Association between measures of treatment quality and disease progression in prostate cancer radiotherapy: an exploratory analysis from the TROG 03.04 RADAR trial

Running Title: Impact of quality for prostate cancer

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Abstract

Introduction Quality assurance methods are incorporated into multicentre radiotherapy clinical trials for ensuring consistent application of trial protocol and quantifying treatment uncertainties. The study's purpose was to determine whether post-treatment disease progression is associated with measures of the quality of radiotherapy treatment.

Methods The TROG 03.04 RADAR trial tested the impact of androgen deprivation on prostate cancer patients receiving dose-escalated external beam radiation therapy. The trial incorporated a plan-review process and Level III dosimetric intercomparison at each centre, from which variables suggestive of treatment quality were collected. Kaplan-Meier statistics and Fine and Gray competing risk modelling were employed to test for associations between quality-related variables and the participant outcome local composite progression.

Results Increased 'dose-difference' at the prostatic apex and at the anterior rectal wall, between planned and measured dose, were associated with reduced progression. Participants whose treatment plans included clinical target volume (CTV) to planning target volume (PTV) margins exceeding protocol requirements also experienced reduced progression. Other quality-related variables, including total accrual from participating centres, measures of target coverage and other variations from protocol, were not significantly associated with progression.

Conclusions This analysis has revealed the association of several treatment quality factors with disease progression. Increased dose and dose margin coverage in the prostate region can reduce disease progression. Extensive and rigorous monitoring has helped to maximise treatment quality, reducing the incidence of quality-indicator outliers, and thus reduce the chance of observing significant associations with progression rates.

Keywords Disease progression; prostate cancer; quality assurance; radiotherapy;

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INTRODUCTION

Technical quality assurance (QA) schemes can be adopted for multicentre radiotherapy clinical trials, enhancing the validity, reliability and consistency of treatment and reporting. Determining the impact of QA-associated parameters on participant outcomes may provide validation of the central role of QA schemes in these trials.

In the past decade, a collection of multicentre radiotherapy-based clinical trials have revealed the impact of QA on participant outcomes, particularly treatment efficacy^(1, 2, 3, 4, 5, 6). Reduced adherence to QA requirements, usually in the form of increased deviation from specified treatment protocols, has frequently^(1, 2, 4, 5, 6) though not always⁽³⁾, been shown to correlate with reduced post-treatment survival. Similar results have been found regarding the relationship between protocol variations and participant toxicity^(1, 7, 8, 9).

Peters et al⁽²⁾ demonstrated the critical importance of radiotherapy quality on the outcomes of chemoradiotherapy in head and neck cancer. Participants with major deficiencies in the quality of their treatment plans experienced significantly less post-treatment freedom from locoregional failure. In that study, and those of others, deviation rates and treatment failure rates have been shown to increase at centres which accrued a smaller number of trial participants⁽⁵⁾. This observation has been echoed in a recent analysis of clinical prostate cancer radiotherapy data from North America⁽¹⁰⁾ where a reduced caseload of high-risk patients was shown to be associated with a reduction in overall survival.

The Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomised Androgen Deprivation and Radiotherapy (RADAR) trial^(11, 12) was primarily aimed at evaluation of variable-duration androgen deprivation (AD) for localised prostate carcinoma, in the context of three-dimensional conformal radiation therapy (3DCRT). The trial incorporated a comprehensive QA scheme which included credentialing of centres intending to accrue participants, assessment of dose delivery in a phantom at each participating centre and the review of individual participant treatment planning data⁽¹³⁾.

A number of variables quantifying QA outcomes were derived. Patient time-to-event data produced the indicator of patient treatment outcome - local composite progression (LC). LC is a combination of local/clinical and biochemical⁽¹⁵⁾ treatment failure. This investigation aimed to determine the relationships between the QA variables and treatment efficacy (LC) in the RADAR dataset.

METHODS AND MATERIALS

RADAR Trial

The RADAR trial (TROG 03. 04, ClinicalTrials.gov identifier NCT00193856), accruing between 2003 and 2008, tested the hypothesis that 12 months of adjuvant androgen deprivation therapy (ADT) starting immediately after standard therapy (i.e. 6 months of ADT before and during radiotherapy) will improve patient treatment efficacy when compared with standard radiotherapy alone^(11, 12). Participants were divided into four treatment arms: those receiving short-term (6 months) androgen suppression only (STAS), STAS and 18 months of zoledronate (STAS + Z), intermediate-term (18 months) androgen suppression only (ITAS), and ITAS and zoledronate (ITAS + Z).

Participants underwent external beam radiation therapy (EBRT), with prescription doses of 66, 70 or 74 Gy administered at 2.0 Gy per fraction. Clinicians could alternatively elect to treat participants with 46 Gy EBRT in combination with a high dose-rate brachytherapy boost. Twenty-three centres accrued participants across Australia and

New Zealand. RADAR was the first TROG trial to incorporate full electronic review of the treatment planning data of accrued participants⁽¹⁴⁾.

Patient Outcomes

One participant outcome (endpoint) was derived from trial data as part of this analysis: local composite (LC) progression. LC was defined as the post-treatment occurrence of either local/clinical failure or PSA progression (defined per the Phoenix definition⁽¹⁵⁾), with a PSA concentration doubling time between 6 and 100 months. Local/clinical failure was confirmed by a combination of CT imaging and digital rectal examination following biochemical failure. This endpoint has been previously investigated and found to correlate well with prescribed dose in competing risks modelling⁽¹¹⁾. For the Kaplan-Meier analysis, which cannot account for competing events, if the participant died or reached the end of follow-up before a relevant event occurred, they were censored. For Fine and Gray analysis⁽¹⁶⁾, however, the following were regarded as competing events: distant progression alone >2 months before local failure (LF); PSA doubling time <6 months or >100 months after PSA progression; and secondary therapeutic intervention (salvage)⁽¹¹⁾.

Variables

All variables were defined in categorical form (except patient age at randomisation, which was kept as a continuous variable), with the dose-difference variables and plan review variables converted to a binary variable about a predetermined threshold value (the median variable value).

Control Variables

Several control variables were considered, namely participant age at randomisation (P_{Age}), participant Gleason score at diagnosis (P_{GS} : ≤ 7 vs > 7), dose group (P_{Dose} : 66, 70 or 74 Gy), cancer stage group (P_{Stage} : T2 vs T3/T4), treatment arm (P_{Arm} : STAS, STAS + Z, ITAS, ITAS + Z), and baseline PSA concentration (P_{PSA} : < 10 ng/mL vs ≥ 10 ng/mL).

Centre Accrual

‘Centre accrual’ (C_{Accrual}) is a value assigned to each participant representing the total number of trial participants recruited from that participant’s centre.

Dose-Difference Variables

In order to assess dose delivery accuracy to clinically-relevant points around the prostate and rectum, level III dosimetry was undertaken in a pelvic phantom during a single visit to each of the participating centres⁽¹⁷⁾. The percentage dose-difference between delivered (measured) and planned dose was determined at five anatomical points of interest, defining five variables for analysis, namely the difference between measured and planned dose at:

- ‘Prostate centre-of-volume’ (C_{PCOV}) corresponding to measurement with an ionisation chamber at the centre-of-volume (COV) of the phantom’s prostate.
- ‘Prostate base’ (C_{Pbase}) corresponding to a point-dose estimate with thermoluminescent dosimetry (TLD) in the central region of the prostate, though towards the base.
- ‘Base of seminal vesicles’ (C_{SVbase}) corresponding to a point-dose estimate with TLD superior to the prostate and between the seminal vesicles.
- ‘Posterior prostate on rectal wall’ (C_{Rwall}) corresponding to a point-dose estimate with TLD on the rectal wall adjacent to the prostate.
- ‘Prostatic apex’ (C_{Papex}) corresponding to a point-dose estimate with TLD at the location of the apex of the phantom’s prostate.

The values of these ‘dose-difference variables’ were allocated to each participant according to the centre at which they were recruited.

Plan-Review Variables

A treatment plan review process was implemented during RADAR to assess the degree to which the treatment protocol was adhered to for each participant⁽¹³⁾. Each participant received a grade for each quality measurement item, ranging from A to E, indicating the degree of variation from the protocol, with B and C grades representing minor and major variations from protocol respectively, defined during protocol development as:

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

The reviews were undertaken with the SWAN software system⁽¹⁴⁾, which was also used to record treatment demographics, review grades and other outcomes of the review process. The reviews were typically performed after participant treatment with the aim to provide report grades and timely feedback to the contributing centre for the review outcome to be considered in the planning of subsequent participants’ treatments⁽¹³⁾. As only a small number of C grades were found in the dataset (86 of 14326 items) compared with B grades (1185 of 14326 items), these grades were combined.

Five variables were derived from the review process. These were referred to as the ‘plan review variables’:

1. ‘Per-centre percentage B or C protocol variations’ (C_{BorC}) – An assessment of the overall adherence to QA protocol of a contributing centre. The average number of B or C grades, as a percentage of the number of graded/reviewed items, received by participants at each centre is calculated. This variable then assigns this average to each participant at the given centre.
2. ‘Per-patient percentage B or C protocol variations’ (P_{BorC}) – An assessment of the overall adherence to protocol of *an individual patient’s treatment plan*. The number of B or C grades, as a percentage of the number of reviewed items, for each individual patient.

The remaining three plan review variables were based specifically on dosimetric coverage of the target volume, as defined in Kearvell 2013⁽¹³⁾:

3. ‘Percentage margin excess’ (P_{Margin}) - which represents the percentage of excess margin, in terms of volume, outside the 0.5-1cm required range, required for expansion of the clinical target volume (CTV) to generate the planning target volume for phase 1 of the treatment (PTV1).

4. 'Conformity index 1' (P_{Conf1}) - which represents the volume of intersection of PTV1 and the 95% isodose surface (normalised to prescription dose), divided by the volume of union of these two structures.
5. 'Coverage' (P_{Coverage}) - differing slightly from conformity index 1, representing the volume of intersection of PTV1 and the 95% isodose surface, divided by the volume of PTV1.

Kaplan-Meier Analysis

Kaplan-Meier (KM) statistics⁽¹⁸⁾ were used to test correlation between the derived QA variables and the participant outcome LC. For each variable, the data set was divided about a threshold value (the median variable value) into two arms and the difference between the groups assessed via a log-rank test⁽¹⁹⁾. The analysis was performed with MATLAB 2014 (Mathworks, Natick MA), initially on the full set of EBRT participants, and then on participants partitioned according to dose group (66 Gy, 70 Gy and 74 Gy) and disease risk category group ($P_{\text{GS}} > 7$ and $P_{\text{GS}} \leq 7$).

Fine and Gray Competing Risks Modelling

Fine and Gray competing risks modelling (FGCR) modelling⁽¹⁶⁾, performed on SAS 9.4 (SAS Institute, Cary NC), enabled testing of the impact of each variable on LC while including control variables, and exploring potential confounder relationships⁽²⁰⁾. Robust standard error estimation was performed to account for potential clustering (correlation) of event times within recruitment sites, specifying treatment centre as a cluster-level variable.

After establishing significant control variables, multivariate modelling was employed to determine whether subject variables (non-control variables) impacted LC individually, while accounting for these controls. This was followed by further multivariate modelling, combining subject variables (that individually influenced LC) together in the model to test for confounder relationships between them.

RESULTS

RADAR Trial, Variables and Patient Outcomes

1071 participants were recruited in the RADAR trial. Following exclusions due to death, loss to follow-up or loss of data, and considering only participants receiving EBRT alone (i.e. without brachytherapy), a maximum of 802 participants were available for KM analysis for accrual and the dose-difference variables, and a maximum of 734 for the plan-review variables. A total of 164 LC events occurred in the participant cohort.

Kaplan-Meier Analysis

Major results from the KM analysis are shown in Figures 2 to 4. 66 KM plots were produced across 11 variables and 6 datasets. Due to the multiple comparisons made and likely variable covariance, p-values between 0.01 and 0.03 were considered borderline significant, and p-values below and above this range were considered significant and non-significant respectively. All data sets were a subset of the EBRT participant set, as shown in Figure 1. Most significant results were revealed within the 70 Gy dose group, while no significant associations resulted from the other two dose groups. The low-risk disease group ($P_{GS} \leq 7$) revealed a borderline significant impact of participant protocol variations on LC.

Figure 1 was displayed here.

Centre Accrual

C_{Accrual} showed borderline significance for LC in the 70 Gy data set (Figure 2).

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Dose-Difference Variables

C_{PCOV} , C_{Rwall} and C_{Pbase} were the dose-difference variables found to be associated with LC. C_{PCOV} showed borderline significance for LC in the EBRT and $P_{\text{GS}} > 7$ data sets (Figure 3). C_{Rwall} and C_{Pbase} both showed a borderline significance for LC in the 70 Gy data set (Figure 3).

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Plan Review Variables

The only plan review variable which showed any evidence of association with LC was P_{BorC} , which showed borderline significance for LC in the $P_{\text{GS}} \leq 7$ patient data sets (Figure 4).

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Fine and Gray Competing Risks Modelling

Establishing Control Variables

The following control variables retained their significant impact upon LC when combined in the model together: P_{Age} , P_{Stage} , P_{Arm} , P_{PSA} . These were therefore used as controls for all subsequent Fine and Gray models.

Multivariate Modelling

C_{Rwall} showed a significant impact on LC, while P_{Margin} showed a borderline significant impact on LC. Results are summarised in Table 1.

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Multivariate Modelling for Confounders

Modelling LC in terms of the controls (P_{Age} , P_{Stage} , P_{Arm} , P_{PSA}) and the two significant subject variables (C_{Rwall} and P_{Margin}) revealed no confounder relationships between these variables. Therefore C_{Rwall} and P_{Margin} retain individual impact upon LC.

DISCUSSION

Multicentre clinical trial QA schemes require a commitment of financial and human resources. Whilst the intention of such a scheme is to ensure consistency in protocol execution and subsequent reporting, the quantification of QA factors enables an assessment of the clinical impact of the QA activities, and this has been demonstrated here. The primary endpoint LC has been previously defined, reviewed and found to be predicted by prescription dose⁽¹¹⁾, making it appropriate for exploration of dosimetry effects.

Several treatment-quality associated variables were shown to be related to a post-treatment outcome. LC was associated, with borderline significance, to participant protocol variations in the KM analysis. This result was demonstrated in the low disease-risk group ($P_{\text{GS}} \leq 7$), containing 559 of the 802 participants, suggesting that it is revealed through a combination of reduced disease-risk and a reduction in statistical noise. These results were consistent with, while not as strong as, the findings of Peters et al⁽²⁾, who showed that participants with deficiencies in their treatment plans experienced significantly more post treatment locoregional failure. This suggests that

increased compliance with protocol, and therefore enhanced quality of treatment, is associated with an improvement in local composite progression. It must be noted, however, that no other dataset, including the overall set of participants, revealed a significant result for this variable, consistent with the Fine and Gray analysis.

The phantom-based dosimetry study yielded several variables relating planned to delivered dose in a patient-representative geometry. Increased dose-difference between measured and planned dose at the prostate COV (C_{PCOV}) at a contributing centre was associated with more progression in participants accrued at that centre. This suggests that measured dose exceeding planned dose was correlated with increased progression. This result is counter-intuitive as increased delivered dose has been shown to reduce progression in prostate cancer patients, as demonstrated by Pollack et al⁽²¹⁾ and others^(22, 23). Consistent with these studies, however, were results at two other points in the prostate region. Increased dose-difference in the central region of the prostate towards the base (C_{Pbase}) and on the rectal wall (C_{Rwall}) at a centre were associated with reduced progression in participants accrued at that centre – an intuitive result, consistent with established expectations. This was confirmed in the Fine and Gray analysis in that participants with increased dose-difference at the rectal wall showing a higher risk of local composite progression.

It should be noted that the Level III dosimetric intercomparison study was performed at each participating centre only once throughout the period of the trial, involving treatment planning and delivery with an anthropomorphic pelvis phantom^(13, 24). To discover a significant impact of that single measurement, with its own uncertainty, on overall trial participant outcomes is surprising. The standard error in C_{PCOV} for example was only 0.2% across all centres. It is hypothesised that any measured deviation is indicative of the overall quality of treatment delivery at a centre rather than a systematic over/under-dose of trial participants. Testing of that hypothesis could have been achieved if intercomparisons were performed periodically throughout the trial or in vivo dosimetry was utilised for all participants – unfortunately resources for this were not available.

The Fine and Gray modelling also revealed a significant association between increased percentage margin excess (P_{Margin}) and reduced local composite progression. This indicates that patients with larger margins applied in expansion of the GTV to the PTV, or margins greater than the upper limit of the protocol-defined range, experienced less progression. This result, coupled with the correlation of increased C_{Pbase} and C_{Rwall} with reduced progression, supports a hypothesis that increased dose coverage of the periphery of the prostate region will result in less progression and perhaps greater local tumour control, consistent with previous findings^(21, 22, 23).

Participants treated at centres with higher participant accrual were found to experience less progression, with borderline significance. This effect is revealed only in the 70 Gy group, containing more than half the cohort, suggesting that it is revealed through a combination of dose escalation and a reduction in statistical noise. A previous analysis presented by Ebert et al in 2015⁽⁷⁾ found that toxicity incidence tended to increase in centres with higher accrual. In combination, this suggests that higher-accruing centres tend to focus on minimising progression, possibly with preferential accrual to higher dose levels (controlled for in FGCR modelling) and/or more generous dose coverage. We have no evidence that accrual is correlated with the general prostate cancer caseload in any of the participating institutions. It is interesting, however, to highlight a suggestion from Chen et al⁽¹⁰⁾ that clinicians in institutions with higher caseloads are generally more willing to accept a higher risk of treatment toxicity in pursuit of a reduced likelihood of progression.

Several facets of this investigation should be highlighted. At the RADAR trial's commencement, 3DCRT was in a relative infancy in Australia and New Zealand. The thorough QA program was implemented as a means of ensuring the relatively advanced techniques were introduced and utilised safely and to quantify the inter-patient homogeneity of treatments. Although the undertaken QA activities provided a series of quantitative variables, the same QA activities were designed to minimise inter-patient and inter-centre variation in those variables. This should have minimised the spread of the variables examined here, and the likelihood of outliers, and consequently reduced the chance of identifying significant associations with any subsequent outcome. The QA

activities themselves were not the subject of the trial - QA was not randomised and the study was not powered to detect its impact. The plan review scheme used in the RADAR trial was retrospective, though subsequent feedback to contributing centres has been shown to lead to a rapid improvement in protocol compliance for each centre's subsequent participants⁽¹³⁾.

All participants within the analysis received 3DCRT and therefore it is unknown whether the results will translate to modern treatment techniques such as volumetric modulated arc therapy with more rigorous image guidance - an appropriate avenue of further investigation. As participant data was drawn from multiple centres, it is difficult to account for centre-specific effects such as treatment bias, local pathology effects (e.g. different interpretations of Gleason score), miss-reporting of treatment etc. It was recently shown⁽¹¹⁾ that accounting for centre-specific effects was required to reveal a dose-response in the RADAR cohort, and therefore in future trials this may be an appropriate option.

Statistically, there is a chance that the observed significant effects are confounded by other correlated variables that were not recorded or investigated. No significance testing correction was performed to account for the multiple comparisons performed on the data. Hence the significance level was reduced from $p \leq 0.05$ to $p \leq 0.01$, with borderline significance regarded in the $0.01 < p \leq 0.03$ range.

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Figure 1 Venn diagram showing the allocation of participants within the various datasets.

[†]A small proportion of patients were treated with slightly different doses (71.3, 72, 73, 74.07, 75.6 and 76 Gy) and so were not strictly a part of the three major dose groups.

Figure 2 Kaplan-Meier curves showing LC since the end of radiation therapy in patients from the 70Gy data set for C_{Accrual} , with the log-rank test result. C_{Accrual} is the number of participants accrued to the centre at which the given participant was treated.

Figure 3 Kaplan-Meier curves showing LC since the end of radiation therapy for the (a) EBRT data set, and (b) $P_{\text{GS}} > 7$ data set for C_{PCOV} , and the (c) 70 Gy data set for C_{Rwall} and (d) 70 Gy data set for C_{Pbase} , with log-rank test results. The variables represent the percentage difference between measured and planned dose in the dosimetry phantom at the participant's centre, at various points around the prostate. C_{PCOV} is that at the centre of volume of the prostate, C_{Rwall} at the rectal wall adjacent to the prostate, and C_{Pbase} in the central region of the prostate towards the base.

Figure 4 Kaplan-Meier curves showing LC for the $P_{\text{GS}} \leq 7$ data set since the end of radiation therapy for P_{BorC} , with the log-rank test result. P_{BorC} is an individual assessment of adherence to treatment planning protocol: number of B or C grades as a percentage of reviewed items.

Table 1 Multivariate FGCR modelling results. LC was modelled in terms of control variables P_{Age} , P_{Stage} , P_{Arm} , P_{PSA} , and the subject variables shown below. For each subject variable, the corresponding sub-hazard ratio and p-value is displayed. A sub-hazard ratio significantly greater than (less than) 1 signifies a significantly greater occurrence of LC in the higher (lower) value group of the given variable. Borderline significant results are highlighted in yellow. There were no highly significant results.

subject variables	Variable definitions	p-value	Sub-hazard ratio with 95% confidence interval
$C_{Accrual}$	The number of participants accrued to the centre at which the given participant was treated.	0.81	0.95 (0.61-1.47)
C_{PCOV}	The percentage difference between measured and planned dose in the dosimetry phantom at the participant's centre, at the centre of volume of the prostate.	0.48	1.15 (0.78-1.71)
C_{Pbase}	The same as C_{PCOV} but in the central region of the prostate towards the base.	0.85	1.04 (0.68-1.60)
C_{SVbase}	The same as C_{PCOV} but superior to the prostate and between the seminal vesicles.	0.55	0.88 (0.56-1.36)
C_{Rwall}	The same as C_{PCOV} but on the rectal wall adjacent to the prostate.	0.01	0.68 (0.51-0.92)
C_{Papex}	The same as C_{PCOV} but at the apex of the prostate.	0.11	0.77 (0.56-1.06)
P_{Margin}	The participant's percentage of excess margin outside the 0.5-1cm required range, required for expansion of the CTV to generate PTV1.	0.03	0.63 (0.42-0.96)
P_{Conf1}	The participant's volume of intersection of PTV1 and the 95% isodose of the surface, divided by their volume of union.	0.73	1.08 (0.70-1.67)
$P_{Coverage}$	The participant's volume of intersection of PTV1 and the 95% isodose of the surface, divided by the volume of PTV1.	0.45	0.91 (0.72-1.16)
P_{BorC}	An individual assessment of adherence to treatment planning protocol: number of B or C grades as a percentage of reviewed items.	0.66	0.92 (0.65-1.32)
C_{BorC}	Similar to P_{BorC} , but taking the mean adherence at the given centre and ascribing this to the participant.	0.57	1.13 (0.73-1.75)

Figure 1:

EBRT only (802)				
	66 Gy (98)	70 Gy (410)	74 Gy (224)	Neither dose group [†]
GS ≤ 7 (559)	66 Gy & GS ≤ 7 (68)	70 Gy & GS ≤ 7 (292)	74 Gy & GS ≤ 7 (148)	GS ≤ 7 (51)
GS > 7 (243)	66 Gy & GS > 7 (30)	70 Gy & GS > 7 (118)	74 Gy & GS > 7 (76)	GS > 7 (19)

Figure 2:

Figure 3:

Figure 4:

Table 1 Multivariate FGCR modelling results. LC was modelled in terms of control variables P_{Age} , P_{Stage} , P_{Arm} , P_{PSA} , and the subject variables shown below. For each subject variable, the corresponding sub-hazard ratio and p-value is displayed. A sub-hazard ratio significantly greater than (less than) 1 signifies a significantly greater occurrence of LC in the higher (lower) value group of the given variable. Borderline significant results are highlighted in yellow. There were no highly significant results.

Categorical subject variables	Variable definitions	p-value	Sub-hazard ratio with 95% confidence interval
$C_{Accrual}$	The number of participants accrued to the centre at which the given participant was treated.	0.81	0.95 (0.61-1.47)
C_{PCOV}	The percentage difference between measured and planned dose in the dosimetry phantom at the participant's centre, at the centre of volume of the prostate.	0.48	1.15 (0.78-1.71)
C_{Pbase}	The same as C_{PCOV} but in the central region of the prostate towards the base.	0.85	1.04 (0.68-1.60)
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GS ≤ 7 (559)	66 Gy & GS ≤ 7 (68)	70 Gy & GS ≤ 7 (292)	74 Gy & GS ≤ 7 (148)	GS ≤ 7 (51)
GS > 7 (243)	66 Gy & GS > 7 (30)	70 Gy & GS > 7 (118)	74 Gy & GS > 7 (76)	GS > 7 (19)

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