Gastro-intestinal dose-volume effects in the context of dose-volume constrained prostate radiotherapy: an analysis of data from the RADAR prostate radiotherapy trial

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CONFLICTS OF INTEREST NOTIFICATION

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SUMMARY

This investigation was aimed at identifying dose-volume factors impacting gastrointestinal toxicity following radiotherapy for prostate carcinoma. Analysis was based on a multicentre trial providing 754 complete patient datasets with median 72 months of follow-up. The importance for toxicity of different dose regions to inferior (anal canal) vs superior (anorectum) anatomy is revealed. An atlas of toxicity-dependent dose-volume constraints is produced to guide future clinical practice.

ABSTRACT

Purpose/Objectives: To utilise a high-quality multicentre trial dataset to determine dose-volume effects for GI toxicity following radiotherapy for prostate carcinoma. Influential dose-volume histogram regions were to be determined as functions of dose, anatomical location, toxicity and clinical endpoint.

Methods and Materials: Planning datasets for 754 participants of the TROG 03.04 ‘RADAR’ trial were available with LENT-SOMA toxicity assessment to a median of 72 months. A rank sum method was utilised to define dose-volume ‘cut-points’ as near-continuous functions of dose to three GI anatomical regions, together with a comprehensive assessment of significance. Univariate and multivariate ordinal regression was used to assess the importance of cut-points at each dose.

Results: Dose ranges providing significant cut-points tended to be consistent with those showing significant univariate regression odds-ratios (representing the probability of a unitary increase in toxicity grade per percent relative volume). Ranges of significant cut-points for rectal bleeding validated previously published results. Separation of the lower GI anatomy into complete ‘anorectum’, ‘rectum’ and ‘anal canal’ showed the

impact of low-mid doses to the anal canal on urgency and tenesmus, completeness of evacuation and stool frequency, and mid-high doses to the anorectum on bleeding and stool frequency. Derived multivariate models emphasised the importance of the high dose region of the anorectum and rectum for rectal bleeding and mid to low dose regions for diarrhoea and urgency and tenesmus, and low-to-mid doses to the anal canal for stool frequency, diarrhoea, evacuation, and bleeding.

Conclusions: The results confirm anatomical dependence of specific GI toxicities. They provide an atlas summarising dose-histogram effects and derived constraints as functions of anatomical region, dose, toxicity and endpoint, for informing future radiotherapy planning.

INTRODUCTION

Association of toxicity incidence with dose-histogram (typically dose-volume) parameters has become standard methodology for the presentation of normal tissue toxicity subsequent to radiotherapy clinical trials [1]. By investigating dose-volume ‘cut-points’ that best discriminate responding from non-responding patients, it is possible to develop objective constraints. Constraints can be used to guide the optimisation of future patient treatments using instruments that are widely available via commercial radiotherapy treatment planning systems.

Multiple studies have been undertaken of gastro-intestinal (GI) toxicity associated with radiotherapy for prostate carcinoma, identifying dosimetric parameters that correlate with overall or individual rectal toxicities to guide ongoing radiotherapy practice [2,3]. Some studies have attempted to anatomically localise dose parameters contributing to specific toxicities. Peeters *et al* [4] examined dosimetric parameters derived for three anatomical regions of the lower GI tract, based on general identification of the ‘anorectum’, being “from the ischial tuberosities until the level of the inferior border of the sacroiliac joints, or when the rectum was no longer adjacent to the sacrum.” [4] This allowed generic identification of the ‘anal canal’ as the caudal 3 cm of the anorectum, and the ‘rectum’ as the remaining cranial part of the anorectum. Peeters *et al* [4] were able to distinguish associations of incontinence to parameters derived for the anal canal from other toxicities associated with parameters for the overall anorectum. Similarly, Heemsbergen *et al* [5] associated bleeding with dose to the more superior parts of anorectum relative to those associated with incontinence. More recently, Stenmark *et al*

[6] demonstrated dominant associations of dosimetric parameters to quality of life factors, including incontinence and urgency, for inferior rectal anatomy.

With maturation of outcomes data from the TROG 03.04 RADAR trial [7,8] we were in a position to undertake an analysis of dose volume histogram (DVH) effects derived in the context of dose-volume constrained radiotherapy. DVH parameters were derived as near-continuous functions of dose, using statistically robust techniques with a focus on calculation of appropriate significance levels, corrected for multiple testing.

METHODS AND MATERIALS

RADAR Trial

The RADAR trial (Randomised Androgen Deprivation and Radiotherapy, TROG 03.04, [7]) examined the influence of duration of androgen deprivation with or without bisphosphonates, adjuvant with radiation therapy, for treatment of prostate carcinoma. Aspects of the extensive activities, aimed at quality-assessment of trial data, have been previously presented [9-11].

Accrual was from Australia and New Zealand between 2003 and 2008. All participants received centre-nominated radiation therapy to the prostate as either 46 Gy external beam radiotherapy (EBRT) followed by a 19.5 Gy high dose rate (HDR) brachytherapy boost, or EBRT to either 66 Gy, 70 Gy, 74 Gy or 78 Gy delivered in up to two treatment phases. Rectal dose constraints were applied, derived from results presented by Boersma *et al* [12], being 65 Gy, 70 Gy and 75 Gy to a maximum 40%, 30% and 5% of rectum volume respectively.

Toxicity Assessment

All patients were assessed at randomisation ('baseline') and then routinely followed up in clinic every 3 months for 18 months, then 6 monthly up to 5 years post randomisation and then annually. At these visits, rectal bleeding, urgency and tenesmus, stool frequency, diarrhoea, ano-rectal pain and completeness of evacuation were assessed according to LENT SOMA scales [13]. Clinician-assessed Common Toxicity Criteria (CTC version 2) proctitis score [14] was also assessed. The grading systems for each toxicity are summarised in Appendix eI. Any patient with a baseline grade above the minimum was excluded from analysis for that toxicity. The endpoints considered for each toxicity in the analysis below were prevalence at the timepoint 36 months subsequent to randomisation (approximately 29 months from the end of radiotherapy, at which time toxicity prevalence had passed through a maximum and reached equilibrium [8]), and peak score across all late follow-up times (> 3 months post radiotherapy).

Dosimetric Data

Review of participant plans indicated poor compliance with protocol definition of the rectum [11]. As such, rectum outlines for all plans were manually re-defined according to the above 'anorectum' definition from Peeters *et al* [4]. The database of archived plans for EBRT-only patients was used to combine multi-phase doses, voxel-by-voxel, into equivalent dose in 2 Gy fractions (EQD2) for $\alpha/\beta = 3$ Gy [3,15]) and 5.4 Gy [16] as well as raw physical dose ($\alpha/\beta = \infty$ Gy). Each dose combination was used to generate and export DVH data in 1 Gy bins for the anorectum, rectum and anal canal. DVH data was independently calculated as defined in Kennedy *et al* [17] and converted to

cumulative form. Subsequent analysis was undertaken in Matlab (2013a, Mathworks, Natick MA).

Cut-point Derivation

At each 1 Gy EQD2 interval, optimal cut-points were derived by considering the cumulative DVH value at that dose as a continuous variable across all included participants. The method of standardised maximally selected rank sums [18] was used to assess the efficacy of splitting the population about any value of such a variable, with rank based on specific recorded grade values (without dichotomization). A free step-down method was used to derive p-values corrected for multiple testing, accounting for the correlation between volume distributions at different dose levels [19]. At each of a minimum of 500 samples per test, the standardised test statistic is calculated for all split values at all doses based on a Monte Carlo resampling of patient outcomes, and the values of all these test statistics ordered according to the ordering of the value for the original (unsampled) patient outcomes. Test statistic values for the resampled data are then adjusted according to a step-down process [19], and the corrected p-value at each dose/split determined as the proportion of all iterations for which the adjusted resampled values exceed the value for the original patient outcomes. A more detailed description and investigation of the method is provided in Ebert *et al* [20]. A standard Bonferroni correction was applied to account for tests covering the three anatomical regions against each endpoint.

Regression Analysis

Association of individual DVH doses, for each GI region, with each toxicity at each endpoint, was explored with regression analysis. Ordinal logistic regression was used at each dose interval to determine an odds-ratio (OR) of an increase in toxicity probability per % volume. p-values were derived by bootstrapping and adjusted for multiple testing using a Holm-Bonferroni step-down method [19]. Multinomial ordinal regression was undertaken using the glmnet resource [21] with variables representing the relative volume values across all patients at each 1 Gy EQD2 interval. Variables were selected from the interval 10 Gy – 70 Gy due to the narrow range in volumes at doses outside that range. Due to the highly correlated nature of volume values at different doses, elastic net regularization [22] was used to reduce the number of variables to those of most influence. 10-fold cross validation was used to reduce the likelihood of over-fitting, with the final model selected as the one with a cross-validated error within one standard error of the minimum.

RESULTS

Participant and Treatment Demographics

1071 patients were recruited from 23 centres. After excluding patients receiving a HDR boost and for whom complete treatment planning data was not archived [11], 754 patient datasets were available for analysis. Summaries of patient, treatment planning and treatment demographics (including DVH distributions) are provided in Appendix eII.

Toxicity Outcomes

Follow-up data used for analysis was as exported at November 13, 2012, with a median follow-up of 72 months and a range of 58 to 108 months. Figure 1 provides a summary of event rates for considered endpoints according to each toxicity.

Cut-point Derivation and Regression

For consistency with previous publications, we present the results for cut-point derivation for peak rectal bleeding, which are summarised in Figure 2, compared with the univariate regression results. Results for stool frequency are shown in Figure 3, and for urgency and tenesmus in Figure 4. Note that in these plots, significance is indicated when $p \leq 0.05$ (following multiple testing correction). Results in each of these figures are for $\alpha/\beta = 3.0$ Gy.

The complete set of cut-point and univariate regression results are presented as figures in Appendix eIII. In addition, all cut-point, OR (for both univariate and multivariate models) and significance values are tabulated in Appendix eIV as an Excel file with results on separate worksheets, with names comprised according to toxicity, region ('AnoRect', 'AnalCanal' or 'Rect'), EQD2 conversion (ie., value of α/β - 3.0, 5.4 - or 'raw' physical dose) and endpoint ('Peak' or '36MTHS'). A summary of observations is provided in Table 1. Note that for ordinal regressions above 65 Gy, we have observed some protective effects of increasing volume resulting in rapidly varying and/or erratic OR distributions. This potentially results, at least in part, from treatment bias with patients accrued to higher prescription doses receiving more conformal treatments [8].

Doses (EQD2 for $\alpha/\beta = 3.0$ Gy) included in optimal multivariate regression models of peak late toxicity are displayed for each anatomical region in Figure 5, according to the associated derived cut-point for each toxicity for which an optimal model was found. For prevalence at the 36 month timepoint, optimal multivariate models were only found for the anal canal and for bleeding. Graphical display of multivariate analysis results across all toxicities, values of α/β , regions and timepoints are provided in Appendix eV. The few doses above 65 Gy that were included in final multivariate models with an OR below 1.0 are not shown in Figure 5 or the graphs of Appendix eV.

DISCUSSION

This investigation has focused on a large dataset for a multicentre clinical trial undertaken under strict quality control and monitoring. Routine assessment has been undertaken on participants using well established instruments [23] over an extensive follow-up period. This allows, where toxicity definitions are consistent, validation of previous observations of dose-volume response for the rectum following radiotherapy for prostate carcinoma.

Although derivation of rectal histogram constraints has been undertaken extensively previously, there has been criticism that inappropriate statistical methods have been used [24]. Criticism relates to the use of parametric test statistics which do not reflect the distributions inherent in the histogram data, and either the absence of significance testing or presentation of significance levels without necessary multiple testing corrections. We have addressed this by utilising non-parametric methods to ascertain volumetric cut-points in combination with robust methods of significance testing and penalization of overly complex models.

The derived cut-points provide clinical guidance regarding regions of dose-histograms to prioritise (or ‘weight’, as described in [25]) when planning future patients. The value in the results also lies in the possibility to localise dose-toxicity effects by anatomical region, providing hypotheses for the underlying pathology. The results provide the opportunity to target alleviation of GI toxicity by focusing on impacting dose regions or applying symptom-specific preventative adjuvant therapies [26]. The multivariate analysis has reduced the derived cut-points to a set of prescriptive thresholds for relative volume, interpretable as DVH constraints that can be applied with consideration of specific anatomical region and toxicity. These constraints, for peak toxicity, are explicitly and clearly summarised in Figure 5 for $\alpha/\beta = 3.0$ Gy, and in Appendix eIV for other values of α/β . High grade ($> G2$) toxicity was rare in the RADAR cohort, as was chronic toxicity according to the definition used by Fiorino for incontinence [27]. In the context of the relatively mild symptoms experienced by patients with low toxicity grades, efforts to minimise toxicity according to the derived models should be considered relative to subsequent impact on target volume doses.

The significance of cut-points for rectal bleeding in the high dose range is consistent with previous observations [2,3,12] and the likely underlying mechanism of epithelial damage and mucositis at parts of the rectal wall receiving maximum doses [28]. The impact of maximum dose has been reduced in this cohort due to the confounding protective effect of dose escalation [8], though the serial nature of the dose-volume effect for bleeding is still apparent via the rise in OR to a peak as shown in the logistic regression results in Figure 2. Significant cut-points were also found for peak bleeding

across mid-high range doses (> 30 Gy). Although mid-range dose constraints have been identified in previous studies [4,29,30], the significant impact of these doses in the RADAR cohort could be amplified by the stipulation of high-dose constraints in the study protocol. The shift of significance from anorectum/rectum anatomy for peak toxicity to more inferior anal canal anatomy (see Figure 2) for prevalence at just the 36 month timepoint is noteworthy. We have seen an increase in reported rectal bleeding rates to a plateau during the first 24 months of follow-up. In combination, these observations suggest an association of earlier bleeding with dose to the rectum and delayed bleeding with anal canal dose. There has been a suggestion that steeper dose gradients provide opportunities for cell migration from low-dose regions to aid healing of vascular sclerosis in high-dose regions [31]. Earlier prevalence of bleeding may therefore result from a focused high-dose region, typically in a section of the anorectum above the anal canal, with more diffuse dose distributions (correlating a large range of doses in the anal canal (see Figure 2)) reducing the chance of such healing and leading to later toxicity incidence [32]. Cut-points for anal canal doses predictive of bleeding approached significance over mid-range doses (30 Gy – 50 Gy), and were included in optimal multivariate models at relative volumes below 40% as shown in Figure 5. The multivariate results demonstrate an importance of high doses (55 Gy – 65 Gy) to anorectum and rectum for peak incidence of bleeding across all values of α/β .

For stool frequency and urgency, significant dose-volume effects are dominant in the anorectum and anal canal regions, but not the superior rectum. This is consistent with previous similar studies that have attempted to anatomically localise dose-volume relationships [4,29,30], reflecting the likely roles played by local fibrosis and the

adjacent pelvic floor muscles in control of related functions, their impairment via radiation damage and subsequent toxicity aetiology [33]. Doses to anorectum below 35 Gy are important for urgency and tenesmus, with no multivariate model obtained when dose fractionation effects were not included. This was similar for diarrhoea where anorectum doses near 30 Gy were included in derived multivariate models, but only for $\alpha/\beta = 3.0$ Gy or 5.4 Gy. Peak incidence of stool frequency, diarrhoea and evacuation were associated on multivariate analysis with doses to the anal canal between 12 Gy and 36 Gy.

The UK MRC RT01 and Italian AIROPROS 0102 trials, [29,34], utilising similar EBRT treatments to RADAR, observed significant increases in stool frequency, urgency and/or incontinence for patients exceeding V40 dose constraints. In the current cohort (see Figure 3 and Figure 4), we see significant dose-volume effects (at least on univariate regression) for similar toxicities over an extensive range of doses below 40 Gy. The uniformity (flatness) of the ORs relating volume to toxicity as a function of dose in Figure 3 and Figure 4 indicate the parallel-like nature of the dose-volume effect for these non-bleeding toxicities [35]. These results translate to derivation of constraints, also for diarrhoea and completeness of evacuation, below 40 Gy across the anorectum and anal canal, as shown in Figure 5.

We have observed some sensitivity to the choice of α/β used to convert dose to 2 Gy/fraction equivalence. Ranges of significant cut-point and regression values move to higher doses with the scaling induced by higher values of α/β . Focusing just on the multivariate results (provided in Appendices eIV and eV), the number of toxicities and

doses providing important constraints generally decreased with increasing α/β (ie., from 3.0 Gy to 5.4 Gy and ∞ Gy). This effect was the same for both the anorectum and anal canal. With a trend towards hypofractionation in clinical practice for prostate radiotherapy, this result suggests that these toxicities will remain as important factors in constraining dose delivery. This is compensated in part by the typical association of hypofractionation irradiation strategies providing greater conformality than the treatment techniques used to generate the data presented here, reducing especially the volumes exposed to mid-range doses.

Several limitations in this study should be highlighted, particularly in relation to the scope for translating the results to other datasets or treatment techniques:

- The analysis method employed makes use of a rank sum rather than a dichotomisation of toxicity grades, requiring the use of toxicity prevalence rather than time-to-event data.
- Although we have been unable to separately find differences in toxicity rates based on patient setup orientation, the dominance of supine orientation in the studied cohort (> 90%) should be acknowledged.
- Anatomical definition was based on a single simulation CT image set and results incorporate the uncertainty of intra-treatment organ motion and deformation. The analysis relies on the large patient numbers and variability in irradiation technique across 23 contributing centres.
- Clinical risk factors have not been incorporated into this analysis, with previous analysis not revealing any specific influence of trial arm or clinical covariates [8].

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Captions

Figure 1: Summary of (a) peak toxicity grades for the entire late follow-up period and (b) incidence at the 36 month timepoint, grouped by toxicity. The number of patient datasets included in analysis after exclusions for each toxicity is indicated.

Figure 2: Cut-point (top) and ordinal regression (bottom) distributions by anatomical definition for bleeding, for a) peak toxicity and b) prevalence at 36 months. Significant cut-points and ORs ($p < 0.05$ after correction for multiple testing) at any value of EQD2 ($\alpha/\beta = 3.0$ Gy) are indicated with a data point displayed as an asterisk.

Figure 3: Cut-point (top) and ordinal regression (bottom) distributions by anatomical definition for stool frequency, for a) peak toxicity and b) prevalence at 36 months. Significant cut-points and ORs ($p < 0.05$ after correction for multiple testing) at any value of EQD2 ($\alpha/\beta = 3.0$ Gy) are indicated with a data point displayed as an asterisk.

Figure 4: Cut-point (top) and ordinal regression (bottom) distributions by anatomical definition for urgency and tenesmus, for a) peak toxicity and b) prevalence at 36 months. Significant cut-points and ORs ($p < 0.05$ after correction for multiple testing) at any value of EQD2 ($\alpha/\beta = 3.0$ Gy) are indicated with a data point displayed as an asterisk.

Figure 5: Important relative dose-volume constraints identified via multivariate regression for the three considered GI regions, a) anorectum, b) anal canal and c)

rectum. All displayed values are for peak toxicity and have $OR > 1$. EQD2 is for $\alpha/\beta = 3.0$ Gy.

Table 1: Summary of significant cut-point and ordinal regression results.