transurethral resection of the prostate) and reported with the Gleason system.

Bowel, bladder, and sexual function assessments were made before hormone therapy (when the patient was already registered for the trial); before radiotherapy; every week during radiotherapy; and at weeks ten, 12, and 18 to assess acute toxicity, with subsequent assessments at 26 weeks and every 6 months for 5 years. Initial symptoms and radiotherapy side-effects were graded with the Late Effects on Normal Tissues: Subjective/Objective/Management (LENT/SOM) and Royal Marsden Hospital (RMH) scoring systems. Radiotherapy side-effects were also graded with the Radiation Therapy Oncology Group (RTOG) scoring system.

Statistical analysis

Stage 1 included 150 patients (50 per treatment group) and was powered (87·8% power; 0·045 one-sided α) with a one-stage Fleming-A’Hern design to rule out an upper limit of 25% of patients with RTOG grade 2 or worse bladder or bowel complications at 2 years for each experimental group, with an expected rate of 10% in the control group. If seven or more patients of 45 patients assessed at 2 years had grade 2 or worse complications, then the study arm was to be rejected. Stage 2 was similarly powered to rule out an upper limit of 20% of patients with RTOG grade 2 or worse bowel or bladder complications at

For more on the phantom see http://www.rttnaloqa.org.uk
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2 years. In each treatment group, 135 evaluable patients were needed (95·2% power; 0·049 one-sided α). If 20 or more patients in one group developed complications of grade 2 or more at 2 years, the study arm was to be rejected. The sample size (stage 1 plus stage 2) was set at 450 patients (150 per group), with a 10% allowance for dropout.

Analyses of side-effect data for prevalence were done according to treatment received and—with the exception of comparisons at 18 weeks—including all available assessments from all patients who received at least one fraction of radiotherapy. The 18 week comparison was restricted to assessments done in a period 2 weeks either side of this time to consistently capture the end of the acute toxicity period across treatment groups.

For the primary endpoint, only patients with an RTOG assessment at 2 years were included in analyses, although we did a sensitivity analysis that included all patients. Proportions of patients with RTOG toxicity of grade 2 or worse at 2 years (the primary endpoint) are presented with exact binomial 95% CIs. Exploratory analyses were done to compare the side-effect profile between the randomised treatment groups. Scores before and after treatment were compared with the Wilcoxon signed-rank test. Time to first occurrence of late (reported on follow-up forms from 6 months after the start of radiotherapy onwards) side-effects of different grades were compared with the Kaplan-Meier method used to calculate cumulative proportion of patients that had events by 2 years. Cox proportional hazards models were used to estimate and test the effect of the experimental treatments against the control group. A hazard ratio (HR) of less than one favoured the experimental group. Analyses presented in this report have not been adjusted for stratification factors, but sensitivity analyses adjusting for risk group showed the results to be robust (data not shown).

Analyses were based on a database snapshot on April 1, 2010, and were done with STATA version 11·2. This study is registered, number ISRCTN97182923.

### Role of the funding source
The funding source provided peer-reviewed approval for the trial, but had no other role in study design, collection, analysis, interpretation of data, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. GS, SH, and EH also had full access to the data.

### Results
457 men were recruited (figure 1). 13 patients received no radiotherapy; four were ineligible at trial entry, five were shown to be technically unsuitable during the planning process, two patients chose to leave, and two for unknown reasons. Of the patients who were technically unsuitable, two had large amounts of small bowel in the target volume, two had small bladders, and
one had a large prostate. Overall, six patients were ineligible: one had abnormal blood counts, two were receiving warfarin, one had stage T3b disease, one had hip prostheses, and one had a perianal fistula (two ineligible patients did receive radiotherapy). Of the 444 treated patients, all but one received the protocol-assigned radiotherapy dose and schedule; one patient in the 74 Gy group stopped treatment after 70 Gy because of acute urinary obstruction.

Median follow-up is 50·5 months (IQR 43·5–61·3); 426 of 457 patients randomly assigned and 424 of 444 treated have been followed up for at least 2 years. Baseline characteristics were evenly distributed across treatment groups (table 1). Patients received a median of 16 weeks (14·0–18·9) hormonal treatment before radiotherapy. Most patients received LHRH analogues and short-term antiandrogens (table 1), similarly distributed across treatment groups and by risk group of the National Comprehensive Cancer Network.

Acute bowel and bladder side-effects, measured with the RTOG scale, seemed to peak sooner in the experimental groups than in the control group (figure 2): at 4–5 weeks in the hypofractionated groups compared with 7–8 weeks in the control group. Of 129 patients in the 74 Gy group who were assessed 18 weeks after start of radiotherapy, three (2·3%) reported bowel side-effects of grade 2 or worse and nine (7·0%) had bladder side-effects of grade 2 or worse. In the 60 Gy group, three (2·3%) of 132 men had bowel side-effects and ten (7·6%) had bladder side-effects of grade 2 or worse. One (0·8%) of 129 men assessed at 18 weeks in the 57 Gy group had bowel side-effects and nine (7·0%) had bladder side-effects of grade 2 or worse. Grade 3 bladder side-effects were reported by two patients who received 57 Gy, and one patient in the 74 Gy group had a grade 4 event. No acute grade 3 bowel toxicity was reported.

Late side-effect profiles by treatment group as reported on each scoring system are shown in figures 3 and 4.
Figure 3: Bowel toxicity of the three treatment groups by assessment timepoint
Cumulative proportion measured with RTOG (A), RMH (D), and LENT/SOM (G). Prevalence measured with RTOG (B), RMH (E), and LENT/SOM (H). Distribution of grade scores with RTOG (C), RMH (F), and LENT/SOM (I). RTOG=Radiation Therapy Oncology Group scale. RMH=Royal Marsden Hospital scale. LENT/SOM=Late Effects on Normal Tissue: Subjective/Objective/Management scale. G1+=score of grade 1 or worse. G2+=score of grade 2 or worse. G3+=score of grade 3 or worse. G0=score of grade 0. G1=score of grade 1. G2=score of grade 2. PH=before hormone treatment. PR=before radiotherapy.
Figure 4: Bladder toxicity of the three treatment groups by assessment timepoint
Cumulative proportion measured with RTOG (A), RMH (D), and LENT/SOM (G). Prevalence measured with RTOG (B), RMH (E), and LENT/SOM (H). Distribution of grade scores with RTOG (C), RMH (F), and LENT/SOM (I). RTOG= Radiation Therapy Oncology Group scale. RMH= Royal Marsden Hospital scale. LENT/SOM= Late Effects on Normal Tissue: Subjective/Objective/Management scale. PH= before hormone treatment. PR= before radiotherapy. G1+= score of grade 1 or worse. G2+= score of grade 2 or worse. G3+= score of grade 3 or worse. G0= score of grade 0. G1= score of grade 1. G2= score of grade 2. PH= before hormone treatment. PR= before radiotherapy.
RTOG toxicity scores at 2 years were available for 138 men given 74 Gy, 137 given 60 Gy, and 143 given 57 Gy. Six (4.3%; 95% CI 1.6–9.2) of 138 men in the 74 Gy group had RTOG bowel toxicity of grade 2 or worse at 2 years, as did five (3.6%; 1.2–8.3) of 137 men in the 60 Gy group and two (1.4%; 0.2–5.0) of 143 men in the 57 Gy group. RTOG bladder toxicity of grade 2 or worse at 2 years was reported by three (2.2%; 0.5–6.2) of 138 men in the 74 Gy group and three (2.2%; 0.5–6.3) of 137 men in the 60 Gy group; no side-effects of grade 2 or worse were reported in the 143 men in the 57 Gy group (97.5% one-sided CI 0.0–2.6). Grade 3 bladder toxicity was not observed, and grade 3 bowel toxicity was reported by one patient in the 60 Gy group at 2 years. None of the estimates of late toxicity suggested a doubling of side-effects in the experimental groups compared with the standard group and, because the upper confidence limits are all less than 20%, the criteria for rejection of any of the treatment groups on the grounds of safety were not met. Results from the sensitivity analysis that included all patients suggested that the findings are robust to missing outcomes (data not shown).

### Table 2: Total number of events, hazard ratios, and cumulative proportion with events by 2 years for bowel, bladder, and sexual dysfunction endpoints by allocated treatment group

| Bowel | HR (95% CI) | p value | HR (95% CI) | p value |
|-------|-------------|---------|-------------|---------|
| **RTOG** | **60 Gy vs 74 Gy** | **57 Gy vs 74 Gy** | **Cumulative events and cumulative proportion of events at 2 years** | **74 Gy (n=149)** | **60 Gy (n=147)** | **57 Gy (n=148)** |
| **Events % (95% CI)** | **Events % (95% CI)** | **Events % (95% CI)** |
| Grade 1 or worse | 0.85 (0.49–1.47) | 0.553 | 18 | 12.3% (7.9–18.8) | 17.4% (12.1–24.6) | 0.53 |
| Grade 2 or worse | 0.32 (0.15–0.68) | 0.094 | 9 | 6.3% (4.9–8.5) | 9.6% (6.6–12.7) | 0.09 |
| Grade 3 or worse | 0.06 (0.01–0.32) | 0.013 | 1 | 0.7% (0.2–2.7) | 0.5% (0.1–1.8) | 0.01 |

| **Bladder** | **60 Gy vs 74 Gy** | **57 Gy vs 74 Gy** | **Cumulative events and cumulative proportion of events at 2 years** | **74 Gy (n=149)** | **60 Gy (n=147)** | **57 Gy (n=148)** |
|-------------|---------------------|---------------------|------------------------------------------------------------------|-------------------|-------------------|-------------------|
| **Events % (95% CI)** | **Events % (95% CI)** | **Events % (95% CI)** |
| Grade 1 or worse | 0.87 (0.56–1.36) | 0.374 | 0.89 (0.56–1.45) | 0.089 | 9 | 6.9% (4.9–9.6) | 7.7% (5.3–10.9) | 1.0% (0.2–4.3) |
| Grade 2 or worse | 1.05 (0.62–1.76) | 0.879 | 1.07 (0.65–1.75) | 0.884 | 7 | 5.6% (3.4–9.1) | 6.1% (3.8–9.6) | 0.7% (0.1–4.7) |
| Grade 3 or worse | 0.07 (0.01–0.46) | 0.015 | 0.07 (0.02–0.26) | 0.015 | 0 | 0 | 0 | 0.7% (0.1–4.7) |

| **Sexual dysfunction** | **60 Gy vs 74 Gy** | **57 Gy vs 74 Gy** | **Cumulative events and cumulative proportion of events at 2 years** | **74 Gy (n=149)** | **60 Gy (n=147)** | **57 Gy (n=148)** |
|------------------------|---------------------|---------------------|------------------------------------------------------------------|-------------------|-------------------|-------------------|
| **Events % (95% CI)** | **Events % (95% CI)** | **Events % (95% CI)** |
| Grade 1 or worse | 0.88 (0.62–1.24) | 0.387 | 0.94 (0.69–1.28) | 0.387 | 140 | 95.0% (92.9–96.4) | 94.4% (92.5–96.0) | 92.6% (90.6–94.6) |
| Grade 2 or worse | 1.03 (0.73–1.46) | 0.894 | 1.02 (0.73–1.42) | 0.894 | 137 | 95% (92.9–97.0) | 94.4% (92.4–96.0) | 92.6% (90.6–94.6) |
| Grade 3 or worse | 0.08 (0.02–0.32) | 0.012 | 0.08 (0.02–0.32) | 0.012 | 128 | 85% (82.6–87.5) | 84.4% (82.4–86.4) | 82.6% (80.6–84.6) |

HR=hazard ratio. RTOG=Radiation Therapy Oncology Group scale. –=Insufficient events to estimate HR. RMH=Royal Marsden Hospital scale. LENT/SOM=Late Effects on Normal Tissue: Subjective/ Objective/Management scale. HRs include all late events reported. Cumulative proportion figures only include events occurring up to 2 years post-radiotherapy and are calculated with the Kaplan-Meier method.
Results of exploratory comparative analyses of cumulative incidence are shown in table 2. The cumulative proportion of patients with late RTOG bowel toxicity of grade 2 or worse at 2 years was 7.6% (95% CI 4.3–13.2) in the 74 Gy group, 6.9% (3.8–12.5) in the 60 Gy group, and 4.8% (2.3–9.7) in the 57 Gy group (figure 3; table 2). For late RTOG bladder toxicity, cumulative proportion values were 3.5% (1.5–8.1), 9.0% (5.4–15.1), and 4.8% (2.3–9.8; figure 4, table 2). With the LENT/SOM assessment system and the RMH symptom score, there was low prevalence of bowel scores of grade 2 or worse before radiotherapy on either of the baseline scores (ie, before hormone or radiotherapy treatment; eight of 451 patients). At 2 years, eight (5.8%) of 138 patients given 74 Gy had RMH bowel scores of grade 2 or worse, four (2.9%) of 137 patients given 60 Gy, and one (0.7%) of 143 patients given 57 Gy had RMH scores of grade 1 or worse. Prevalences of bladder scores of grade 2 or worse were similar in the three groups before radiotherapy: 25 (17.2%) of 145 men given 74 Gy; 22 (15.1%) of 146 given 60 Gy, and 21 (14.7%) of 143 given 57 Gy. After 2 years, 15 (10.8%) of 139 men given 74 Gy, 17 (12.3%) given 60 Gy, and 15 (10.6%) of 142 in the 57 Gy group experiencing grade 1 events, 13 (9.4%) experiencing grade 2 events, and two (1.4%) experiencing grade 3 events versus 23 (16.8%) of 137 men in the 74 Gy group experiencing grade 1 events, six (4.2%) experiencing grade 2 events, and one (0.7%) experiencing grade 3 events (p=0.023). The 6, 12, 18, and 24 month scores after radiotherapy all showed significant increases compared to pre-radiotherapy levels (p=0.0001 for 6 month scores; p<0.0001 for other timepoints).

With the RMH symptom score, there was low prevalence of bowel scores of grade 2 or worse before radiotherapy on either of the baseline scores (ie, before hormone or radiotherapy treatment; eight of 451 patients). At 2 years, eight (5.8%) of 138 patients given 74 Gy had RMH bowel scores of grade 2 or worse, four (2.9%) of 137 patients given 60 Gy, and one (0.7%) of 143 patients given 57 Gy had RMH scores of grade 1 or worse. Prevalences of bladder scores of grade 2 or worse were similar in the three groups before radiotherapy: 25 (17.2%) of 145 men given 74 Gy; 22 (15.1%) of 146 given 60 Gy, and 21 (14.7%) of 143 given 57 Gy. After 2 years, 15 (10.8%) of 139 men given 74 Gy, 17 (12.3%) given 60 Gy, and 15 (10.6%) of 142 in the 57 Gy group experiencing grade 1 events, 13 (9.4%) experiencing grade 2 events, and two (1.4%) experiencing grade 3 events versus 23 (16.8%) of 137 men in the 74 Gy group experiencing grade 1 events, six (4.2%) experiencing grade 2 events, and one (0.7%) experiencing grade 3 events (p=0.023). The 6, 12, 18, and 24 month scores after radiotherapy all showed significant increases compared to pre-radiotherapy levels (p=0.0001 for 6 month scores; p<0.0001 for other timepoints).

Before hormone treatment, 45 (18.8%) of 239 patients had LENT/SOM grade 1 bladder scores, 61 (25.5%) had grade 2 scores, and 26 (10.9%) had grades 3 or 4. Prevalences were similar before radiotherapy treatment across the three randomised groups (figure 4). Scores were lower at 6, 12, 18, and 24 months than they were before radiotherapy (p<0.0001 at all timepoints). At 2 years, 28 (20.4%) of 137 men in the 74 Gy group had grade 1 scores, as did 25 (18.2%) of 137 in the 60 Gy group and 28 (19.7%) of 142 in the 57 Gy group. Additionally, 21 (15.3%) men given 74 Gy, 17 (12.3%) given 60 Gy, and 17 (12.0%) given 57 Gy had grade 2 scores. Six (4.4%) in the first group, eight (5.8%) in the second, and five (3.5%) in the third were grade 3 or worse.

Figure 5: LENT/SOM sexual dysfunction toxicity of the three treatment groups by assessment timepoint
(A) Cumulative proportion. (B) Prevalence. (C) Distribution of grades. LENT/SOM=Late Effects on Normal Tissue: Subjective/Objective/Management scale. G1+=score of grade 1 or worse. G2+=score of grade 2 or worse. G3+=score of grade 3 or worse. G0=score of grade 0. G1=score of grade 1. G2=score of grade 2. G3=score of grade 3. G4=score of grade 4. PH=before hormone treatment. PR=before radiotherapy.
Before hormone treatment, sexual dysfunction (a score greater than 2 on the LENT/SOM scale) was recorded in 102 (43.6%) of 234 men. As expected, scores deteriorated during neoadjuvant hormone therapy, with 350 (83.5%) of 419 men recording scores of grade 2 or worse before radiotherapy (p<0.0001). Partial recovery was reported: scores of grade 2 or worse were reported in 310 (75.4%) of 411 patients 24 months after radiotherapy treatment (figure 5). LENT/SOM sexual dysfunction scores were not significantly different in randomised groups at any point (table 2).

Discussion
This planned interim analysis of stages 1 and 2 of the CHHiP trial has shown no clinically meaningful differences in acute toxicity between standard and hypofractionated radiotherapy schedules. Preliminary safety assessment of late side-effects to 2 years raised no concerns about the safety of the experimental treatments as delivered in a multicentre trial setting. The safety criteria for stopping were not met and the trial completed accrual in June, 2011.

Acute reactions occurred earlier in the hypofractionated groups than in the control group, in which the pattern of acute toxicity was very similar to that reported in the group of men randomised to receive 74 Gy in a previous trial. However, the cumulative proportion of both bowel and bladder side-effects at 2 years is lower in the CHHiP trial than in the 74 Gy group in the previous trial (in which incidence of RTOG bowel toxicity of grade 2 or worse was 20% and bladder toxicity of grade 2 or worse was 8%). This difference might be a result of patient selection factors (although age and PSA distributions are very similar), or of the favourable dose distributions and adherence to normal tissue dose constraints with the forward-planning or inverse-planning methods used in the CHHiP trial. Data from randomised controlled trials have shown that treatment technique, planning target margin, and dose, can all affect outcomes of prostate cancer radiotherapy. Therefore, meaningful assessment of the biological effects of altered fractionation schedules can be made only by controlling for these other factors.

Although not included as part of this safety analysis, we have measured patient-reported outcomes with the same instruments as those used in the previous trial. This continuing longitudinal quality-of-life substudy that recruited 1958 men will help to establish whether altered fractionation affects different symptom complexes and will be analysed and published separately.

The choice of treatment in our control group was based on level 1 evidence and a meta-analysis of trials assessing dose escalation and the addition of hormonal therapy for men with intermediate-risk and high-risk disease. The dose of 74 Gy was preferred to a higher dose because it has become the standard dose in the UK after the MRC RT01 trial, which is the largest reported study of dose escalation and the only study to routinely include short-course androgen suppression. The median duration of androgen suppression of 5 months is roughly what was recommended in the updated TROG 96.01 trial that compared radiotherapy alone with the addition of either 3 or 6 months of androgen deprivation.

The experimental high-dose hypofractionated groups were designed as they were because retrospective data reviews have suggested that the α-β ratio might be low (panel). Large multicentre reviews and a meta-summary have suggested estimates of 3.7 Gy, and 1.4 Gy. However, a 2008 review of studies that used altered hypofractionated treatments showed that evidence is insufficient to recommend a change to doses larger than 2 Gy per fraction and that results from continuing randomised controlled trials were needed. 4 week schedules with 3 Gy fractions were chosen because there was some data and experience with similar, but lower dose schedules in the UK.

Other investigators of international studies of hypofractionated radiotherapy have also reported favourable toxicity. A small Italian phase 3 trial included 168 men and was designed to establish whether a high-dose hypofractionation schedule (62 Gy in 3.1 Gy daily fractions) was associated with lower radiation-related toxicity than was a high-dose conventional schedule (80 Gy in 2 Gy daily fractions). Frequency of side-effects after 3 years of follow-up and PSA control was reported to be at least as good in the hypofractionated cohort as in the control group (PSA control 87% vs 79%, p=0.04). Additionally, reports from phase 1 or 2 trials of high-dose hypofractionated radiotherapy treatments in prostate cancer are encouraging. Three reports document schedules of 3 Gy per fraction to give total doses of

Panel: Research in context

Systematic review
Before the CHHiP trial began, reports based on retrospective series of patients suggested that the α-β ratio for prostate cancer might be low, but only two small randomised trials (with relatively low doses of radiotherapy) existed and neither was large enough to confirm or refute a benefit. Since CHHiP started, reviews of two large patient databases have been done, suggesting that the best estimates for the α-β ratio are 3.7 Gy and 1.4 Gy. However, these retrospective analyses and reviews have not changed clinical practice, hence the need for a randomised controlled trial. Dose escalation and neoadjuvant androgen deprivation improve disease control, but dose escalation increases bowel side-effects. However, conformal and intensity-modulated radiotherapy improves dose distributions of radiotherapy and conformal radiotherapy reduces side-effects.

Interpretation
The findings from this pre-planned safety analysis of the first 457 patients enrolled in the CHHiP trial suggest that high-dose hypofractionated schedules using 3 Gy fractions and intensity-modulated radiotherapy are safe. Safety and efficacy data from the full trial is essential to fully assess hypofractionated schedules, but these safety results should enable investigators to safely pursue these avenues of research. Clinicians and patients should be strongly encouraged to support trials using fractions of 3 Gy or more.
the two groups. A second randomised controlled trial32 of A phase 3 trial31 in 936 men has compared 52·5 Gy in used only modest radiation doses by present standards.

0·99–1·41). Late grade 3 or 4 toxicity was roughly 3% in 59·95%) in the vs 20 fractions to 66 Gy in 33 fractions. Results show a 7% schedule of 50 Gy in 16 fractions (3·125 Gy per fraction) was equivalent to a contemporaneously treated series with 65–70 Gy in 1·8–2·0 Gy fractions.43 Previously reported dose-fractionation escalation study in 210 men (2·94 Gy fractionation sensitivity of both prostate cancer and normal tissues with improved precision.

clinical role of hypofractionation for prostate cancer and comparisons of toxicity data by fractionation schedules are although the trial occurred in 11 centres overall. Therefore, comparisons of toxicity data by fractionation schedules are preliminary. Stage 3 of this trial aims to show non-inferiority of biochemical PSA control between experimental and control groups and includes an additional 2759 patients recruited from 41 centres, and will provide an opportunity to validate the findings presented here. Planned associated translational research includes comparative dose-volume histograms and side-effect analysis for the hypofractionated groups, collection of germline DNA for radiogenomics,50 and tissue microarray assessment of predictive factors for fraction sensitivity.

Preliminary estimates of PSA control rates in these studies49–53 are comparable to those in standard fractionation schedules. A large single-institute series of 705 men in Manchester, UK, is valuable, because it suggests that a schedule of 50 Gy in 16 fractions (3·125 Gy per fraction) was equivalent to a contemporaneously treated series with 65–70 Gy in 1·8–2·0 Gy fractions.41 Previously reported randomised controlled trials of hypofractionation have used only modest radiation doses by present standards. A phase 3 trial18 in 936 men has compared 52·5 Gy in 20 fractions to 66 Gy in 33 fractions. Results show a 7% reduction in PSA control rate (52·95% vs 59·95%) in the 20 fraction group with HR for failure of 1·18 (95% CI 0·99–1·41). Late grade 3 or 4 toxicity was roughly 3% in the two groups. A second randomised controlled trial19 of 120 men compared a dose of 64 Gy in 32 fractions with 55 Gy in 20 fractions. After median follow-up of 44 months, 4 year PSA control rates were alike (86·2% for hypofractionation vs 85·4% for standard fractionation); rectal bleeding was more frequent in the hypofractionated group (appendix). All these studies are compatible with an α-β ratio for prostate cancer of 1·5–3·0 Gy.49

Phase 2 third randomised controlled trials are underway: in Canada, investigators are comparing 60 Gy in 20 fractions with 78 Gy in 39 fractions in a planned cohort of 1204 patients (ISRCTN 43853433); and in the Netherlands, researchers are comparing 64·6 Gy in 19 fractions with 78 Gy in 39 fractions, with a planned cohort of 800 patients (ISRCTN 85138529). The Dutch study regimen treats in 7 weeks rather than 4 weeks to keep the total treatment time constant, avoiding the possible time-related increase in damage. After a pilot study, a Scandinavian collaborative group is comparing increased hypofractionation with 42·7 Gy in seven fractions given in 15–19 days with 78 Gy in 39 fractions in 7·8 weeks in a group of 592 men (ISRCTN 45905321). The combination of studies should clearly define the clinical role of hypofractionation for prostate cancer and the fractionation sensitivity of both prostate cancer and normal tissues with improved precision.

Analyses in our study were not powered for formal comparisons and 84% of patients were from two sites, although the trial occurred in 11 centres overall. Therefore, comparisons of toxicity data by fractionation schedules are preliminary. Stage 3 of this trial aims to show non-inferiority of biochemical PSA control between experimental and control groups and includes an additional 2759 patients recruited from 41 centres, and will provide an opportunity to validate the findings presented here. Planned associated translational research includes comparative dose-volume histograms and side-effect analysis for the hypofractionated groups, collection of germline DNA for radiogenomics,50 and tissue microarray assessment of predictive factors for fraction sensitivity.

Contributors

DD was the chief investigator and was involved with study design, recruitment of patients, data interpretation, and writing of the report. IS was involved with protocol development, patient recruitment, writing of the report, and is a member of the trial management group and trial steering committee. GS did the statistical analyses, data interpretation, and writing of the report. DD, IS, CSe, CC, AG, JS, PK, DB, VK, HP, MR, EH, SH, HM, PM, MB, and CS were all members of the trial management group. SH is the trial manager and reviewed the report. ON leads the Physics Quality Assurance Group and reviewed the manuscript. HM, PM, CSo, CC, and MB contributed to radiotherapy planning and quality assurance, and reviewed the report. AH, VK, RH, DB, AG, PK, MR, JS, HP, CSe, and CP contributed to trial design, patient recruitment, data collection, follow-up, and reviewed the report. EH was responsible for central management of the trial at ICR-CTSU and for all statistical analyses, is a member of the trial steering committee, and was involved in data interpretation and writing of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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