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Original Article

Radiotherapy Quality Assurance for the CHHiP Trial: Conventional Versus Hypofractionated High-Dose Intensity-Modulated Radiotherapy in Prostate Cancer

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Abstract

Aims: The CHHiP trial investigated the use of moderate hypofractionation for the treatment of localised prostate cancer using intensity-modulated radiotherapy (IMRT). A radiotherapy quality assurance programme was developed to assess compliance with treatment protocol and to audit treatment planning and dosimetry of IMRT. This paper considers the outcome and effectiveness of the programme.

Materials and methods: Quality assurance exercises included a pre-trial process document and planning benchmark cases, prospective case reviews and a dosimetry site visit on-trial and a post-trial feedback questionnaire.

Results: In total, 41 centres completed the quality assurance programme (37 UK, four international) between 2005 and 2010. Centres used either forward-planned (field-in-field single phase) or inverse-planned IMRT (25 versus 17). For pre-trial quality assurance exercises, 7/41 (17%) centres had minor deviations in their radiotherapy processes; 45/82 (55%) benchmark plans had minor variations and 17/82 (21%) had major variations. One hundred prospective case reviews were completed for 38 centres. Seventy-one per cent required changes to clinical outlining pre-treatment (primarily prostate apex and base, seminal vesicles and penile bulb). Errors in treatment planning were reduced relative to pre-trial quality assurance results (49% minor and 6% major variations). Dosimetry audits were conducted for 32 centres. Ion chamber dose point measurements were within ±2.5% in the planning target volume and ±8% in the rectum. 28/36 films for combined fields passed gamma criterion 3%/3 mm and 11/15 of IMRT fluence film sets passed gamma criterion 4%/4 mm using a 98% tolerance. Post-trial feedback showed that trial participation was beneficial in evolving clinical practice and that the quality assurance programme helped some centres to implement and audit prostate IMRT.

Conclusion: Overall, quality assurance results were satisfactory and the CHHiP quality assurance programme contributed to the success of the trial by auditing radiotherapy treatment planning and protocol compliance. Quality assurance supported the introduction of IMRT in UK centres, giving additional confidence and external review of IMRT where it was a newly adopted technique.

Key words: CHHiP trial; hypofractionation; prostate cancer; quality assurance; radiotherapy

Introduction

CHHiP (CRUK/06/016; ISRCTN97182923) is a randomised phase III multicentre trial of conventional or hypofractionated high-dose intensity-modulated radiotherapy (IMRT) for prostate cancer (T1b–T3a N0 M0). The conventional arm used a dose schedule of 74 Gy in 2 Gy fractions and the hypofractionated groups used 60 Gy/20 fractions and 57 Gy/19 fractions. From October 2002 to June 2011, 3216 men were recruited from 41 radiotherapy centres. The 5-year outcome data have been reported [1] and 60 Gy/20 fractions has been recommended as the new standard of care by NHS England for external beam radiotherapy of localised prostate cancer.

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As IMRT was a novel technique in the UK at the time of trial inception, a comprehensive quality assurance programme was developed, based on the UK RT01 [2] and PARSPORT [3] trial quality assurance programmes, but focussed more on prospective review. The programme was essential to ensure the technical and dosimetric quality of treatment delivered, evidence of compliance with the radiotherapy treatment protocol and consistency between radiotherapy centres. All UK National Institute for Health Research (NIHR) Clinical Research Network radiotherapy clinical trials have quality assurance programmes included from their inception.

Materials and Methods

Radiotherapy Protocol

Clinical demographics of the trial population have been previously reported [1]. Patients were imaged and treated with a comfortably full bladder (>150 ml) and an empty rectum. Patients were treated supine using the centre's standard immobilisation technique.

Treatment was planned and delivered using a simultaneous integrated boost technique with target volumes illustrated in Figure 1. Doses were prescribed following the recommendations of ICRU Report 62 [5].

Radiotherapy treatment planning was carried out using forward-planned (fp-IMRT) or inverse-planned (ip-IMRT) three-dimensional methods. The complex forward-planned multi-segment simultaneous integrated boost technique has been previously described [6]. Mandatory dose constraints were defined for planning target volumes (PTV) and organs at risk (OAR) (see Appendix A) and reported for every trial patient using a standard plan assessment form. Radiotherapy treatment and delivery procedures were identical for all trial arms within a centre. Portal imaging was used to verify treatment set-up accuracy with a maximum 3 mm tolerance and use of image-guided techniques was encouraged.

Quality Assurance Programme

The completion and approval of all quality assurance exercises was a prerequisite for a centre starting trial recruitment. The comprehensive quality assurance programme evaluated the following elements of radiotherapy treatment: local radiotherapy treatment and delivery procedures (using a process document), clinical outlining, treatment planning and accuracy of radiotherapy dosimetry. Results were categorised as 'no variation', 'minor variation' (deviation from the protocol or optimal practice but unlikely to affect the clinical outcome) and 'major variation' (unacceptable deviation with potential to influence the clinical outcome).

Planning Benchmark Case

Computed tomography images with clinical target volumes and OARs pre-outlined were provided for two prostate patients (one low risk of seminal vesicle involvement [4] and one moderate-risk seminal vesicle case) for pre-trial planning benchmark cases. Centres were instructed to grow the PTVs and prepare treatment plans in accordance with the CHHiP trial protocol for the 74 and 60 Gy arms, respectively. Plans were reviewed by the trial radiotherapy quality assurance (RTQA) physicist using VODCA v4.4.2d software (MSS Medical Software Solutions). Plans were assessed for compliance with ICRU Report 83 [7], specifically checking conformance of isodoses to PTVs, minimising dose to critical organs, hot and cold spots, dose constraints achieved and suitable beam configuration.

Prospective Case Reviews

Prospective case reviews of clinical outlining, by the chief investigator, and treatment planning, by the RTQA physicist, were carried out for the first two patients recruited per centre. An additional moderate-risk case was reviewed if the first two patients were low risk, and extra reviews were requested if significant errors persisted. The principal investigator for each site was centrally reviewed and was responsible for internal accreditation of outlining for any additional co-investigators at their centre.

Dosimetry Site Visit

A dosimetry site visit was conducted during the course of the trial. Centres were instructed to prepare a CHHiP treatment plan (74 Gy/37 fractions) on a pre-outlined computed tomography dataset of the CIRS pelvic semi-anthropomorphic phantom. Additional measurements were carried out if multiple planning techniques or treatment delivery equipment were used.

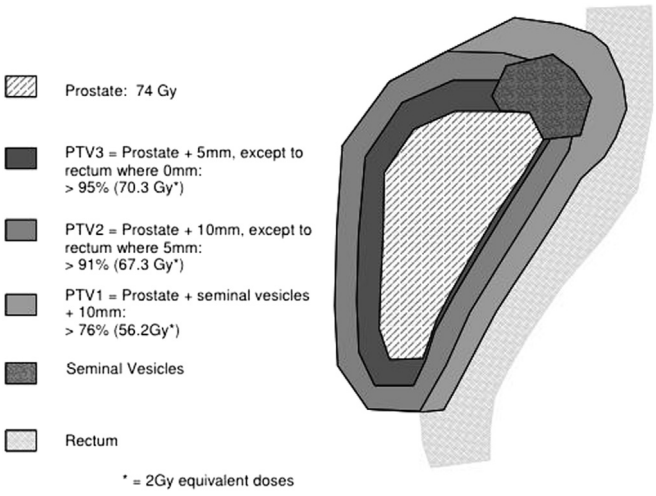

Fig 1. Planning target volume (PTV) margins and doses for the CHHiP trial. In patients with a low risk [4] of seminal vesicle involvement, the base of the seminal vesicles (proximal 2 cm) was included; those with a moderate or high risk of involvement had all of the seminal vesicles included.

Point Dose Measurements

The dose for a single 2 Gy fraction was measured using a PTW SemiFlex 0.125 cm^3 ion chamber at two measurement locations (in the PTV near the isocentre and in the rectum) and compared with the centre's treatment planning system (TPS) calculated dose. The relative dose was measured, normalised to the measured standard output for a 10 cm × 10 cm field. The results were evaluated for total dose and dose per field.

Planar Film Measurements

An axial two-dimensional dose distribution through the PTV was measured in the CIRS pelvic phantom using Kodak EDR2 film. Single field film measurements (fluence maps) were carried out for ip-IMRT plans at a depth of 10 cm in a 15 cm × 15 cm × 20 cm solid water phantom with the gantry set to 0° using Kodak XV film.

Films were analysed using the OmniPro™ I'mRT software using relative dosimetry (normalised to a value of 100% in a region of high-dose and low-dose gradient). A gamma analysis [8] was carried out using 4% dose/4 mm distance to agreement and 3%/3 mm gamma criteria with a 10% dose threshold. The results were recorded as the percentage of pixels with gamma <1.

The results were evaluated using literature-derived criteria (Table 1). No hard pass/fail criteria were set.

Feedback Questionnaire

A questionnaire was sent to all participating centres 4 months after the trial closed to recruitment. This sought views on the impact of undertaking the CHHiP trial at the centre and requested feedback on the quality assurance process.

Results

The quality assurance exercises were completed by all 41 participating centres between December 2004 and March 2010. The average time taken to complete the quality assurance process was 14 months (range 3–32 months).

Equipment

Twenty-seven centres used Varian linear accelerators, 16 used Elekta and three used Siemens. Photon beams had a nominal energy in the range 6–25 MV; most centres used 6 or 10 MV, with 6 MV used preferentially for ip-IMRT and 10 MV for fp-IMRT.

Seven different TPSs were used: Eclipse (15 centres), Pinnacle (eight), Oncentra MasterPlan (eight), CMS XiO (seven), Plato (three), TMS Helax (one) and ARPS (one). Seventeen centres used ip-IMRT, 25 used fp-IMRT (one centre used both) and three centres changed from fp-IMRT to ip-IMRT during the course of the trial. Ip-IMRT used step and shoot or dynamic multileaf collimator delivery with five fields and one centre used rotational radiotherapy.

Treatment verification was primarily carried out using electronic portal imaging, comparing MV images of bony anatomy with simulator-produced kV images or digitally reconstructed radiographs (as these became available); one centre used film. Techniques such as kV planar imaging, cone-beam computed tomography and computed tomography on rails were used by centres in the latter stages of the trial, matching to gold fiducial markers or soft tissue (prostate gland). Thirty-six centres used an offline treatment verification procedure, imaging the first three fractions and then weekly; five centres carried out daily online verification and correction.

Process Document

Process documents highlighted minor protocol deviations in radiotherapy procedures in 7/41 centres. Issues were resolved with the centres before quality assurance approval and included:

- Patients treated with an empty bladder (one centre)
- No bowel preparation/assessment (four centres)
- No patient immobilisation (two centres)
- Treatment verification frequency too low (two centres)
- Treatment verification tolerance >3 mm (seven centres)

A variety of bladder and bowel preparation techniques were used, indicating the lack of a definitive best practice in these areas. There was a large degree of variation in patient protocols for achieving a comfortably full bladder, despite this being standard practice in most UK departments [13].

Planning Benchmark Case

All 41 recruiting radiotherapy centres completed the two benchmark cases. Twenty-four per cent (20/82) of plans were approved with no variation and 55% (45/82) reported minor variations (unlikely to affect the clinical outcome). Major variations (with potential to influence the clinical outcome, re-plan required) were reported in 21% (17/82) of cases. The results are summarised in Table 2, together with the case review results to enable a comparison.

A difference was noted in the volumes of the PTVs grown by the different TPSs (using identical margins) of up to 16% between the smallest (Eclipse) and the largest (Pinnacle) PTV volumes. This has been investigated and reported in more detail [15].

Prospective Case Reviews

Clinical Outlining

Prospective individual outlining case reviews were completed for 100 patients from 38 centres (two pilot centres were exempt and one centre's principal investigator was pre-approved at a different hospital). The results categorised as 'minor variations' were amended at the

Table 1
Literature-derived clinical tolerances for patient quality assurance measurements for intensity-modulated radiotherapy (IMRT) prostate plans

Source of data	IPEM Report 96 [9]	Budgell *et al.* [10]	Royal Marsden Hospital*	EqualESTRO and IROC audits [11,12]
Example clinical tolerances for point doses				
Individual beam tolerance	3%	3%	5%	
Total dose tolerance	2%	2%	3%	5%
Critical organ tolerance (rectum, total dose)	2%			
Example clinical tolerances for combined dose distributions				
Dose/DTA criterion	3%/3 mm	3%/3 mm	4 %/4 mm	
Tolerance	98% of pixels inside 80% isodose	98% of pixels inside 80% isodose	95% (no lower dose threshold)	
Example clinical tolerances for fluence maps				
Dose/DTA criterion and dose threshold	4%/4 mm			
Tolerance	98% of pixels inside 20% isodose			

DTA, Distance to agreement.
* Using knowledge from a process used at the Royal Marsden Hospital.

discretion of the principal investigator; 'major variations' required modifying pre-treatment.

Outlines were approved for 29/100 cases with no variation or minor variations. Major variations were identified in 71/100 cases. The frequencies of outlining variations (major and minor variations combined) per anatomical structure are summarised in Table 3. Figure 2 presents examples of major variations in prostate and urethral bulb outlining.

Treatment Planning

Ninety-seven prospective treatment plan reviews were completed for 39 centres (two pilot centres were exempt) and the results are summarised in Table 2, using the same classification as the benchmark plans.

Dosimetry Site Visit

Dosimetry site visits were completed for all UK CHHiP centres (except one, which only recruited a single patient) between 2005 and 2011. However, data are only available for 32 centres and 39 treatment plans due to technical problems.

Ion Chamber Measurements

Dose point measurement results are presented as the percentage difference between the measured and TPS-

Table 2
Treatment planning results for pre- and on-trial quality assurance for CHHiP

	Pre-trial benchmark case		On-trial prospective case review	
Variation type	Major variation	Minor variation	Major variation	Minor variation
PTV margin growing error	11 (13%)	32 (39%)	14 (14%)	20 (21%)
Inadequate conformance of high dose to PTV	11 (13%)	25 (30%)	2 (2%)	24 (25%)
Inadequate dose coverage of PTVs	3 (4%)	6 (7%)	2 (2%)	9 (9%)
Dose distribution suboptimal	5 (6%)	1 (1%)	0	0
Hotspots in dose distribution	5 (6%)	9 (11%)	2 (2%)	3 (3%)
Dose constraints missed	7 (9%)	15 (18%)	2 (2%)	29 (30%)‡
Beam configuration suboptimal*	1 (1%)	8 (10%)	0	0
Plan assessment form completion errors	n/a	47 (57%)	n/a	29 (30%)
Patient data not anonymised	n/a	n/a	n/a	6 (6%)
Overall plan review result†	82 cases		97 cases	
No variation	20 (24%)		43 (44%)	
Minor variation	45 (55%)		48 (49%)‡	
Major variation	17 (21%)		6 (6%)	

IMRT, intensity-modulated radiotherapy; PTV, planning target volume.
* A beam configuration of three orthogonal fields was recommended for forward-planned IMRT [14] and five fields for inverse-planned IMRT.
† PTV margin errors were not included in the overall plan review result as these were considered outlining errors; however, PTV margins were assessed during treatment plan review.
‡ 10/48 minor variations were solely due to missed bladder dose constraints owing to inadequate bladder filling.

Table 3
Outlining quality assurance results for CHHiP prospective case reviews

Outlining variation	No. occurrences 100 cases	Breakdown by review number First review (38 cases)	Second review (37 cases)	Third review (21 cases)	Fourth review (3 cases)
Location of prostate apex	44% (44)	42% (16)	51% (19)	38% (8)	33% (1)
Location of prostate base	29% (29)	29% (11)	32% (12)	19% (4)	67% (2)
Other prostate outlining	13% (13)	11% (4)	14% (5)	14% (3)	33% (1)
Seminal vesicle outlining	39% (39)	50% (19)	30% (11)	38% (8)	33% (1)
Location of recto-sigmoid junction	43% (43)	50% (19)	38% (14)	48% (10)	0% (0)
Rectum inferior endpoint	32% (32)	37% (14)	30% (11)	33% (7)	0% (0)
Large rectal distension	4% (4)	5% (2)	0% (0)	10% (2)	0% (0)
Bowel not adequately outlined	38% (38)	55% (21)	24% (9)	33% (7)	33% (1)
Inadequate bladder filling	18% (18)	24% (9)	11% (4)	24% (5)	0% (0)
Bladder outlining	9% (9)	13% (5)	5% (2)	10% (2)	0% (0)
Femoral head outlines (included femoral neck)	28% (28)	34% (13)	22% (8)	33% (7)	0% (0)
Urethral bulb outlining*	62% (50/81)	68% (21/31)	50% (15/30)	76% (13/17)	33% (1/3)
Overall review result					
Approved	5% (5)	0% (0)	11% (4)	0% (0)	0% (0)
Minor variation	24% (24)	21% (8)	16% (6)	43% (9)	33% (1)
Major variation	71% (71)	79% (30)	73% (27)	57% (12)	67% (2)

* Urethral bulb outlining was introduced mid-trial; earlier plans did not outline the bulb.

calculated dose and have been normalised to the machine's daily output.

All measurements in the high-dose prostate PTV region agreed with the TPS calculation to within ±2.5% (mean 0.6% ± 1.0%). Measurements were carried out in the rectal location for 25/39 plans. Dose differences were larger in the rectum, with a maximum difference of +7.9% (mean 1.5% ± 3.4%).

Measurements of dose in the prostate PTV from individual fields agreed with the TPS-calculated dose to within ±5% for all but one centre (5.7% for one field).

Film Measurements

Film measurements are summarised in Table 4. For individual field fluence maps, the individual result with the largest deviation for each plan is shown. Results have been presented in two ways: statistics for all plans using 3%/3 mm and 4%/4 mm gamma parameters; and the number of plans achieving various tolerances (Table 1).

One hundred per cent of combined field films passed using 4%/4 mm gamma criteria and a 95% tolerance (i.e. >95% of the analysed film gave a gamma index <1); 78% passed using more stringent criteria of 3%/3 mm and a 98% tolerance. Seventy-three per cent of fluence maps passed using 4%/4 mm gamma parameters and a 98% tolerance.

Feedback Questionnaire

Twenty-five centres (61%) completed the feedback questionnaire. Representative quotes are included in Supplementary Material.

Patient Preparation

Two centres changed from treating with empty bladders to treating with full bladders. The trial procedures encouraged almost a half (10/25) of centres to update or formalise their bladder filling requirements. Discussions have reinforced the need for better bowel preparation and four centres used CHHiP to pilot the use of rectal enemas and dietary advice.

Clinical Outlining

Twelve of 25 centres adapted their prostate and/or rectum outlining as a result of CHHiP. Ten of 25 stated that it helped them with the audit or consistency of outlining within their department.

Intensity-Modulated Radiotherapy Treatment Planning

Ten of 16 centres using fp-IMRT adopted the technique into routine practice. Seven of 10 centres using ip-IMRT used CHHiP to help implement IMRT within their department; 4/10 of these centres rolled out IMRT to treat routine prostate patients as a direct result of CHHiP.

Ten of 25 centres reported benefitting from advice given by the CHHiP quality assurance team, primarily with planning techniques and optimisation. Additionally, the RTQA physicist co-ordinated networking between centres using the same TPS or delivery equipment to resolve equipment-specific issues.

Dosimetry Audit Visit

The consensus was that, although no major errors were discovered, the measurements gave centres confidence in their treatment plan delivery and supplied evidence of peer-assessed external audit.

Dose Constraints

Most centres used some dose constraints before the trial, but 12/25 modified their practice to reflect the

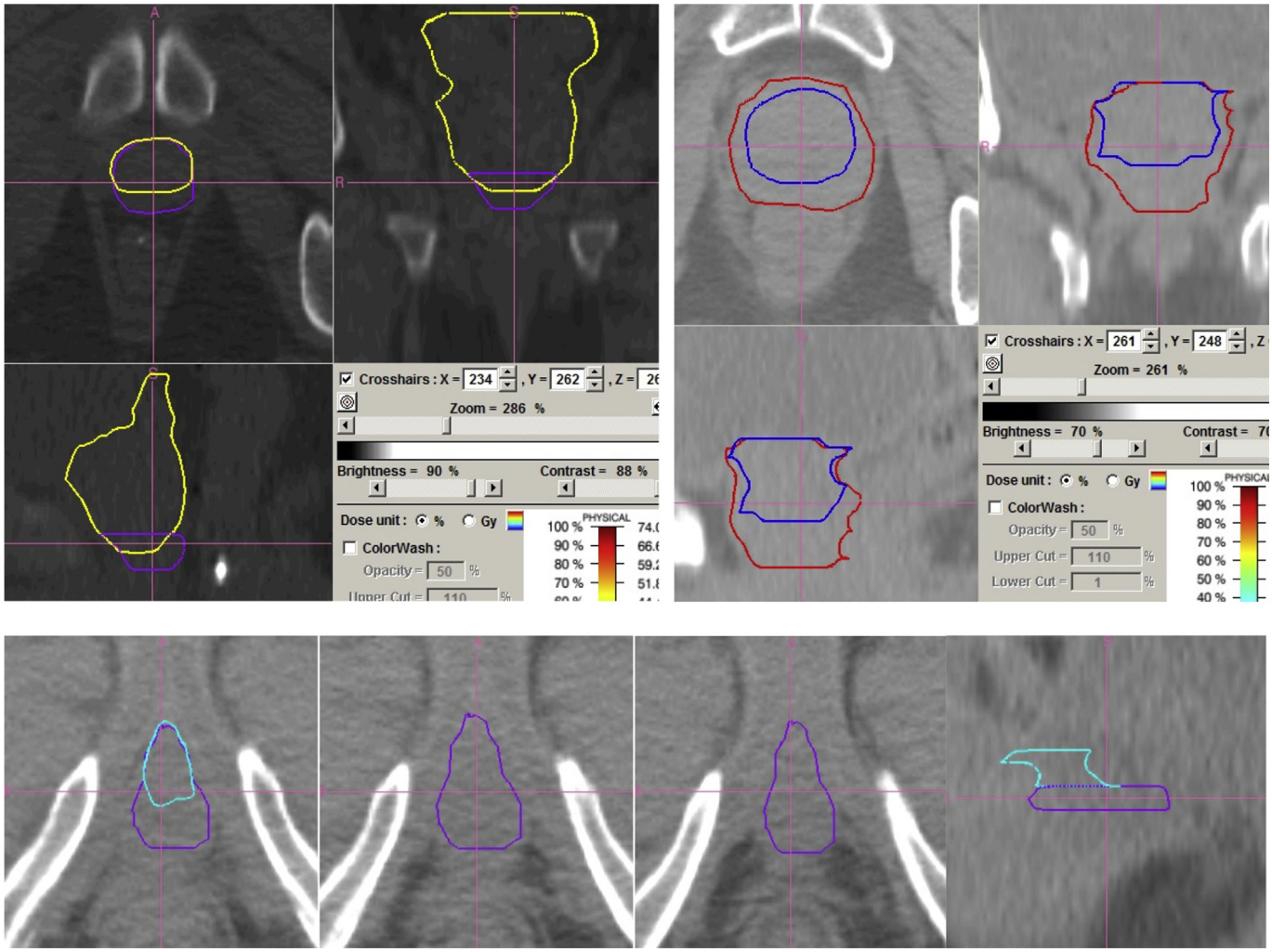

Fig 2. Examples of major variations in outlining the prostate target volume and the urethral bulb. In (a) and (b) (top left and right) the prostate apex has been inadequately outlined. In (a) prostate outlines did not encompass the whole gland posteriorly (centre outlines are yellow, review outlines purple); in (b) outlines were generally too small (centre outlines blue, review outlines red). (c) shows three consecutive axial views of urethral bulb outlining and one sagittal view (right); centre outlines are cyan, review outlines are purple.

comprehensive set of normal tissue dose constraints specified in the CHHiP trial protocol.

Implementation of Change

Participation in the CHHiP trial helped to develop and accelerate the centres' IMRT programmes, reduced resistance to change and supported the quality and evolution of practice and integration into daily departmental practice.

Discussion

Development of Intensity-Modulated Radiotherapy

An important objective of the CHHiP trial was to help centres implement IMRT. The feedback from the post-trial questionnaire indicates that this was achieved, with 7/10 ip-IMRT centres having used CHHiP to commission IMRT and 14/25 centres using CHHiP to roll out ip- or fp-IMRT for routine prostate treatment.

Clinical Outlining Reviews

Seventy-one of 100 clinical outlining cases needed amending before treatment and in retrospect a pre-trial benchmark outlining case would have been beneficial. There was a progressive reduction in the number of centres needing additional reviews for major variations with each review round, although the proportion of unsatisfactory outlines changed only slightly. It is possible that major variations persisted in some centres during the remainder of the trial. The impact of such variation on treatment efficacy or toxicity is uncertain, but overall trial outcomes were very satisfactory, as previously reported [1,16].

Table 4
Film results for CHHiP dosimetry audits, evaluated using gamma analysis

Gamma parameters	Combined plan results (36 plans)		Individual field (fluence map) results (15 plans)	
	3%/3 mm	4%/4 mm	3%/3 mm	4%/4 mm
% pixels with gamma <1	98.9% ± 1.7%	99.7% ± 0.9%	94.6% ± 6.8%	97.5% ± 4.5%
% films passing, using a threshold of:				
>98% pixels gamma <1	78% (28/36)	97% (35/36)	33% (5/15)	73% (11/15)
>95% pixels gamma <1	97% (35/36)	100% (36/36)	73% (11/15)	87% (13/15)

In common with other prostate studies [17–20], errors were reported in prostate apex and base outlines. This is due to the inherent difficulty of visualising the prostate on computed tomography images, compounded by subjective interpretation by different clinicians. Early CHHiP centres used 5 mm computed tomography slices, so the resolution was limiting for outlining. Recent UK prostate radiotherapy trials (PACE [ISRCTN 17627211], PIVOTALboost [CRUK/16/018]) have recommended a planning magnetic resonance imaging (MRI) scan to help delineate the prostate due to its enhanced soft-tissue contrast [21], but UK centres currently have variable access to MRI resources.

Urethral bulb outlining was implemented during part II of the trial following RT01 trial analyses [22]. However, the urethral bulb is difficult to visualise without MRI, despite the provision of a computed tomography-based outlining atlas, as shown by the large proportion of outlining errors reported (62% of cases).

Eighteen of 100 patients reviewed had an inadequately filled bladder, which meant achievement of bladder dose constraints was difficult. This highlights the importance of having consistent bladder filling instructions for patients; almost half the centres did formalise their bladder filling procedures as a result of the trial.

Outlining reviews remain an important tool to achieve consistency, and in post-trial feedback 10/25 centres reported that the CHHiP quality assurance reviews helped to improve the consistency of outlining for prostate radiotherapy within their department. Pre-trial benchmark outlining cases are now incorporated into most UK NIHR-portfolio trials. If resources allow, ongoing outlining quality assurance during trials may also be of value.

Treatment Planning Quality Assurance

PTV margin growing was the most common source of error for both pre- and on-trial planning quality assurance. The results highlighted that the instructions for the complex PTV margins defined in the trial protocol needed clarification and these were consequently modified. Margin growing errors can be avoided by implementing automated protocols, although some small differences between TPSs will remain.

Considering both pre- and on-trial plan review results, the proportion of major variations was substantially reduced from 21% to 6% following pre-trial quality assurance. Errors of all types were reduced and, in particular, issues with beam configuration and dose distribution were corrected. The proportion of minor variations was similar at both stages; however, 10/48 minor variations reported at case review were due to missed bladder dose constraints owing to a small bladder size. The plan assessment form proved to be a useful tool for a quick assessment of plans and indeed the concept is now being introduced into TPSs.

The most common treatment planning errors were inadequate conformance of the prescription isodoses to their respective PTVs and suboptimal dose distribution. IMRT was a new technique for many centres and dose distributions for IMRT may differ considerably from three-dimensional conformal radiotherapy. Dose conformance requirements are difficult to define in a trial protocol, although use of a conformity index [5] could be considered; it is assumed that individual trial centres can produce a clinically acceptable dose distribution based on the limitations of their TPS optimiser and delivery technique.

In many cases, the two benchmark cases were planned and submitted at the same time, resulting in the repetition of errors. It would have been advisable to instruct centres to wait for feedback for their first plan before attempting the second case.

Dosimetry Site Visit

At the time of the dosimetry site visits there were no formal recommendations as to suitable tolerances for IMRT verification and post-hoc rules were derived from subsequent publications. Current criteria are generally stricter since IMRT and the associated planning and delivery systems have evolved, and errors in measurement and calculation have reduced.

PTV dose point results were comparable with those from the PARSPORT head and neck IMRT trial dosimetry audit [23]. Measurements in the rectal location were more variable due to the high dose gradient and lower dose. The combined plan film results were an improvement over the PARSPORT results, possibly due to the complexity of modulation in the head and neck plans compared with the prostate.

The results of the dosimetry site visits gave reassurance in the consistency and accuracy of the treatment plan delivery for patients in the CHHiP trial. In addition, this was

the first IMRT audit for many centres and provided external review of their IMRT process.

The results indicated that there may be potential to scale back the scope of dosimetry site visits for future trials. A streamlined 'postal audit', using alanine and film, has recently been instigated for UK NIHR radiotherapy clinical trials to accredit centres who have previously undertaken a full dosimetry audit [24]. The European Organization for Research and Treatment of Cancer (EORTC) Radiation Oncology Group are now using 'virtual phantom credentialing' [25], where measurements are carried out on the centre's own quality assurance phantom and then submitted for central analysis. This could generate savings in both time and cost, although the value of such credentialing remains controversial [26,27].

Feedback Questionnaire

The post-trial feedback questionnaire was novel, and a useful tool to measure the impact of trial quality assurance on the on-going delivery of radiotherapy, as well as on the trial. The results also confirm the importance of radiotherapy trials in improving clinical practice.

CHHiP OAR dose constraints were adopted as standard by some trial centres and additionally by some non-trial centres after the study closed to recruitment. Several non-trial centres requested RTQA support to help implement the CHHiP technique, which is now the standard treatment protocol in many UK centres. Treatment planning, delivery and verification procedures mandated by the trial protocol encouraged centres to commit resources to commission new techniques, which consequently became standard practice. This was aided by support from the CHHiP quality assurance team and networking with other trial centres using similar equipment. This helped those centres that had not commissioned IMRT to overcome technical problems, improve their treatment planning technique and roll out the new technique into clinical practice in a more logical, robust, quicker and externally reviewed manner.

A quality assurance programme is essential to ensure the consistency and quality of radiotherapy delivery in trials using novel radiation techniques. However, quality assurance is resource intensive and may delay trial recruitment or deter participation. Harmonisation of quality assurance between the various international RTQA groups in order to facilitate the streamlining of quality assurance in international trials [28] is underway and is to be welcomed.

Conclusion

Implementation of the CHHiP trial has shown how a clinical trial requiring quality-assured high-technology radiotherapy delivery can benefit the general standard of radiotherapy delivered in participating centres by improving consistency, sharing best practice and supporting the implementation of new techniques through a structured RTQA programme. This in turn may improve the quality of the trial data by limiting variation in the radiotherapy treatment delivered to trial patients.

Conflict of Interest

D. Dearnaley reports grants from CRUK and NIHR/RMH/ICR Biomedical Research Centre during the conduct of the study as well as personal fees from Takeda, Amgen, Janssen, Astellas, Sandoz and ICR, outside the submitted work. In addition, D. Dearnaley has a patent issued (EP1933709B1). V. Khoo reports personal fees and non-financial support from Accuray, Astellas and Bayer and non-financial support from Janssen, outside the submitted work, as well as Honoraria for Speakers Bureaus with Accuray, Astellas, Bayer, Ipsen, Janssen, Takeda and Tolmar. E. Hall reports grants from Cancer Research UK during the conduct of the study and grants from Accuray Inc. outside the submitted work.

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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.05.009.

Appendix A

Table A1: Normal tissue dose constraints for the CHHiP trial.

Organ	Prescribed Dose (Gy)			Dose (%)	Maximum volume	
	74 Gy/37 fractions	60 Gy/20 fractions	57 Gy/19 fractions		Optimal	Mandatory
Rectum	30	24.3	23.1	41%	80%	–
	40	32.4	30.8	54%	70%	–
	50	40.5	38.5	68%	–	60%
	60	48.6	46.2	81%	–	50%
	65	52.7	50.1	88%	–	30%
	70	56.8	53.9	95%	–	15%
	74	60	57	100%	–	3%
Bladder	50	40.5	38.5	68%		50%
	60	48.6	46.2	81%		25%
	74	60	57	100%		5%
Bowel	50	40.5	38.5	68%		17cc
Penile bulb	50	40.5	38.5	68%	50%	
	60	48.6	46.2	81%	10%	
Femoral heads	50	40.5	38.5	68%	–	50%

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