

Title

Radiotherapy Quality Assurance for the CHHiP Trial: Conventional versus Hypofractionated High-dose Intensity-modulated Radiotherapy in Prostate Cancer

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Abstract

Purpose

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

Methods and Materials

QA 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

41 centres completed the QA programme (37 UK, 4 international) between 2005 and 2010. Centres used either forward-planned (field-in-field single phase) or inverse-planned IMRT (25 vs 17).

For pre-trial QA exercises, 7/41 (17%) centres had minor deviations in their radiotherapy processes; 45/82 (55%) benchmark plans had minor variations and 17/82 (21%) major variations.

100 prospective case reviews were completed for 38 centres. 71% 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 QA results (49% minor and 6% major variations).

Dosimetry audits were conducted for 32 centres. Ion chamber dose point measurements were within $\pm 2.5\%$ in the PTV and $\pm 8\%$ in the rectum. 28/36 films for combined fields passed gamma criterion 3%/3mm and 11/15 of IMRT fluence film sets passed gamma criterion 4%/4mm using a 98% tolerance.

Post-trial feedback demonstrated that trial participation was beneficial in evolving clinical practice, and the QA programme helped some centres implement and audit prostate IMRT.

Conclusion

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

Keywords

Radiotherapy; Quality assurance; Prostate cancer; Hypofractionation; CHHIP trial

Abbreviations

fr fractions; fp-IMRT forward-planned IMRT; ip-IMRT inverse-planned IMRT; PAF plan assessment form; CI Chief Investigator; PI Principal Investigator; SV seminal vesicles; TPS treatment planning system; RTQA radiotherapy quality assurance

Introduction

CHHiP (CRUK/06/016; ISRCTN97182923) is a randomised phase 3 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 74Gy in 2Gy fractions (fr) and the hypofractionated groups used 60Gy/20fr and 57Gy/19fr. From October 2002 to June 2011, 3216 men were recruited from 41 radiotherapy centres. The five year outcome data have been reported [1] and 60Gy/20fr has been recommended as the new standard of care by NHS England for external beam radiotherapy of localised prostate cancer.

As IMRT was a novel technique in the UK at the time of trial inception a comprehensive quality assurance (QA) programme was developed, based on the UK RT01 [2] and PARSPORT [3] trial QA 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 NIHR (National Institute of Health) Clinical Research Network radiotherapy clinical trials have QA programmes included from their inception.

Methods

Radiotherapy Protocol

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

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

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

Quality Assurance Programme

Completion and approval of all QA exercises was a pre-requisite for a centre commencing trial recruitment. The comprehensive QA 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 protocol or optimal practice but

unlikely to affect clinical outcome) and 'major variation' (unacceptable deviation with potential to influence clinical outcome).

Planning benchmark case

CT images with clinical target volumes and OARs pre-outlined were provided for two prostate patients (one low risk of seminal vesicle (SV) involvement [4] and one moderate SV risk 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 74Gy and 60Gy arms respectively. Plans were reviewed by the trial radiotherapy QA (RTQA) physicist using VODCA v4.4.2d software (MSS Medical Software Solutions GmbH). 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 (CI), and treatment planning, by the RTQA physicist, were performed 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 (PI) 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 (74Gy/37fr) on a pre-outlined CT dataset of the CIRS pelvic semi-anthropomorphic phantom (Figure 2). Additional measurements were performed if multiple planning techniques or treatment delivery equipment were used.

Point dose measurements

Dose for a single 2Gy fraction was measured using a PTW SemiFlex 0.125cm³ ion chamber at two measurement locations (in the PTV near the isocentre and in the rectum (Figure 2a)) and compared to the centres' treatment planning system (TPS) calculated dose. Relative dose was measured, normalised to the measured standard output for a 10cmx10cm field. Results were evaluated for total dose and dose per field.

Planar film measurements

An axial 2D dose distribution through the PTV was measured in the CIRS pelvic phantom using Kodak EDR2 film (Figure 2b). Single field film measurements (fluence maps) were performed for ip-IMRT plans at a depth of 10cm in a 15cmx15cmx20cm 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). Gamma analysis [8] was performed using 4% dose/4mm distance to agreement and 3%/3mm gamma criteria with a 10% dose threshold. Results were recorded as the percentage of pixels with $\gamma < 1$.

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 four 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 QA process.

Results

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

Equipment

27 centres used Varian linear accelerators, 16 Elekta and 3 Siemens. Photon beams had a nominal energy in the range 6-25MV; most centres used 6MV or 10MV, with 6MV used preferentially for ip-IMRT and 10MV for fp-IMRT.

7 different TPSs were used: Eclipse (15 centres), Pinnacle (8), Oncentra MasterPlan (8), CMS XiO (7), Plato (3), TMS Helax (1), ARPS (1). 17 centres used ip-IMRT, 25 used fp-IMRT (1 centre used both), and 3 centres changed from fp-IMRT to ip-IMRT during the course of the trial. Ip-IMRT employed step and shoot or dynamic multi-leaf collimator delivery with 5 fields, and 1 centre used rotational radiotherapy.

Treatment verification was primarily performed using electronic portal imaging, comparing MV images of bony anatomy with simulator-produced kV images or digitally reconstructed radiographs (as these became available); 1 centre used film. Techniques such as kV planar imaging, cone-beam CT, and CT on rails were used by centres in the latter stages of the trial, matching to gold fiducial markers or soft tissue (prostate gland). 36 centres used an offline treatment verification procedure, imaging the first 3 fractions and then weekly; 5 centres performed 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 prior to QA-approval and included:

- Patients treated with empty bladder (1 centre)
- No bowel preparation/assessment (4 centres)
- No patient immobilisation (2 centres)
- Treatment verification frequency too low (2 centres)
- Treatment verification tolerance >3mm (7 centres)

A variety of bladder and bowel preparation techniques were employed, 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 the majority of UK departments [13].

Planning benchmark case

All 41 recruiting radiotherapy centres completed the 2 benchmark cases. 24% (20/82) of plans were approved with no variation and 55% (45/82) reported minor variations (unlikely to affect clinical outcome). Major variations (with potential to influence clinical outcome, re-plan required) were reported in 21% (17/82) of cases. Results are summarised in Table 2, jointly with the case review results to enable 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 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 (2 pilot centres exempt and 1 centre's PI was pre-approved at a different hospital). Results categorised as 'minor variation' were amended at the discretion of the PI; '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 frequency 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

97 prospective treatment plan reviews were completed for 39 centres (2 pilot centres 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 2005-2011. 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-calculated dose, and have been normalised to the machine's daily output.

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

Measurements of dose in the prostate PTV from individual fields agreed with the TPS-calculated dose to within $\pm 5\%$ 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%/3mm and 4%/4mm gamma parameters; and the number of plans achieving various tolerances (Table 1).

100% of combined field films passed using 4%/4mm gamma criteria and a 95% tolerance (i.e. >95% of the analysed film gave a gamma index of <1); 78% passed using more stringent criteria of 3%/3mm and a 98% tolerance. 73% of fluence maps passed using 4%/4mm gamma parameters and a 98% tolerance.

Feedback questionnaire

25 centres (61%) completed the feedback questionnaire. Representative quotes from the feedback questionnaire are included in Appendix B.

Patient preparation

2 centres changed from treating with empty to full bladders. The trial procedures encouraged almost half (10/25) of centres to update or formalise their bladder filling requirements. Discussions have reinforced the need for better bowel preparation, and 4 centres used CHHiP to pilot the use of rectal enemas and dietary advice.

Clinical outlining

12/25 centres adapted their prostate and/or rectum outlining as a result of CHHiP. 10/25 stated it helped them with audit or consistency of outlining within their department.

IMRT treatment planning

10/16 centres using fp-IMRT adopted the technique into routine practice. 7/10 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.

10/25 centres reported benefit from advice given by the CHHiP QA 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, while 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 pre-trial, but 12/25 modified their practice to reflect the comprehensive set of normal tissue dose constraints specified in the CHHiP trial protocol.

Implementation of change

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

Discussion

Development of IMRT

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

71/100 clinical outlining cases needed amending pre- 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 will have 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].

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 CT images, compounded by subjective interpretation by different clinicians. Early CHHiP centres used 5mm CT slices so the resolution was limiting for outlining. Recent UK prostate radiotherapy trials (PACE [ISRCTN 17627211], PIVOTALboost [CRUK/16/018]) have recommended a planning MRI scan to help delineate the prostate due to its enhanced soft tissue contrast [21], but UK centres currently have variable access to MRI resource.

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 MR imaging, despite the provision of a CT-based outlining atlas, as shown by the large proportion of outlining errors reported (62% of cases).

18/100 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, and almost half of 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 of centres reported that the CHHiP QA reviews helped improve consistency of outlining for prostate radiotherapy within their department. Pre-trial benchmark outlining cases are now incorporated in most UK NIHR-portfolio trials. If resources permit, ongoing outlining QA during trials may also be of value.

Treatment planning QA

PTV margin growing was the most common source of error for both pre- and on-trial planning QA. 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 nowadays 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 following pre-trial QA from 21% to 6%. 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 small bladder size. The PAF proved a useful tool for 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 sub-optimal dose distribution. IMRT was a new technique for many centres, and dose distributions for IMRT may differ considerably from 3D 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 2 benchmark cases were planned and submitted at the same time resulting in 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 to 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 to 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 EORTC Radiation Oncology Group are now using "virtual phantom credentialing" [25] where measurements are performed on the centre's own QA 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 QA 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 QA team and networking with other trial centres using similar equipment. This helped those centres who had not commissioned IMRT 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 QA programme is essential to ensure the consistency and quality of radiotherapy delivery in trials using novel radiation techniques. However QA is resource intensive and may delay trial recruitment or deter participation. Harmonisation of QA between the various international RTQA groups in order to facilitate streamlining of QA in international trials [28] is underway and 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 radiotherapy QA programme. This in turn may improve the quality of the trial data by limiting variation in the radiotherapy treatment delivered to trial patients.

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References

- [1] Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol*. 2016;17(8):1047-60.
- [2] Mayles WP, Moore AR, Aird EG, Bidmead AM, Dearnaley DP, Griffiths SE, et al. Questionnaire based quality assurance for the RT01 trial of dose escalation in conformal radiotherapy for prostate cancer (ISRCTN 47772397). *Radiother Oncol*. 2004;73(2):199-207.
- [3] Clark CH, Miles EA, Urbano MT, Bhide SA, Bidmead AM, Harrington KJ, et al. Pre-trial quality assurance processes for an intensity-modulated radiation therapy (IMRT) trial: PARSPORT, a UK multicentre Phase III trial comparing conventional radiotherapy and parotid-sparing IMRT for locally advanced head and neck cancer. *Br J Radiol*. 2009;82(979):585-94.
- [4] Diaz A, Roach M, Marquez C, Coleman L, Pickett B, Wolfe JS, et al. Indications for and the significance of seminal vesicle irradiation during 3D conformal radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 1994;30:323-9.
- [5] ICRU Report 62: Prescribing, Recording and Reporting Photon Beam Therapy.
- [6] South CP, Khoo VS, Naismith O, Norman A, Dearnaley DP. A comparison of treatment planning techniques used in two randomised UK external beam radiotherapy trials for localised prostate cancer. *Clin Oncol (R Coll Radiol)*. 2008;20(1):15-21.
- [7] ICRU Report 83: Prescribing, Recording, and Reporting Intensity-Modulated Photon-Beam Therapy (IMRT).
- [8] Low DA, Harms WB, Mutic S, Purdy JA. A technique for the quantitative evaluation of dose distributions. *Med Phys*. 1998;25(5):656-61.
- [9] IPEM Report 96: Guidance for the Clinical Implementation of Intensity Modulated Radiation Therapy.
- [10] Budgell GJ, Perrin BA, Mott JH, Fairfoul J, Mackay RI. Quantitative analysis of patient-specific dosimetric IMRT verification. *Phys Med Biol*. 2005;50(1):103-19.
- [11] Roué A, Van Dam J, Dutreix A, Svensson H. The EQUAL-ESTRO external quality control laboratory. *Cancer Radiother*. 2004;8 Suppl 1:S44-9.
- [12] Alvarez P, Kry SF, Stingo F, Followill D. TLD and OSLD dosimetry systems for remote audits of radiotherapy external beam calibration. *Radiat Meas*. 2017;106:412-5.
- [13] O'Doherty UM, McNair HA, Norman AR, Miles E, Hooper S, Davies M, et al. Variability of bladder filling in patients receiving radical radiotherapy to the prostate. *Radiother Oncol*. 2006;79(3):335-40.
- [14] Khoo VS, Bedford JL, Webb S, Dearnaley DP. Evaluation of the optimal co-planar field arrangement for use in the boost phase of dose escalated conformal radiotherapy for localized prostate cancer. *Br J Radiol*. 2001;74(878):177-82.

- [15] Pooler AM, Mayles HM, Naismith OF, Sage JP, Dearnaley DP. Evaluation of margining algorithms in commercial treatment planning systems. *Radiother Oncol.* 2008;86(1):43-7.
- [16] Wilkins A, Mossop H, Syndikus I, Khoo V, Bloomfield D, Parker C, et al. Hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate-risk localised prostate cancer: 2-year patient-reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol.* 2015;16(16):1605-16.
- [17] Seddon B, Bidmead M, Wilson J, Khoo V, Dearnaley D. Target volume definition in conformal radiotherapy for prostate cancer: quality assurance in the MRC RT-01 trial. *Radiother Oncol.* 2000;56(1):73-83.
- [18] Fenton PA, Hurkmans C, Gulyban A, van der Leer J, Matzinger O, Poortmans P, et al. Quality assurance of the EORTC 22043-30041 trial in post-operative radiotherapy in prostate cancer: results of the Dummy Run procedure. *Radiother Oncol.* 2013;107(3):346-51.
- [19] Kearvell R, Haworth A, Ebert MA, Murray J, Hooton B, Richardson S, et al. Quality improvements in prostate radiotherapy: outcomes and impact of comprehensive quality assurance during the TROG 03.04 'RADAR' trial. *J Med Imaging Radiat Oncol.* 2013;57(2):247-57.
- [20] Matzinger O, Poortmans P, Giraud JY, Maingon P, Budiharto T, van den Bergh AC, et al. Quality assurance in the 22991 EORTC ROG trial in localized prostate cancer: dummy run and individual case review. *Radiother Oncol.* 2009;90(3):285-90.
- [21] Sander L, Langkilde NC, Holmberg M, Carl J. MRI target delineation may reduce long-term toxicity after prostate radiotherapy. *Acta Oncol.* 2014;53(6):809-14.
- [22] Mangar SA, Sydes MR, Tucker HL, Coffey J, Sohaib SA, Gianolini S, et al. Evaluating the relationship between erectile dysfunction and dose received by the penile bulb: using data from a randomised controlled trial of conformal radiotherapy in prostate cancer (MRC RT01, ISRCTN47772397). *Radiother Oncol.* 2006;80(3):355-62.
- [23] Clark CH, Hansen VN, Chantler H, Edwards C, James HV, Webster G, et al. Dosimetry audit for a multi-centre IMRT head and neck trial. *Radiother Oncol.* 2009;93(1):102-8.
- [24] <https://phys.org/news/2014-12-video-dosimetry.html>
- [25] Weber DC, Vallet V, Molineu A, Melidis C, Teglas V, Naudy S, et al. IMRT credentialing for prospective trials using institutional virtual phantoms: results of a joint European Organization for the Research and Treatment of Cancer and Radiological Physics Center project. *Radiat Oncol.* 2014;9:123.
- [26] Kry SF, Molineu A, Kerns JR, Faught AM, Huang JY, Pulliam KB, et al. Institutional patient-specific IMRT QA does not predict unacceptable plan delivery. *Int J Radiat Oncol Biol Phys.* 2014;90(5):1195-201.
- [27] Seravalli E, Houweling AC, Van Battum L, Raaben TA, Kuik M, de Pooter JA, et al. Auditing local methods for quality assurance in radiotherapy using the same set of predefined treatment plans. *Physics and Imaging in Radiation Oncology* 2018;5:19–25.

[28] Melidis C, Bosch WR, Izewska J, Fidarova E, Zubizarreta E, Ishikura S, et al. Radiation therapy quality assurance in clinical trials--Global Harmonisation Group. *Radiother Oncol.* 2014;111(3):327-9.

Appendix A: Normal Tissue Dose Constraints for the CHHiP Trial

Organ	Prescribed Dose [Gy]			Dose (%)	Maximum Volume	
	74Gy/37fr	60Gy/20fr	57Gy/19fr		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%

Table A.1. Normal tissue dose constraints for the CHHiP trial

Appendix B: CHHiP Feedback Questionnaire and Results

This appendix reports quotes from the CHHiP Feedback Questionnaire, sent to centres after the trial closed, on changes to their local prostate radiotherapy procedures directly resulting from participation in the CHHiP trial.

Patient preparation

Advice to patients regarding bladder filling

“Prior to CHHiP empty bladder instructions were given, but once CHHiP opened this was changed to comfortably full bladder for all patients across the department.”

“Implementation of a bladder filling protocol as department standard for all prostate patients. Incorporated into patient information leaflets.”

“At CT planning scan stage, control slices (1-2 slices) were introduced to check rectal/bladder filling before performing prostate scan.”

Procedures regarding rectal filling

“Micro-enemas were initially introduced for CHHiP trial patients only. Then clinicians implemented this for all prostate patients.”

“Positive impact. We now have robust protocols in place, partly as a result of CHHiP trial influence.”

“We introduced re-scans about 5 years ago, and rectal enemas about two years ago. Not directly due to CHHiP, but the regularity of the teleconferences and general awareness of the issues was repetitively drummed home!”

Clinical outlining

Procedures for outlining prostate, seminal vesicles, urethral bulb, rectum

“We now outline as per CHHiP protocol for all low and medium risk patients having radiotherapy to prostate. Previously outlining was variable (most used ProtecT trial protocol).”

“Improvement with regard to prostate apex, membranous urethra, and urethral bulb.”

“Urethral bulb not normally outlined. Due to the difficulty of outlining, we probably won’t continue in normal practise.”

Clinical audit and consistency of clinical outlining within the department

“The CHHiP outlining exercise has been the principal training and audit mechanism.”

“Established with clinicians that contouring OAR should be standard practice.”

“It has helped to get agreement between consultants with regard to outlining, dose, tolerances, etc., and also hormone therapy.”

“The review process has proved a very useful tool, and one which we would be keen to participate in again should the opportunity arise. Certainly it has sparked debate within our centre and reinforced the need for a clinical audit to measure consistency.”

Radiotherapy treatment planning

Forward-planned IMRT

Changes in forward-planning technique, e.g. beam arrangements

“Our forward-planned IMRT was developed through CHHiP, and extended to our standard departmental prostate planning protocols.”

“Previously we treated patients with anterior, left and right posterior oblique beams. Now all prostate patients are treated with anterior, left and right lateral beams.”

“Radiographers like having a single plan rather than phase 1 and phase 2. CHHiP segmented plans helped to introduce the concept of segments and control points to treatment radiographers.”

“Introducing CHHiP using segmented techniques helped everyone to be less fearful of full-blown inverse-planned IMRT.”

Inverse-planned IMRT

Did you use CHHiP to help implement IMRT within your department?

“CHHiP was used to implement IMRT in our department; and the CHHiP patients were our first IMRT patients.”

“CHHiP was used as the basis for developing our IMRT programme.”

“We used the CHHiP patients to develop our IMRT patient QA methodology.”

“Useful way of increasing IMRT numbers in a safe/controlled way.”

Are you planning your routine prostate patients using IMRT as a result of CHHiP?

“CHHiP trial helped us to introduce IMRT for prostate patients in a very controlled and confident manner. “

“We changed to inverse-planning part-way through the trial. After we had gained experience with the technique and confidence with the per-patient QA/delivery, the technique was adapted for routine prostate radiotherapy and all our prostates are now treated with IMRT.”

What help did you receive with IMRT from the CHHiP team?

“The intellectual gain for the department with respect to planning and QA of IMRT technique is very significant and we are very grateful for it.”

“We used the beam selection from the Clatterbridge CHHiP protocol. They suggested extra volumes as outlined in the Royal Marsden protocol, following failure in the planning exercise, which was invaluable even though it used the Eclipse planning system.”

“Decided to use segmented forward-planned CHHiP technique provided by Royal Marsden (Sutton).”

“Put in touch with another centre using the same TPS, which helped during development of the planning process. Feedback from planning exercises was also helpful in refining the planning process.”

“Networking with other Elekta and OMP users.”

Dosimetry audit

How did the dosimetry audit visit help you?

“Useful as a pre-implementation check for inverse-planned IMRT.”

“It gave us confidence in the dosimetry of our set-up.”

“Gave reassurance, and we were able to do our own film dosimetry and compare with audit. Report gave useful information for future gamma analysis for film dosimetry.”

Dose constraints

“As a result of participating in the CHHiP trial, we have adopted the normal tissue constraints and applied them to all of our prostate patients.”

“We now use the CHHiP dose constraints for the rectum and bladder (previously no constraints for OARs).”

“No, in fact the constraints are ‘lighter’ in the trial, e.g. our V60Gy is 35%.”

“Enabled the adoption of 74Gy as standard prescription.”

Treatment verification

“As a result of the CHHiP trial, we are now routinely acquiring portal images for the first 3 fractions and weekly thereafter for all radical treatments. This has required changes to protocol and development of appropriate documentation to support these changes.”

“Our tolerance levels were not as tight as CHHiP’s originally for imaging, but we have now brought down the acceptable margins to CHHiP levels for all our patients having prostate radiotherapy.”

Departmental and staff development

Have the requirements for the CHHiP trial helped to implement changes within the department?

“Our radiotherapy staff are now enthused to continue to develop a routine IMRT service. The experience has also highlighted to the management in the Trust the ability of the department to implement change of this type.”

“The usual ‘resistance to change’ was met with hard deadlines that had to be met due to participation in a trial. This obviously raised the priority of CHHiP above other clinical developments and bypassed the usual politics involved in introducing a new technique.”

“The trial helped with: general departmental enthusiasm; involvement of research nursing staff in radiotherapy trials rather than medical oncology trials; other staff groups’ and members’ involvement in research trials; confidence in the introduction of different techniques in a controlled manner.”

“For the staff that have been involved it has been beneficial, increasing their experience, expertise and, to some extent, their confidence.”

“Research radiographers are doing prostate trial (not only CHHiP) patients’ follow-ups in clinics personally; this was not the case at the beginning of the trial. This has made an impact on the workload of the consultant teams as they no longer follow up these patients themselves unless they develop recurrence, and has led to role development for the research radiographers.”

“The control arm of clinical trial protocols can provide useful information for smaller departments when updating techniques.”

Radiotherapy trial participation

“It has played a major part in getting our radiotherapy trials team up and running.”

“As the CHHiP trial was a large radiotherapy trial, along with the IMPORT trial it helped promote radiotherapy trials in our department and this is an area we are continuing to promote and encourage.”

“As a centre we had quite a low level of recruitment to radiotherapy clinical trials before going live with CHHiP. CHHiP alone in 2010 has provided us with almost the same amount of total recruitment as to all radiotherapy clinical trials in 2009. It is our largest recruiting study this year, and has helped show that large-scale recruitment is possible.”

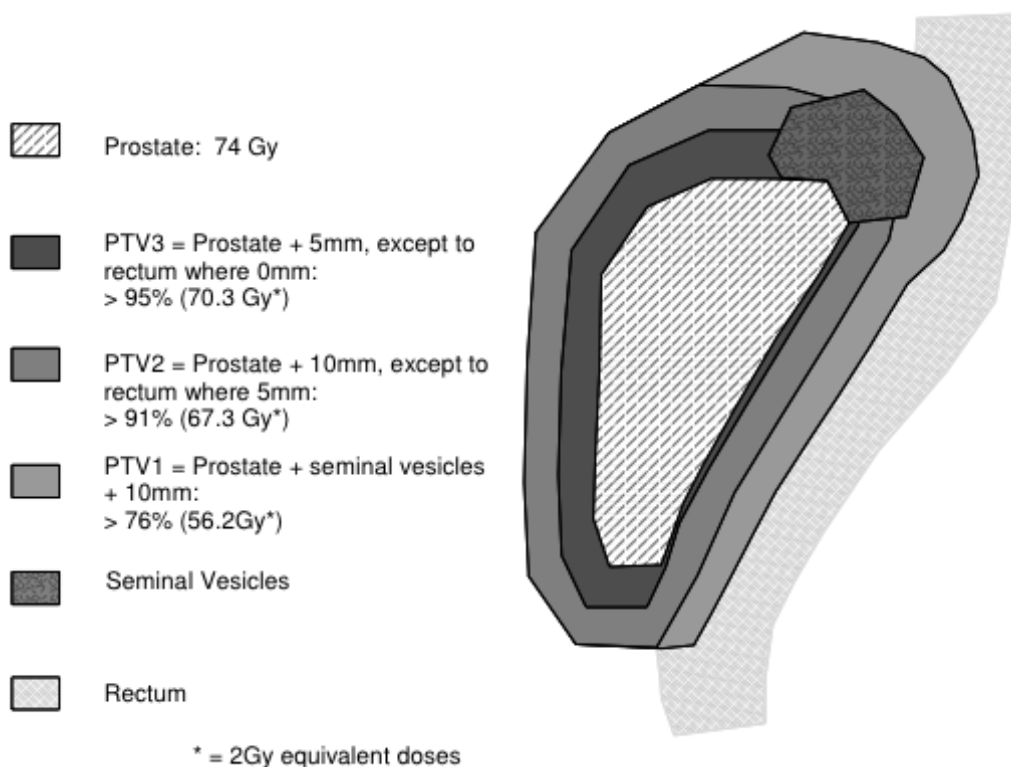


Figure 1. PTV margins and doses for the CHHiP trial. In patients with a low risk [4] of seminal vesicle (SV) involvement the base of SV (proximal 2cm) was included, those with moderate or high risk had all of SV included.

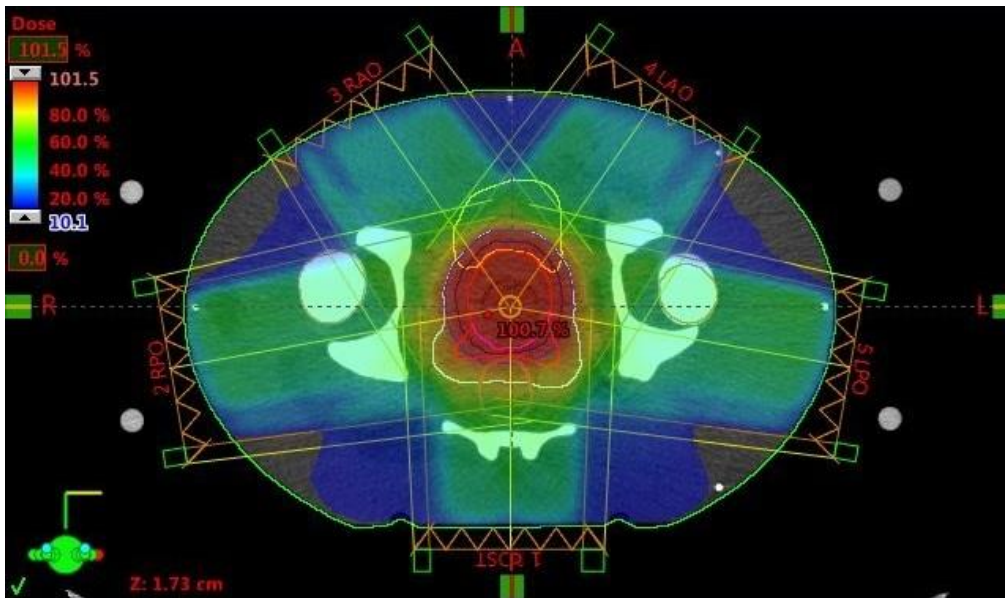
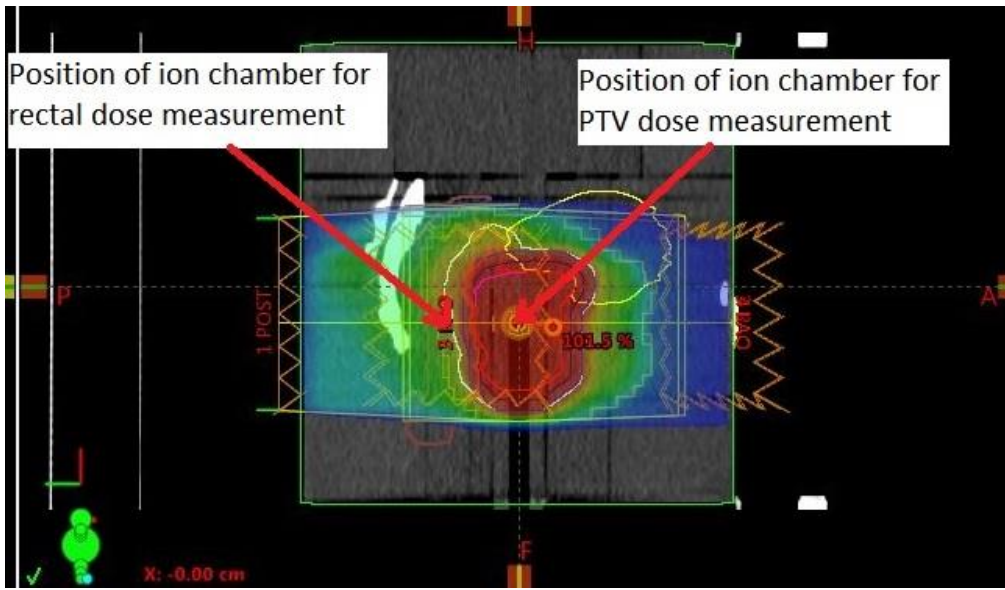


Figure 2. Measurement of (a, top) dose to PTV and rectum using ion chamber and, (b, bottom) full plan delivery to axial film for a CHHiP ip-IMRT plan in the CIRS pelvic phantom.

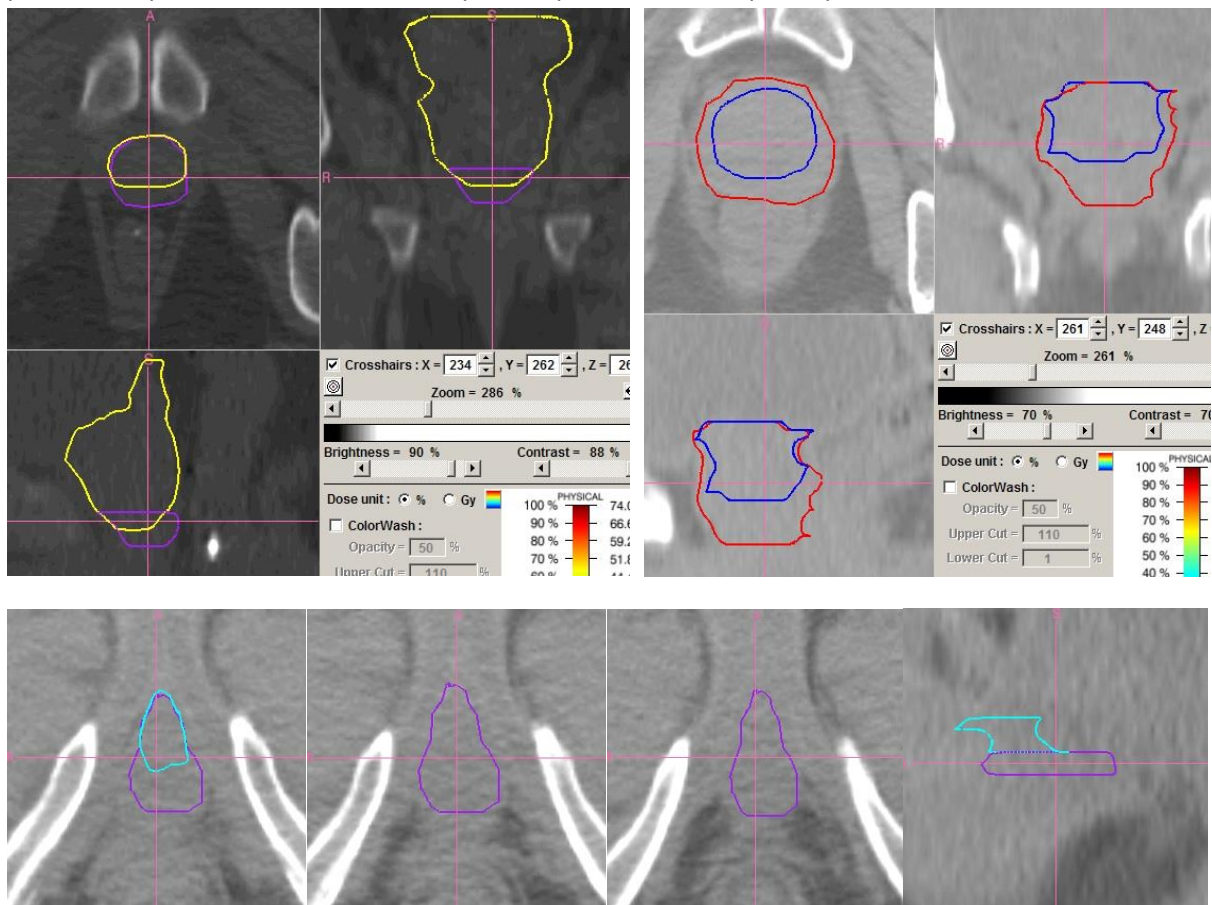


Figure 2. Examples of major variations in outlining the prostate target volume and the urethral bulb. In Figures 2a and b (top left and right) the prostate apex has been inadequately outlined. In 2a prostate outlines did not encompass the whole gland posteriorly (centre outlines are yellow, review outlines purple); in 2b outlines were generally too small (centre outlines blue, review outlines red). Figure 2c shows 3 consecutive axial views of urethral bulb outlining and 1 sagittal view (right); centre outlines are cyan, review outlines purple.

Source of data	IPEM Report 96 [9]	Budgell et al [10]	Royal Marsden Hospital (RMH) *	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% / 3mm	3% / 3mm	4% / 4mm	
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% / 4mm			
Tolerance	98% of pixels inside 20% isodose			

* Using knowledge from process used at RMH

Table 1. Literature-derived clinical tolerances for patient QA measurements for IMRT prostate plans

Variation type	Pre-trial benchmark case		On-trial prospective case review	
	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 sub-optimal	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 sub-optimal #	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%)	

A beam configuration of 3 orthogonal fields was recommended for fp-IMRT [14] and 5 fields for ip-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 2. Treatment planning results for pre- and on-trial QA for CHHiP

Outlining variation	No. occurrences 100 cases	Breakdown by review number			
		1 st Review (38 cases)	2 nd Review (37 cases)	3 rd Review (21 cases)	4 th 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

Table 3. Outlining QA results for CHHiP prospective case reviews

Gamma parameters	Combined plan results (36 plans)		Individual field (fluence map) results (15 plans)	
	3%/3mm	4%/4mm	3%/3mm	4%/4mm
% pixels with $\gamma < 1$	98.9% \pm 1.7%	99.7% \pm 0.9%	94.6% \pm 6.8%	97.5% \pm 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)

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

