Quality improvements in prostate radiotherapy: Outcomes and impact of comprehensive quality assurance during the TROG 03.04 'RADAR' trial


Published in:
Journal of Medical Imaging and Radiation Oncology

DOI:
10.1111/1754-9485.12025

Document Version
Peer reviewed version

Link to publication in the UWA Research Repository

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Download date: 12. May. 2018

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This is the peer reviewed version of the following article: Kearvell, R., Haworth, A., Ebert, M. A., Murray, J., Hooton, B., Richardson, S., Joseph, D. J., Lamb, D., Spry, N. A., Duchesne, G. and Denham, J. W. (2013), Quality improvements in prostate radiotherapy: Outcomes and impact of comprehensive quality assurance during the TROG 03.04 ‘RADAR’ trial. Journal of Medical Imaging and Radiation Oncology, 57: 247–257. doi: 10.1111/1754-9485.12025, which has been published in final form at http://dx.doi.org/10.1111/1754-9485.12025. This article may be used for non-commercial purposes in accordance With Wiley Terms and Conditions for self-archiving.

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<thead>
<tr>
<th>Journal:</th>
<th>Journal of Medical Imaging and Radiation Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID:</td>
<td>JMIRO-12-0209.R1</td>
</tr>
<tr>
<td>Manuscript Type:</td>
<td>Radiation Oncology Original Article</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>n/a</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Kearvell, Rachel; Sir Charles Gairdner Hospital, Radiation Oncology Haworth, Annette; Peter MacCallum Cancer Centre, Physical Sciences; Ebert, Martin; Sir Charles Gairdner Hospital, Radiation Oncology; University of Western Australia, School of Physics Murray, Judy; University of Otago, Pathology and Molecular Medicine Hooton, Ben; Sir Charles Gairdner Hospital, Radiation Oncology Richardson, Sharon; Sir Charles Gairdner Hospital, Radiation Oncology Joseph, David; Radiation Oncology, SCGN Lamb, David; University of Otago, Pathology and Molecular Medicine Spry, Nigel; Sir Charles Gairdner Hospital, Radiation Oncology Duchesne, Gillian; Director of Radiation Oncology, Peter MacCallum Cancer Institute Denham, James</td>
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<tr>
<td>Keywords:</td>
<td>Radiation Oncology, Prostate cancer, Quality Assurance, Clinical trials</td>
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Quality improvements in prostate radiotherapy: Outcomes and impact of comprehensive quality assurance during the TROG 03.04 ‘RADAR’ trial

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Number of pages: 21
Number of figures: 4
Number of tables: 2
Supporting online material to be included.

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Running Title: Technical QA for the RADAR trial
ABSTRACT

Introduction: The Trans-Tasman Radiation Oncology Group (TROG) 03.04 ‘RADAR’ multicentre prostate cancer trial examined the optimal duration of androgen deprivation in combination with dose-escalated radiotherapy. Rigorous quality assurance (QA) processes were undertaken to ensure the validity and reliability of the RT treatment plan data.

Method: QA processes included a planning benchmarking exercise and a periodic audit of target and normal tissue delineation. Centralised electronic review of digital plan data for external beam radiotherapy was undertaken to detect protocol variations. The impact of clinical factors and feedback to submitting centres during the trial on variation rates was investigated.

Results: 23 centres across Australia and New Zealand recruited 1071 participants to the trial. Treatment plans for 754 participants receiving external-beam treatment alone were reviewed. From these, 1185 minor and 86 major variations were identified leading to feedback to treating centres to reduce variations for subsequent patients’ treatment and plans, suggesting improvement in treatment quality through these QA programs. Participant anatomical factors (delineated CTV and rectal volume) and treatment planning factors (beam energy, beam definition, patient position orientation) were found to significantly impact variation rates. The dummy-run demonstrated disagreement in identification of the base of the prostate and the superior extent of the rectum. Feedback from the periodic audit led to a change of practice at five contributing centres.
Conclusion: The application of a suite of complementary QA activities allows the quality of trial data to be optimised and quantified, and can provide a catalyst for reforming treatment practices.

Key words: prostate cancer; radiotherapy; quality assurance; clinical trials
INTRODUCTION

In multicentre radiotherapy clinical trials, lack of consistency in trial protocol interpretation, treatment planning and delivery can reduce the ability of the trial to generate significant results (1-6). Several collaborative trials groups have adopted procedures for quality assurance (QA) of treatment planning data for assessing centres’ abilities to meet protocol requirements or for review of individual trial participants’ plans (7, 8). The complexity of such reviews can vary from simple visual inspection of hardcopy information (9), to more automated reviews based on electronic submission and review systems (10-13). The importance of rigorous QA of radiotherapy was highlighted by the results of the TROG 02.02 ‘HeadSTART’ trial for head and neck chemoradiotherapy, where it was shown that the influence of radiotherapy quality could be greater than that of the intervention being evaluated in the trial. (5)

The Trans-Tasman Radiation Oncology Group (TROG) 03.04 ‘RADAR’ (Randomised Androgen Deprivation and Radiotherapy) trial was principally aimed at evaluation of variable-duration androgen deprivation (AD) for localised prostate carcinoma.(14) The trial also examined the role of three-dimensional conformal radiation therapy (3DCRT) including dose escalation. RADAR built on the TROG 96.01 prostate trial which required a dose prescription of 66 Gy and was carried out in the era of early computed tomography (CT) planning (< 60% of plans were based on CT imaging). Late Grade 2 rectal toxicity was consistent with that reported by Pollack et al (15, 16) who demonstrated that rectal toxicity will significantly increase as the dose prescription is increased unless rectal sparing can be achieved via stringent conformal techniques.
To facilitate the generation of quality data for the RADAR trial and provide a safe environment for the introduction of techniques that were novel to many centres, the technical requirements were audited through a series of complementary QA studies. These were aimed at ensuring protocol compliance and allowed quantification of the variability between centres and participants in planning/treatment methodology. The ability of participating centres to deliver accurate radiotherapy was assessed by means of (previously published) setup accuracy (SUA) (17) and phantom-based dosimetric (18-21) studies. These two studies provided a quality framework for the RADAR trial, establishing minimum requirements for spatial and dosimetric accuracy, quantifying the related underlying uncertainties and challenging contributing centres to meet the trial protocol requirements. This paper describes three additional QA activities around treatment planning which provided complementary and ongoing quality assessment during the trial. The overall influence of these activities was examined via their impact on the quality of planned radiotherapy delivery for trial participants and general radiotherapy practice at participating centres. Future publications will report on the non-technical QA activities associated the RADAR trial.

**METHODS AND MATERIALS**

**Trial Overview**

The RADAR trial (TROG 03.04, NIH trial identifier NCT00193856) was conducted between 2003 and 2008 and accrued 1071 participants. The trial aimed to determine the optimal duration of AD for intermediate (T2a) and high (T2b+) risk prostate cancer patients undergoing radiotherapy. Radiotherapy dose escalation (66 Gy, 70 Gy, 74 Gy, 78 Gy) was a key feature of the trial, as was the alternative to provide external beam
radiotherapy (46 Gy) combined with a high dose rate (HDR) brachytherapy boost (3 fractions to total dose 19.5 Gy). Twenty-three sites accrued participants across Australia and New Zealand following approval of the trial protocol and consent form by local Human Research Ethics Committees.

The trial protocol provided external beam radiotherapy (EBRT) treatment planning guidelines largely based on the recommendations of a consensus workshop (22). For doses above 66 Gy, participation in the QA program described in this paper was mandatory.

**Development of Electronic Plan Review Software (SWAN)**

Plan review software, ‘SWAN’, was conceived to allow electronic treatment plan review, via RTOG [format of the North American Radiation Therapy Oncology Group, based on AAPM Report #10 (23)] and DICOM [Digital Imaging and Communication in Medicine (24)] formatted plan exports, for multicentre trials in Australasia (25, 26). RADAR plans were exported from SWAN to a relational database, allowing manually-reported treatment information to be directly linked to each treatment plan. It also allowed retrieval of plans from the database directly into SWAN, and the ability to perform operations on the stored data without requiring that it be re-imported in full. The database can be queried using standard Structured Query Language (SQL) operations. Functionality was incorporated to enable specific treatment fields and dosimetric parameters to be compared with protocol requirements (26). The resultant treatment plan’s protocol conformity was then summarised and provided to the submitting institution. The variability in dose-volume histogram (DVH) calculation
between treatment planning systems (27) was overcome using independent DVH calculations in SWAN.

**Treatment Planning QA Exercises**

*Benchmarking Exercise*

A benchmarking exercise (‘dummy-run’) was undertaken to identify ambiguities in protocol recommendations and to collect plan data in electronic format for validation of the QA process. Participation in the benchmarking exercise was encouraged, though was not mandatory for trial participation. Participating centres were asked to contour one intermediate and one high risk case (using supplied DICOM CT data) according to the protocol. In addition, sites were required to plan the high risk case to a dose of 74 Gy prescribed to the ICRU reference point (28).

*Treatment Plan Review and Post-Treatment Verification*

Centres exported the electronic treatment plans for submission to the radiotherapy review team (RTRT), together with a report that ensured that reviewed data were consistent with those from the original treatment planning system (TPS). Electronic plan submission was not mandatory for patients receiving the combined EBRT/HDR boost treatment approach. All submitted EBRT plans were reviewed by an expert RTRT radiation therapist, in addition to automated review using the auto-report function in SWAN (see Table 1). ‘Variation’ of items relative to protocol were categorised as either:

- ‘Minor’ – outside protocol recommendations but unlikely to influence clinical outcome;
• ‘Major’ - outside protocol recommendations and may influence clinical outcome.

The definitions of these specific to each reviewed item are provided in Table 1.

Periodic Contour Audit

A separate QA program was developed to audit contouring practices. The audit team included 8 experienced radiation oncologists (RO) and 4 radiation therapists (RT) from 4 institutions. At each of 5 periodic rounds a small number of submitted treatment plans were reviewed by all auditors and the remaining treatment plans equally shared.

The auditors rated the planning target volumes (PTVs) according to their assessment of the margins applied to the clinical target volume (CTV). Any plan scored “Feedback Required”, or “Equivocal” was subsequently reviewed by at least one additional audit RO before feedback to the treating centre. Those with systematic errors requiring feedback had subsequent plans audited to confirm practice change.

RESULTS

Benchmarking Exercise

Thirteen centres participated. For centres that did not participate, submission of data for their first accrued participant was used as an opportunity to validate the centre’s ability to submit correctly formatted, complete and compliant data.

One centre submitted 5 sets of contours from 5 clinicians. Variability was seen in contouring practices particularly in the superior-inferior direction – in a coronal plane...
through the centre of the prostate, the prostatic base (superior extent of prostate) varied 23 mm and 15 mm across observers for the intermediate and high risk cases respectively, the apex varying 33 mm and 24 mm respectively). Further quantitative results for the two test cases are provided in online supporting material, demonstrating that for the high-risk case the greatest variation in contouring is at the base, with some variation also at the apex and posterior prostate. There was reasonable agreement in defining the mid-gland CTV. Similar variability was observed with the intermediate case which did not require the seminal vesicles to be contoured. Although rectal contouring was more consistent due to better definition on CT, there was considerable variation in the extent of rectum to be contoured. For the high risk case, definition of the inferior extent of the rectum varied by 24 mm and the superior extent by 39 mm, with a resulting variation in rectal volume from 39.8 cm$^3$ to 67.6 cm$^3$. As a result, rectal contouring for many trial cases was considered inconsistent with protocol definition (see Figure 2) and corrected prior to re-calculating the DVH using the SWAN analysis tools.

**Treatment Plan Review and Post-Treatment Verification**

Figure 1 summarises trial accrual and treatment plan reviews, including issues that prevented plan archive review (no plans were reviewed/archived for participants receiving a HDR boost). All 23 participating centres submitted plans for review. Although plan review and feedback was provided within 1 week of receipt of a plan, submission of the plan relative to RT treatment commencement was variable (median 70 days, range -286 to 1158 days). A total of 1185 minor and 86 major variations were identified across 14,326 reviewed items spanning 754 plans, distributed by item as shown in Figure 2, Figure 3 shows the number of participants accrued
by each centre (reverse-ordered by accrual number), together with the number of plan reviews undertaken per centre and the rate of protocol variations. The variation rate (minor, major or either) does not correlate with the number of participants accrued per centre, and no significant cut-point in accrual number could be identified.

As shown in Figure 4, variation rate decreased as the trial progressed. Increasing compliance with the margin definitions of the PTVs and 95% coverage of the PTVs (both automatically reviewed items) made a significant contribution to this pattern, as did increasing compliance with definition of the femoral head (manually reviewed). When arranged by the time from which each centre accrued their first participant (assuming this reflects the time from which each centre began receiving review feedback), a similar pattern is seen (see Figure 4a) with an initial rapid decrease in variation rates. Figure 4b shows the mean variation rate per review calculated according to the number of previous plans submitted for a centre, the variation rate consistently decreasing with increasing centre experience. (Note that the delay between plan submission and feedback to centre has not been included in this analysis). Trends for three sample centres (low, medium and high accruing) are also shown in Figure 4b. Quantitative data on review of margins are provided in Table e1 of the supporting online material.

It has been suggested that treatment planning factors including plan complexity and patient anatomy may weigh heavily on variation rates (29). As such, other factors were investigated for their impact on compliance as summarised in Table 2. In order to attempt to identify which aspects of the protocol were leading to differences in variation
rate, for dichotomised items in Table 2 showing a significant difference between the
groups, the entire list of review items for individual participants was reviewed in order
to determine which review items most contributed to the observed difference.

**Periodic Contour Audit**

19 of the 23 sites were audited. Sites were audited according to accrual numbers, with
the highest being in the first round. Of the other four centres, two treated only two
participants with EBRT alone and two centres (accruing 13 participants each) did not
provide any treatment plan data until the trial had closed.

A systematic error was detected as part of the audit at seven centres. In round 1, one
centre consistently failed to have the 95% isodose line encompass the PTV in the
superior-inferior direction. Round 2 identified one centre that consistently failed to
apply a PTV margin superiorly or inferiorly. Round 3 identified 3 centres that had
difficulty determining the superior and inferior extents of the CTV. Round 4 identified
2 centres with systematic errors: one centre consistently treated to 74 Gy in one phase
with margins smaller than that stated in the protocol (i.e. < 10mm) and the other
consistently failed to delineate a CTV at all. Five out of the seven centres changed their
practice as a direct result of the feedback provided from the audit.

**DISCUSSION**

**Benchmarking Exercise**

The aim of the benchmarking exercise was to identify ambiguities in the protocol and
test the plan review process prior to recruitment of a large number of participants. Based
on earlier publications (30, 31), some variation in contouring the prostate was expected. The amount by which the contouring practices for the target volume and PTV varied was more than expected (41.2 cc – 158.8 cc for the gross tumour volume (GTV) or CTV and 144.4 cc – 435.5 cc for the PTV). In cases where it was clear that the planning-target margin had not been applied according to the protocol, feedback was provided to the centre. For the remaining data sets, the review team were faced with considerable difficulty in reaching a consensus on classifying acceptability of the GTV/CTV. The variation in prostate contouring revealed by the benchmarking exercise highlighted the need for a periodic contour audit to minimise the risk of extreme contouring practices.

As the definition of the inferior rectum was linked to the definition of the prostatic apex, a large variability of the inferior extent of the rectum was expected. The variability in defining the superior extent was not expected, though in some cases this was because the centre had defined the superior rectum to be 15 mm above the prostate, rather than using the anatomical definition.

Overall the benchmarking exercise for this trial served to alert the RTRT that variations in contouring were likely and that centres would need to be reminded to correctly apply PTV margins and follow the protocol definition for rectal length. Generally, treatment planning complied with the protocol.

**Treatment Plan Review and Post-Treatment Verification**

Review of treatment plans prior to treatment was not possible for this trial as submission was on compact disk requiring postal delivery. Major variations were
identified in 86 cases and delays in plan submission meant losing the opportunity for plan modification. However, it was still possible to influence a change in practice for future participants and the incidence of major and minor variations over time did decrease, as shown in Figure 4. When the variation rate is viewed according to time from first accrual for each centre, a rapid initial decrease is seen, suggesting an initial impact of feedback to submitting centres. In Figure 4b, a decrease in protocol variation rate is seen with increasing experience of submitting centres. With multiple centres submitting smaller numbers of plans (see Figure 3), it is difficult in such visualisation to separate the impact of the resources and experience of a contributing centre from the influence of review feedback.

The SWAN system enabled multiple treatment and dosimetric parameters to be quickly assessed and passed, without transposition errors, to the trial database. The automated functionality of the system enabled multiple variables to be objectively assessed for 93% of participants treated using EBRT alone in this trial, providing reliable information on the quality of plan data submitted and a quantitative measure of protocol conformity.

The patient anatomical factors shown to impact on protocol compliance (Table 2) reflect the difficulty to meet protocol requirements with increasing prostate and rectal volumes. The investigated treatment planning factors suggest that the use of lower beam energies, MLCs for field definition and prone patient orientation will lead to a plan of poorer quality. This is only according to the definitions within the RADAR protocol however. These factors will be prime candidates for assessment against toxicity and progression.
rates. The factors listed in Table 2 were not the subject of the trial and were accordingly not randomised.

The significant results displayed in Table 2 should be considered in light of potential underlying correlations with other treatment factors. For the dichotomised factors showing significant difference in mean variation rates between groups for example, it was determined that the impact of the factors ‘beam energy’ and ‘rectal filling protocol’ was due to difficulty in meeting dosimetric constraints. For the factors ‘field definition’ and ‘patient setup orientation’ however, some main influencing review items (e.g., applied margin and immobilisation technique) would not likely be influenced by those factors and more than likely the association is simply via the contributing centre.

With 754 treatment plans stored in the SWAN database, comparing dosimetric parameters with patient outcomes will provide definitive correlation. For example, the planned rectal contours varied greatly. Using the SWAN software, rectal contours have subsequently been amended. These modified volumes will be used for correlation of a range of rectal toxicity endpoints with the dose volume relationship using analysis methods similar to those reported in the MRC RT-01 trial (32, 33).

**Periodic Contour Audit**

Auditing CTV contouring practices presented a challenge for the audit team as no clear guidelines existed for the definition of major and minor protocol variations. Even among reviewers consensus of opinion was difficult to achieve. Feedback to trial centres was therefore limited to identifying outliers such as CTVs that clearly extended inferiorly into the urogenital diaphragm, which did not include the proximal seminal
vesicles in high risk cases, or had failed to have the correct margins applied when creating the PTV. Since the RADAR trial opened, there has been much discussion on variations in contouring practices and strategies for limiting contouring variations [eg., (34)]. With the use of magnetic resonance imaging (MRI) to guide delineation of the prostate along with credentialing of the audit team, it is expected that a tighter control on contouring variations can be achieved in future trials. Ensuring all participating centres complete a benchmarking or credentialing exercise prior to accrual is also useful.

Impact of QA Program

The results of the RADAR trial are still maturing and the clinical impact of protocol non-conformity is yet to be tested. We have found that rigorous pre-trial credentialing provides an opportunity to identify and correct for systematic planning deficiencies before they have the opportunity to impact on trial outcomes. To this we add that it also provides an ideal opportunity for the development of consensus guidelines for plan review and for centres to become familiar with the plan submission process. Furthermore, electronic systems such as SWAN that allow for collection, semi-automated review and analysis of treatment plan data will facilitate rapid feedback and hence may increase protocol conformity. Reviewing departmental practice under the auspices of clinical trial QA also provides an effective and non-confrontational means of introducing new technologies and techniques safely and effectively into treatment centres. It has recently been suggested that new technologies are most appropriately introduced in the context of a multicentre trial with associated rigorous trials QA (35). This was certainly the experience for the RADAR trial in Australasia.
The set-up accuracy study previously reported (17) resulted in more than 65% of centres changing their patient positioning and/or immobilisation protocols. This further demonstrates the benefit of QA studies conducted within clinical trials. In most cases position verification was based on matching the bony anatomy in the post-treatment image with the DRR. Whilst this method is rapidly becoming obsolete in the prostate cancer patient as real-time image guidance becomes practical and feasible, QA protocols remain useful in identifying centres where the quality of radiotherapy has the potential to impact on clinical outcomes.

RADAR was a high-recruitment multicentre trial that placed stringent requirements on the use of CT guided conformal therapy. The associated QA program successfully reduced and rectified inconsistencies in rectum identification though revealed an unresolved variability in prostate definition. We speculate that with the inherent deficiencies in CT identification of prostatic boundaries, the QA program is likely to have had a greater impact on reducing morbidity than increasing efficacy. The morbidity results of the RADAR trial are maturing and eagerly anticipated to confirm or refute this hypothesis. Preliminary analysis from RADAR indicates no increase in rectal and urinary morbidity with increasing prescription dose (from outcomes analyses currently underway by author JD), which supports the hypothesis that increasing QA requirements can minimise the impact of treatment variations.

ACKNOWLEDGEMENTS

We acknowledge funding from Cancer Australia and the Diagnostics and Technology Branch of the Australian Government Department of Health and Ageing (grant 501106 supporting SWAN development), the National Health and Medical Research Council
(grants 300705, 455521, 1006447), the Hunter Medical Research Institute, the Health Research Council (New Zealand), the University of Newcastle and the Calvary Mater Newcastle, Abbott Laboratories, Novartis Pharmaceuticals. We gratefully acknowledge the support of the Sir Charles Gairdner Hospital, the ‘Elvis’ study team, the contour audit team, participating RADAR centres, the Trans-Tasman Radiation Oncology Group, Jean Ball, Chantelle Wilcox, Cate Sproston, Sean Hall, Celia Gordon, Dr Sarat Chander, A/Prof Scott Williams, Dr Mahesh Kumar, Prof Sean Bydder, Rhonda Coleman.
References


TABLE CAPTIONS

Table 1: Treatment plan review parameters and variation criteria

Table 2: Factors investigated for their impact on review variations. For dichotomised factors, variations for individual participants were further investigated to determine which review items most contributed to (affected) the difference in variation rate.
FIGURE CAPTIONS

Figure 1: Summary of participant accrual according to treatment groups, treatment plan reviews and issues preventing final review and archive of treatment plans

Figure 2: Distribution of protocol item variations

Figure 3: Accrual, reviews and variation rates (major and minor) ordered by centre accrual.

Figure 4: Variation in variation rate for reviewed items with a) time throughout trial (time from start of trial and time from each centre’s first accrual, cut into 9 equal time intervals), and b) number of previous plans reviewed per centre (with sample results for 3 individual centres). Scores have been categorised simply into protocol compliance and non-compliance (minor or major variation). Only centres contributing > 15 treatment plans have been included.
<table>
<thead>
<tr>
<th><strong>Review Item</strong></th>
<th><strong>Criteria</strong></th>
<th><strong>Minor Variation</strong></th>
<th><strong>Major Variation</strong></th>
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<tr>
<td>Automated review</td>
<td>Planned prescription dose (estimated from total dose to centre of PTV)</td>
<td>To be consistent with dose nominated at randomisation</td>
<td>Within ± 5%</td>
</tr>
<tr>
<td>Dose per fraction</td>
<td>2 Gy per week-day fraction</td>
<td>Dose per fraction between 1.9 Gy – 1.96 Gy, or between 2.04 Gy – 2.1 Gy</td>
<td>Dose per fraction &lt; 1.9 Gy or &gt; 2.1 Gy</td>
</tr>
<tr>
<td>Margins applied to each Planning Target Volume (PTV)</td>
<td>PTV1 = CTV + 1-1.5 cm, posterior margin 0.5-1.0 cm</td>
<td>PTV differs from allowable margin range by 5% - 10% by volume</td>
<td>PTV differs from allowable margin range by &gt; 10% by volume</td>
</tr>
<tr>
<td>95% coverage of each PTV</td>
<td>95% isodose should encompass PTV</td>
<td>95% - 98% coverage</td>
<td>&lt; 95% coverage</td>
</tr>
<tr>
<td>CT slice thickness</td>
<td>≤ 5 mm</td>
<td>N/A</td>
<td>Slice thickness &gt; 5 mm</td>
</tr>
<tr>
<td>Number of treatment fields</td>
<td>≥ 3</td>
<td>N/A</td>
<td>All treatment phases used less than 3 fields</td>
</tr>
<tr>
<td>Beam energy</td>
<td>≥ 6 MV</td>
<td>N/A</td>
<td>One or more beams &lt; 6 MV</td>
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<td>--------</td>
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<tr>
<td>Conformity Index (CI) (28) for each PTV</td>
<td>CI ≤ 1.5</td>
<td>CI &gt; 1.58% (allowing 5% calculation uncertainty)</td>
<td></td>
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<tr>
<td>Rectal dose constraints</td>
<td>65 Gy to maximum 40%</td>
<td>N/A</td>
<td>DVH outside constraints</td>
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<tr>
<td></td>
<td>70 Gy to maximum 30%</td>
<td></td>
<td>(allowing 2% calculation uncertainty)</td>
</tr>
<tr>
<td></td>
<td>75 Gy to maximum 5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral head dose constraints</td>
<td>35 Gy to maximum 100%</td>
<td>N/A</td>
<td>DVH outside constraints</td>
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<tr>
<td></td>
<td>45 Gy to maximum 60%</td>
<td></td>
<td>(allowing 2% calculation uncertainty)</td>
</tr>
<tr>
<td></td>
<td>60 Gy to maximum 30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum dose to PTV</td>
<td>Complies with ICRU definition (28)</td>
<td>N/A</td>
<td>Maximum dose &gt; 107% or &lt; 95% prescription dose</td>
</tr>
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<td>Expert review Rectal wall contouring</td>
<td>Sigmoid flexure to 15mm inferior to prostate apex</td>
<td>Minor deviations according to subjective assessment reviewer</td>
<td>Blatantly misjudged rectal contour according to subjective assessment reviewer</td>
</tr>
<tr>
<td>Left femoral head contouring</td>
<td>Acetabulum to inferior border of field.</td>
<td>Minor deviations according to subjective assessment reviewer</td>
<td>Blatantly misjudged femoral head contour according to subjective assessment reviewer</td>
</tr>
<tr>
<td>Digitally Reconstructed Radiographs (DRR) created</td>
<td>DRRs for patient set-up verification</td>
<td>DRRs not created</td>
<td>N/A</td>
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<tr>
<td>Prescription point</td>
<td>Complies with ICRU definition</td>
<td>N/A</td>
<td>Prescription point does not comply with ICRU definition (28)</td>
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<tr>
<td>Immobilisation device appropriate</td>
<td>Should be consistent with that used in SUA study</td>
<td>Immobilisation devices differ</td>
<td>N/A</td>
</tr>
<tr>
<td>Percentage isodose encompassing rectum</td>
<td>≤ 50%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
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Table 2: Factors investigated for their impact on review variations. For dichotomised factors, variations for individual participants were further investigated to determine which review items most contributed to (affected) the difference in variation rate (N = sample/group size).

<table>
<thead>
<tr>
<th>Investigated Factor</th>
<th>Impact on Variation Rate</th>
<th>Most Affected Review Items (dichotomised factors only)</th>
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<tbody>
<tr>
<td>Rectal distension (Ant-Post width at centre of PTV)</td>
<td>No significant impact†</td>
<td>N/A</td>
</tr>
<tr>
<td>PTV-Rectum separation</td>
<td>No significant impact†</td>
<td>N/A</td>
</tr>
<tr>
<td>PTV Volume</td>
<td>Variation rate increased with increasing volume (coefficient $0.016 % / \text{cm}^3$, $p = 0.0002$)†‡</td>
<td>N/A</td>
</tr>
<tr>
<td>Rectum volume</td>
<td>Variation rate increased with increasing volume (coefficient $0.024 % / \text{cm}^3$, $p = 0.0006$)†‡</td>
<td>N/A</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>No significant impact†</td>
<td>N/A</td>
</tr>
<tr>
<td>Bladder filling protocol</td>
<td>No significant impact§</td>
<td>N/A</td>
</tr>
<tr>
<td>Rectal filling protocol</td>
<td>Higher variation rate when laxatives are given prior to CT ($N = 33$, mean 18.0 %)</td>
<td>• Femoral head dose constraints</td>
</tr>
<tr>
<td></td>
<td>than when a bulking agent is used ($N = 700$, mean = 7.5 %)</td>
<td>• CI PTV1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CI PTV2</td>
</tr>
<tr>
<td>Variable</td>
<td>Impact</td>
<td>Notes</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>---------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Prescription dose (by dose group)</td>
<td>No significant impact(^8)</td>
<td>N/A</td>
</tr>
<tr>
<td>Number of beams</td>
<td>No significant impact(^†)</td>
<td>N/A</td>
</tr>
<tr>
<td>Beam energy</td>
<td>Higher variation rate for beams ≤ 10 MV (N = 252, mean 10.4 % ) than for beams &gt; 10 MV (N = 497, mean 7.0 % ) (p &lt; 10(^{-11})) (^§)</td>
<td></td>
</tr>
<tr>
<td>Field definition</td>
<td>Higher variation rate for beams defined by multileaf collimators (MLCs) (N = 481, mean 9.3 % ) than by collimators/custom blocks (N = 260, mean 5.8 % ) (p &lt; 10(^{-11})) (^§)</td>
<td></td>
</tr>
<tr>
<td>Patient setup orientation</td>
<td>Higher variation rate for prone orientation (N = 64, mean 11.6 % ) than supine orientation (N = 684, mean 7.8 % ) (p &lt; 10(^{-5})) (^§),(^††)</td>
<td></td>
</tr>
</tbody>
</table>

\(^†\) Assessed via linear regression
‡ Note that rectum volume and PTV volume are correlated with BMI ($p = 0.004$ and $p = 0.002$ respectively), though PTV volume and rectal volume are poorly correlated ($p = 0.07$)

§ Assessed via 2-sided t-test for difference in means between groups

†† Note that only three centres contributed patients where laxatives had been used prior to planning CT

‡‡ Note that only three centres contributed plans for patients to be treated with a prone orientation
Figure 1: Summary of participant accrual according to treatment groups, treatment plan reviews and issues preventing final review and archive of treatment plans

1 These plans were for patients receiving 66 Gy conventional treatment for whom electronic data submission/review was optional.  
2The version of Bronte current at that time required absolute dose information. These plans could have contouring and beam information assessed but not dose-related items.

Figure 1: Summary of participant accrual according to treatment groups, treatment plan reviews and issues preventing final review and archive of treatment plans
189x274mm (200 x 200 DPI)
Figure 2: Distribution of protocol item variations

189x274mm (200 x 200 DPI)
Figure 3: Accrual, reviews and variation rates (major and minor) ordered by centre accrual.

189x274mm (144 x 144 DPI)
Figure 4: Variation in variation rate for reviewed items with a) time throughout trial (time from start of trial and time from each centre’s first accrual, cut into 9 equal time intervals), and b) number of previous plans reviewed per centre (with sample results for 3 individual centres). Scores have been categorised simply into protocol compliance and non-compliance (minor or major variation). Only centres contributing > 15 treatment plans have been included.