Radiotherapy dose-distribution to the perirectal fat space (PRS) is related to gastrointestinal control-related complications

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Running Title: Dosimetric response of the Peri-Rectal Space

Keywords: Perirectal space, radiotherapy, atlas of complication, rectal toxicity

Abstract

Traditionally rectal symptoms following pelvic/prostate radiotherapy are correlated to the dosimetry of the anorectum or a substructure of this. It has been suggested that the perirectal fat space (PRS) surrounding the rectum may also be relevant. This study considers the delineation and dosimetry of the PRS related to both rectal bleeding and control-related toxicity. Initially, a case-control cohort of 100 patients from the RADAR study were chosen based on presence/absence of rectal control-related toxicity. Automated contouring was developed to delineate the PRS. 79 of the 100 auto-segmentations were considered successful. Balanced case-control cohorts were defined from these cases. Atlas of Complication Incidence (ACI) were generated to relate the DVH of the PRS with specific rectal symptoms; rectal bleeding and control-related symptoms (LENT/SOM). ACI demonstrated that control-related symptoms were related to the dose distribution to the PRS which was confirmed with Wilcoxon rank sum test ($p<0.05$). To the authors knowledge this is the first study implicating the dose distribution to the PRS to the incidence of control-related symptoms of rectal toxicity.

INTRODUCTION

The range of rectal/bowel symptoms reported following prostate radiotherapy is diverse including rectal bleeding and control-related symptoms such as loose stools and urgency. The dosimetric relationship to the specific toxicity of rectal bleeding has been comprehensively studied and characterised [1]. For other endpoints the aetiology and relationship with dosimetry is less well defined and the subject of ongoing investigations [2-4]. However several studies reporting the rectal toxicity from large prospective clinical trials found differences in the anatomical subregions and dosimetric variables which related to individual toxicity outcomes[5-9]. A study by Smeenk et al which considered the dosimetric relationship between the anal wall and pelvic floor muscle groups and incontinence-related toxicity demonstrated specific dose-response relationships with individual muscle groups [10]. Buettner at al [11] demonstrated that spatial descriptors of the dose received by the surface of anal canal (defined as the caudal 3cm of the anorectum) were correlated to sphincter control (LENT SOM)[12]. It is apparent that different manifestations of toxicity are related to different underlying pathophysiology, including inflammatory responses and epithelial damage [9, 10].

It is well recognised that rectal dose volume histograms (DVHs) obtained during prostatic irradiation differ from those derived during the radiotherapy planning process [13]. However, the surrounding region, the perirectal fat space (PRS), is thought to remain relatively immobile. If this is true, then it may also be true that the DVH of the PRS derived during planning will correlate more satisfactorily with subsequent radiation induced dysfunctional rectal symptoms than the rectal DVH generated during planning.

Moreover, if peri-rectal fat is as radiosensitive as other fatty tissue regions in the body, it is possible that a course of prostatic irradiation will reduce the elasticity of peri-rectal fat, which may in its own right alter rectal function adversely. Therefore, in this study we test the hypothesis that DVHs of the PRS obtained at planning correlates better with the severity of dysfunctional rectal symptoms and their underlying injuries than planning rectal DVHs.

METHODS AND MATERIALS

Data source and description

The RADAR trial (Randomised Androgen Deprivation and Radiotherapy, TROG 03.04) [14] examined the influence of duration of androgen deprivation (AD) with or without bisphosphonates, adjuvant with radiation therapy, for treatment of prostate carcinoma. 1071 participants were accrued from 23 centres across Australia and New Zealand between 2003 and 2007.

All participants received centre-nominated radiation therapy to the prostate with 46 Gy 3D conformal external beam radiation therapy (EBRT – "Phase 1") followed by either a 19.5-Gy high dose-rate (HDR) brachytherapy boost or EBRT to either 66, 70, 74, or 78 Gy (at clinician discretion - "Phase 2"). Phase 1 was determined by PTV1, being CTV plus 10 mm margin in all directions except posteriorly where it was 5 mm. Phase 2 was determined by PTV2, being CTV plus 0 - 10 mm margin in all directions except posteriorly where it was 0 – 5 mm. Fractionation is shown in Table 1. No participants

receiving the HDR boost were considered in this current study. Image guidance was via bony anatomy only.

Rectal dose volume constraints, derived from results presented by Boersma et al [15], were applied during treatment planning. They were 65, 70, and 75 Gy to a maximum 40%, 30%, and 5% of rectum , respectively.

All patients were assessed at randomization (baseline) and then routinely followed in clinic every 3 months for 18 months, then at 6 months up to 5 years post randomization and then annually. At these visits, toxicity was assessed according to Late Effects of Normal Tissues Subjective, Objective, Management, and Analytic (LENT SOMA) scales [12].

Participant treatment planning data (CT images, planned dose distributions, delineate anatomy, beam configurations and treatment demographic data) were archived in a database using the SWAN software system [16], enabling subsequent query and arbitrary analysis.

Definition of the PRS region

The PRS is here defined as the region of tissue, mostly fat, which the rectum can expand into or contract from [17]. Although the spatial extent of the fat region is relatively apparent on CT images, the extent of the fat which, when irradiated, could lead to rectal toxicity is ambiguous. As such, for this investigation, the entire region of fat adjacent to the prostate, rectum and bladder, though excluding any of the interior of

those structures, was initially incorporated into defining the PRS. In order to optimise potentially causal dosimetric correlations, a sub-section of this region was then examined for statistical analysis as described below.

Segmentation of PRS

Due to the complexity and convoluted nature of the PRS region, manual segmentation on a large number of cases was considered infeasible. An auto-segmentation method was established based on manual delineation by a single observer (JD) on a series of ten test cases. A thorough description of the auto-segmentation process has been presented elsewhere [18].

In summary, on each analysed CT image set, the auto-segmentation involved defining a probability map for the PRS region based on non-rigid registration to the test cases. The voxels within the volume of interest were then labelled using an expectation maximisation clustering. The resulting structure was represented as a binary mask on each patient's CT images. For the purpose of correlating PRS dosimetric factors with toxicity, the structure was refined by only including defined PRS image-pixels within 50 mm of the previously-delineated anorectum structure [8], as well as caudal to the bladder neck, and excluding any pixels within the outer wall of the rectum, as delineated at patient treatment planning. This ensured that the fat region immediately adjacent to the rectum was included in the dosimetric analysis excluding the fat region posterior to the bladder. It was also desired that the superior-inferior extent of the region should encompass the borders of the coplanar beams oriented about the cranio-caudal axis.

The auto-segmentation process was computationally intensive and, as such, a subset of 100 of the available RADAR patients (treated entirely with EBRT) was selected for auto-segmentation. This was a case-control analysis representing patients with control-related toxicity (requiring LENT SOMA 'stool frequency' ≥ grade 2 and 'urgency and tenesmus' ≥ grade 2 at any time throughout a minimum 60 months follow-up) and without control-related toxicity (grade = 0 throughout a minimum 60 months follow-up). The anorectum and anal canal were also outlined separately for comparison. The anorectum was delineated as the outer rectal wall from the ischial tuberosities until the level where the rectum turns horizontally into the sigmoid colon, of which the anal canal was considered to be the caudal 3cm [5].

Once segmented, cohorts with balanced characteristics were defined based on prescription dose, rectal and PRS volume and age at treatment.

Derivation of DVHs

Dose distributions from each treatment phase were combined on a voxel-by-voxel basis. DVH for the anorectum, anal canal and refined PRS regions were independently calculated as defined in Kennedy et al [19]. Since the PRS is an undescribed structure in terms of radiobiology, physical dose was used for the study. The DVH data were imported, with toxicity data, to Matlab version 2013a (Mathworks, Natick, MA). The relationship between dosimetry and toxicity was explored using Atlas of Complication Incidence (ACI) [20, 21] which were generated using a grid of 5 Gy dose and 10% volume bins. The denominator in each grid square indicates the number of patients whose DVH passed through whilst the numerator indicates the number of those patients

who reported complications. ACI were generated to present the incidence of control-related toxicity for each of the outlined structures. For completeness ACI were also generated for rectal bleeding >= G2.

Statistical Considerations

A spearman's correlation matrix was generated to assess correlations between dosimetric descriptors of the 3 structures considered in this study PRS, anorectum and anal canal. Non parametric comparisons between the dosimetry of patients who did/did not report toxicity were made using Wilcoxon rank sum test. A Holm-Bonferroni correction was made to account for multiple testing of different dose levels. All statistical analysis was undertaken using R.[22]

RESULTS

Of the 100 patients chosen for auto-segmentation, 79 datasets were considered sufficiently well delineated for inclusion in the analysis. Figure 1 present examples of the automatically defined PRS regions. 34 patients who did not report rectal control related toxicity had successful PRS delineation and these were balanced against 34 patients who reported rectal control-like toxicity. Table 1 details the patient characteristics of the 68 patients included in the dosimetric analysis. There were no significant differences between the groups with and without control-related toxicity in terms of prescription, rectal and PRS volume, BMI or age at treatment. The correlation matrix (Appendix Figure A5) indicates a high degree of correlation between the dosimetric variables of a particular structure but low correlation between structures.

The ACI relating the dose distribution to the PRS with rectal control-related toxicity is presented in Figure 2. Figure 3 shows the ACI for the subgroup of patients who reported control-related toxicity but who did not report rectal bleeding. The ACI relating the dose distribution to the PRS with rectal bleeding (≥G2) is shown in Figure 4. Wilcoxon rank sum test results are presented in Table 2 where a number of dose levels were shown to be related to control-related toxicity for the PRS, when including all patients and also when excluding patients with rectal bleeding. However no results remained statistically significant after applying the Holm-Bonferroni correction. There were no statistically significant results when relating the PRS to Grade 2 Rectal Bleeding.

The ACI for the anorectum (Appendix Figures A1 and A2) do not demonstrate a clear dosimetric relationship with either rectal bleeding or control-related toxicity. However, the ACI for the anal canal (Appendix Figures A3 and A4) indicate a dose-response for both toxicity endpoints. These results were confirmed by statistical analysis, but did not remain significant when the Holm-Bonferroni correction was applied.

DISCUSSION

Technological improvements enable radiotherapy delivery to be optimised to individual anatomy and function. This provides an opportunity to capitalise on an improved understanding of dose-response for discrete treatment complications. This study has focused on elucidating a more complete aetiology for a subset of gastrointestinal complications, utilising recent developments in non-linear image registration and autosegmentation.

The ACI and statistical analysis indicate that the strongest relationship between the outlined structures and control-related toxicity is described by the dose distribution to the PRS. Although the definition of the region is still ambiguous, it is hoped that development of voxel-level investigations as a means of refining the definition will develop a consensus of the structure delineation. Associated analysis, including assessment of inter-observer agreement, is underway.

The ACI relating anorectal DVH with rectal bleeding did not demonstrate a clear dose response. This study presents results on a small cohort reflecting the development efforts in auto-segmentation of the PRS and case selection to specifically explore the relationship with control related toxicity. It has been shown that the dose distribution of the PRS is not highly correlated with that of the anorectum and anal canal, However, the results from a previous study utilising all available data from the RADAR study [8] do demonstrate a relationship between mid-high doses and rectal bleeding and between lower doses to the anal canal and urgency. Previous publications [11, 23] have also indicated that the dose distribution to the anal canal is related to control-related symptoms. These results appear to be corroborated by the anal canal atlas presented in this study.

The ACI relating PRS DVH to control-like toxicities (Figure 2) shows a clear pattern of increasing incidence rates with increasing dose and volume. This is apparent even when isolated just to patients without incidence of rectal bleeding (Figure 3). The statistical results presented in Table 2 strongly support the hypothesis that the PRS behaves as a parallel-responding structure with significant dose-volume parameters across a broad

range of doses, and a significant dependence on the mean but not maximum dose. It must be highlighted that duration of AD was significantly different between the patient groups (see Table 1). Although an attempt was made to match the groups based on their toxicity incidence using prescription dose, rectal volume and age at treatment, there were not sufficient patient numbers to allow control of all other factors. Previous analyses of the entire RADAR cohort have not uncovered significant impacts of AD duration or age [24, 25]. Similarly note that no rectal filling procotol was specified for the trial and uniform proportions of any applied protocols between the toxicity groups cannot be guaranteed.

Given the role of the PRS in facilitating rectal motility, compliance and control, and the potential for fatty atrophy and fibrosis on irradiation, there is reason to hypothesise a causal relationship between dose to the PRS and subsequent control-related gastrointestinal symptoms. Moreover, a large number of sympathetic, parasympathetic and non-autonomic nerve fibres are to be found in the perirectal fat space. Radiation injury to the vasa nervorum may therefore directly lead to nerve dysfunction and contribute to control-related symptoms (personal communication 2017 Drs Jervoise Andreyev and Andrew Wotherspoon).

To our knowledge, this is the first study of the dosimetric relationship between the PRS and control-related gastrointestinal toxicity. The dataset utilised was selected on the basis of availability, number of available participants, completeness and extent of follow-up. It must be acknowledged that the use of relatively dated treatment techniques, without image-guidance other than for bony anatomy, will likely influence

applicability to contemporary treatments. The use of soft-tissue image-guidance and more conformal delivery techniques are known to impact on delivered dose distributions and toxicity incidence [26, 27]. Validation in relevant datasets is desirable, including assessment of the mobility of the PRS on inter-fraction images. Further study of the individual structures within the PRS may provide more specific information relating dosimetry to toxicity.

ACKNOWLEDGEMENTS

We acknowledge funding from Cancer Australia and the Diagnostics and Technology Branch of the Australian Government Department of Health and Ageing (grant 501106), the National Health and Medical Research Council (grants 1006447, 1077788), Cancer Research UK Programme Grant (C33589/A19727) and the University of Western Australia (Research Collaboration Award). We thank the Cancer Council Western Australia for a John Nott Fellowship for travel support. We are grateful to Annette Haworth, Rachel Kearvell, Michelle Krawiec, Sharon Richardson and the RADAR trial team for providing high quality trial data. We thank Drs Jervoise Andreyev and Andrew Wotherspoon of the Royal Marsden Hospital Trust, Sutton, Surrey for their helpful advice.

Figure Captions

Figure 1: Examples of autosegmented and and processed PRS regions shown as a light-grey mask on axial, coronal and sagittal reconstructions.

Figure 2: Atlas of complication incidence (ACI) relating the perirectal space (PRS) with control-like rectal toxicity described using LENT/SOMA. The denominator in each box indicates the number of patients whose dvh passes through whilst the numerator details how many of those patients reported control-like rectal toxicity. Hot (red) regions of the colour scale indicate high incidence and cold (blue) regions indicate low incidence. The bottom right hand box indicates overall incidence in the cohort (shaded green).

Figure 3: Atlas of complication incidence (ACI) relating the perirectal space (PRS) with control-like rectal toxicity described using LENT/SOMA. Patients who reported rectal bleeding were excluded.

Figure 4: Atlas of complication incidence (ACI) relating the perirectal space (PRS) with Grade 2 rectal bleeding (LENT/SOMA).

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	Whole Group	No Control-related Rectal -Toxicity	Control-related Rectal Toxicity
N	68	34	34
Trial arm[a], n (%)			
A	17 (25%)	9 (26%)	8 (24%)
B	17 (25%)	11 (32%)	6 (18%)
C	16 (24%)	6 (18%)	10 (29%)
D	18 (26%)	8 (24%)	10 (29%)
Prescription dose group, n (%)			
66 Gy[b]	10 (15%)	6 (18%)	4 (9%)
70 Gy[c]	35 (51%)	13 (38%)	22 (65%)
74 Gy[c]	23 (34%)	15 (44%)	8 (22%)
Rectal volume, mean (SD)	77.1 (40.7) cm^3	84.5* (48.0) cm^3	69.7 (30.8) cm^3
Risk group			
Intermediate	47 (69%)	20 (59%)	27 (71%)
High	21 (31%)	14 (41%)	7 (21%)
BMI, mean (SD)	27.6 (3.4)	27.9 (3.4)	27.4 (3.5)
PRS volume, mean (SD)	140.7 (51.4) cm^3	149.3 (49.0) cm^3	132.2 (53.1) cm^3
Age at treatment, mean (SD)	70.6 (6.1)	71.4 (5.5)	69.7 (6.6)
≥ G2 peak rectal bleeding, n (%)	23 (34%)	5 (15%)	18 (55.9%)

Table 1. Patient Characteristics

[a] A – 6 months androgen suppression; B – 6 months androgen suppression + zoledronic acid; C – 18 months androgen suppression; D – 18 months androgen suppression + zoledronic acid

[b] 33 fractions, 2 Gy/fraction, PTV1 within 95% isodose

[c] Phase 1 - 30 fractions, 2 Gy/fraction, PTV1 within 95% isodose. Phase 2 - additional dose in 2 Gy/fraction, PTV2 within 95% isodose

	Perirectal Space DVH			Ano-Rectum DVH			Anal Canal DVH		
Dose Metric	Other Toxicity	Other Toxicity (RB < G2)	Rectal Bleeding G2	Other Toxicity	Other Toxicity (RB < G2)	Rectal Bleeding G2	Other Toxicity	Other Toxicity (RB < G2)	Rectal Bleeding G2
	n=68	n=44	n=68	n=68	n=44	n=68	n=68	n=44	n=68
V5	0.163	0.620	0.088	0.154	0.421	0.454	0.123	0.168	0.328
V10	***0.031***	0.293	0.184	0.421	0.413	0.974	0.085	0.110	0.280
V15	***0.025***	0.168	0.571	0.611	0.620	0.568	0.173	0.143	0.433
V20	***0.029***	0.070	0.964	0.677	0.544	0.107	0.195	0.276	0.332
V25	***0.034***	0.063	0.894	0.579	0.314	***0.050***	0.071	0.235	0.411
V30	***0.014***	***0.030***	0.854	0.332	0.103	0.073	***0.048***	0.200	0.302
V35	***0.037***	***0.013***	0.448	0.296	0.114	0.157	0.066	0.302	0.326
V40	***0.015***	***0.005***	0.362	0.083	***0.047***	0.264	0.057	0.338	0.130
V45	0.072	0.146	0.904	0.424	0.677	0.864	0.185	0.922	***0.028***
V50	0.107	0.192	0.954	0.308	0.732	0.964	0.164	0.748	***0.013***
V55	0.089	0.175	0.954	0.258	0.788	0.814	0.164	0.902	***0.013***
V60	0.089	0.209	0.814	0.206	0.864	0.411	0.112	0.795	***0.005***
V65	0.189	0.291	0.774	0.118	0.677	0.181	0.085	0.406	***0.011***
V70	0.931	0.535	0.748	0.602	0.553	0.255	0.740	0.806	0.316
mean	***0.025***	0.067	0.995	0.134	0.248	0.794	0.065	0.418	0.071
max	0.289	0.872	0.653	0.374	0.569	0.379	0.492	0.473	0.087

Table 2 Wilcoxon rank sum test p values, relating individual dose metrics for the PRS, anorectum and anal canal to rectal control-like symptoms and bleeding. Results with an (uncorrected) p value <0.05 shown in bold.

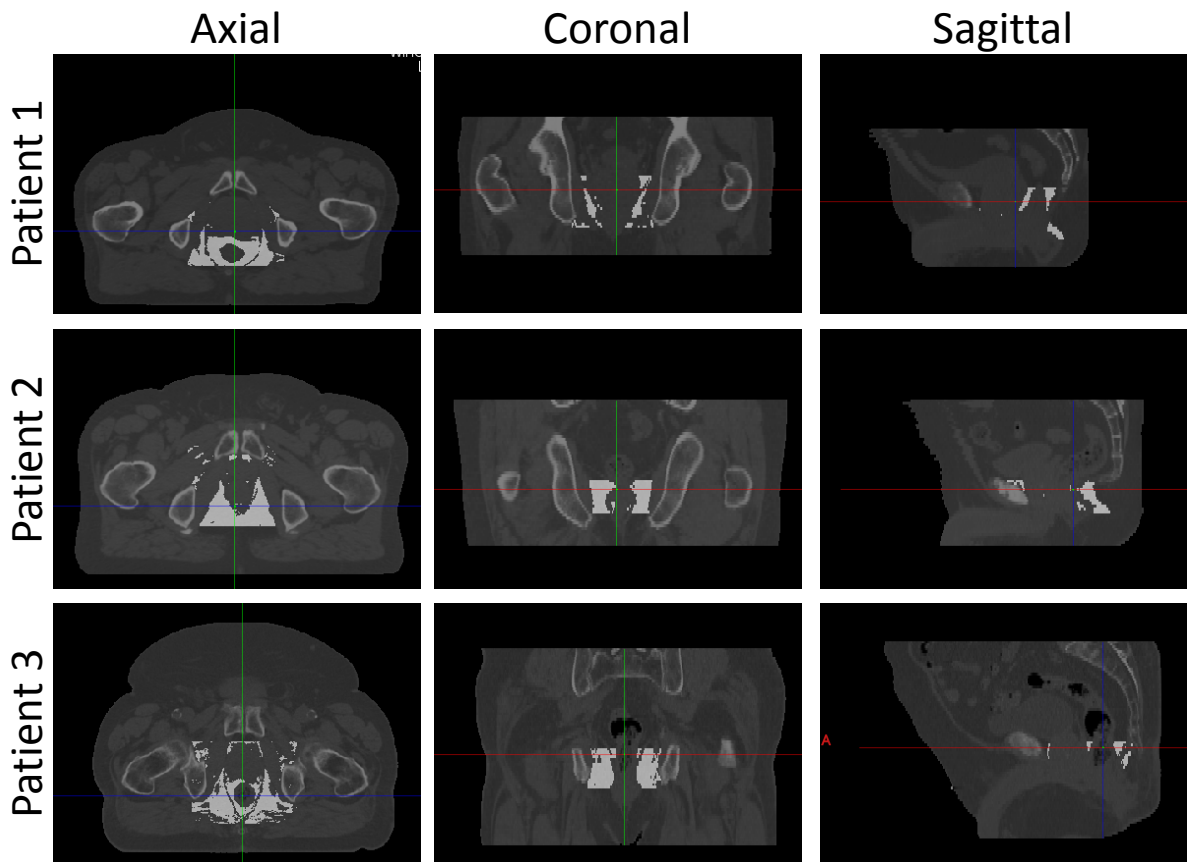

Figure 1: Examples of autosegmented and processed PRS regions shown as a light-grey mask on axial, coronal and sagittal reconstructions.

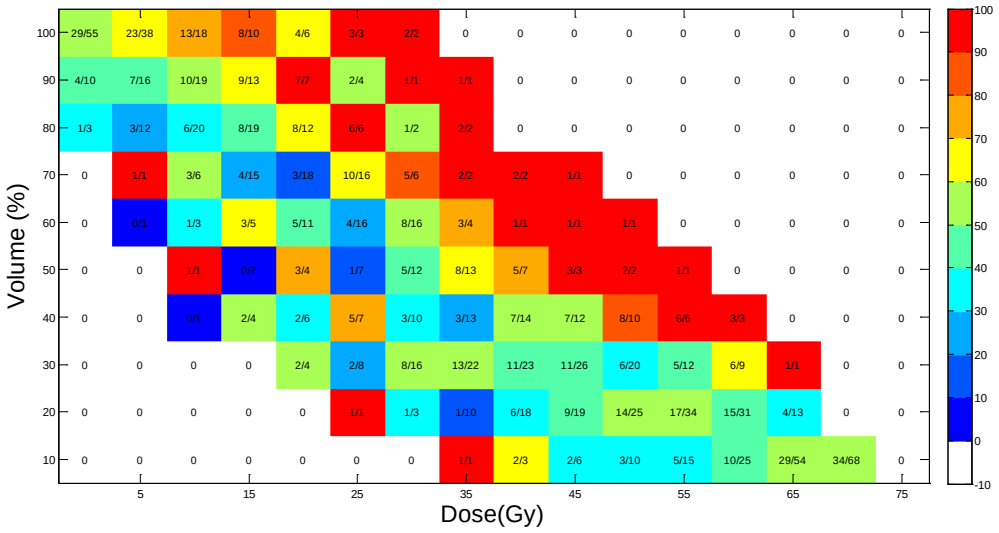

Figure 2: Atlas of complication incidence (ACI) relating the perirectal space (PRS) with control-like rectal toxicity described using LENT/SOMA. The denominator in each box indicates the number of patients whose dvh passes through whilst the numerator details how many of those patients reported control-like rectal toxicity. Hot (red) regions of the colour scale indicate high incidence and cold (blue) regions indicate low incidence. The bottom right hand box indicates overall incidence in the cohort (shaded green).

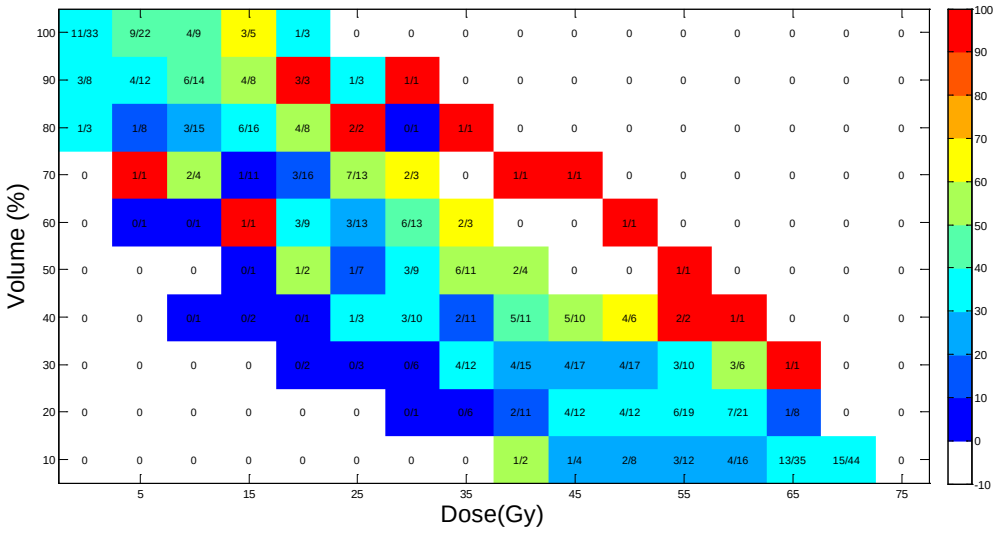

Figure 3: Atlas of complication incidence (ACI) relating the perirectal space (PRS) with control-like rectal toxicity described using LENT/SOMA. Patients who reported rectal bleeding were excluded.

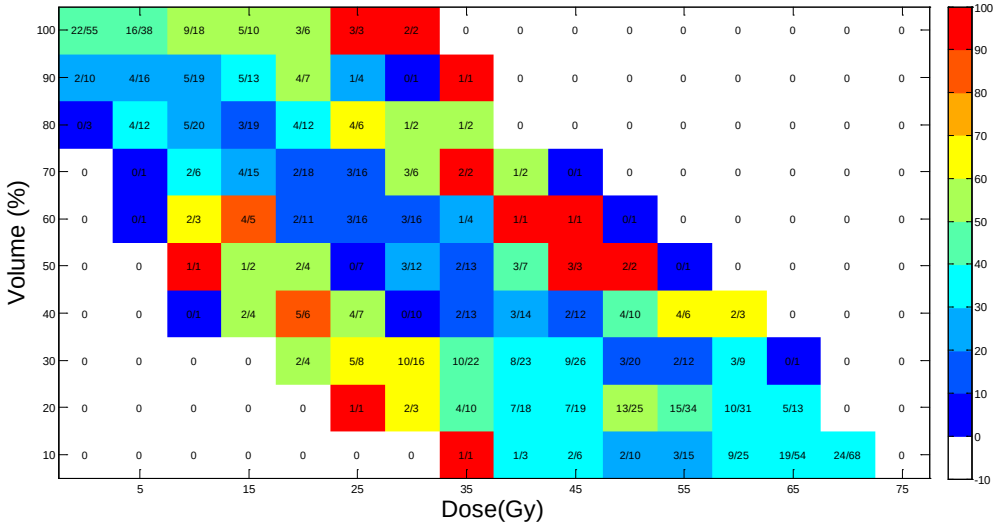

Figure 4: Atlas of complication incidence (ACI) relating the perirectal space (PRS) with Grade 2 rectal bleeding (LENT/SOMA).

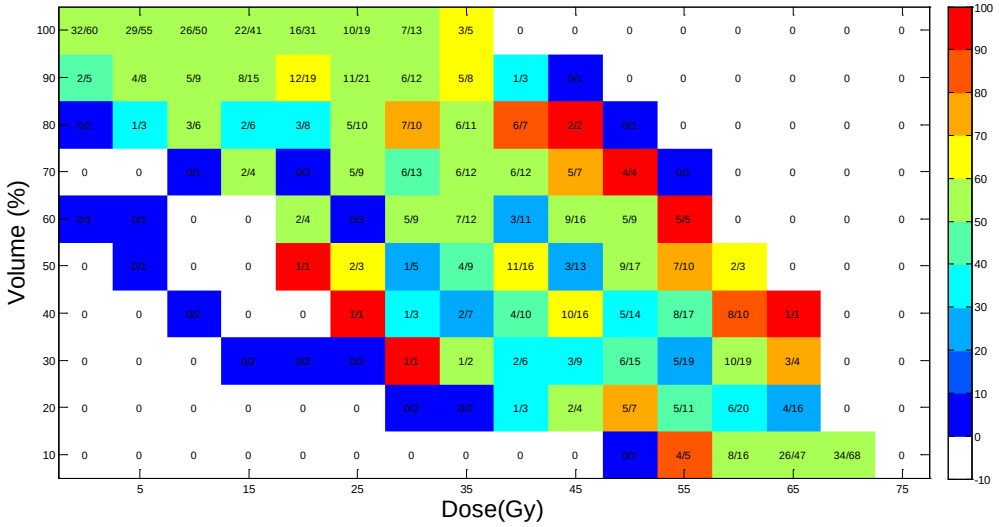

Figure A1: Atlas of complication incidence (ACI) relating the anorectum with control-like rectal toxicity described using LENT/SOMA. The denominator in each box indicates the number of patients whose dvh passes through whilst the numerator details how many of those patients reported control-like rectal toxicity. Hot (red) regions of the colour scale indicate high incidence and cold (blue) regions indicate low incidence. The bottom right hand box indicates overall incidence in the cohort (shaded green).

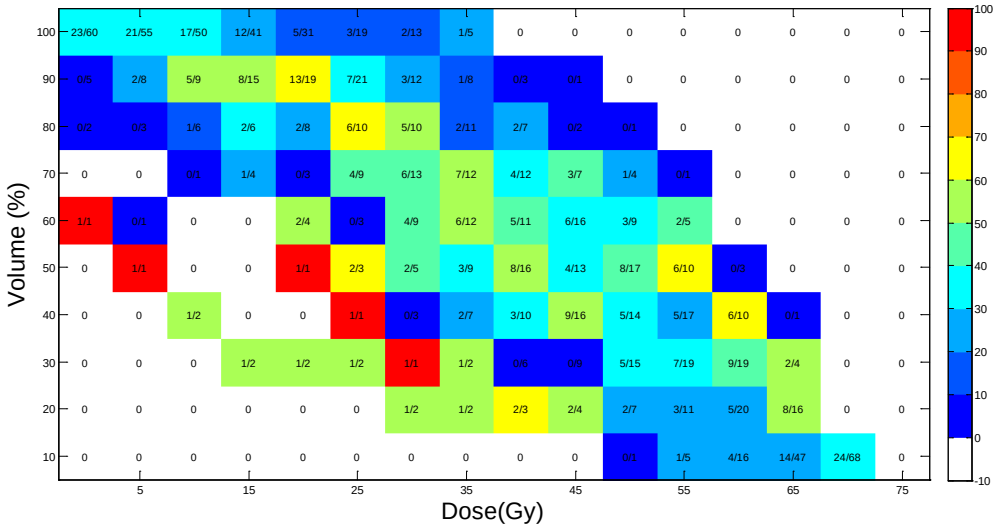

Figure A2: Atlas of complication incidence (ACI) relating the anorectum with Grade 2 rectal bleeding described using LENT/SOMA.

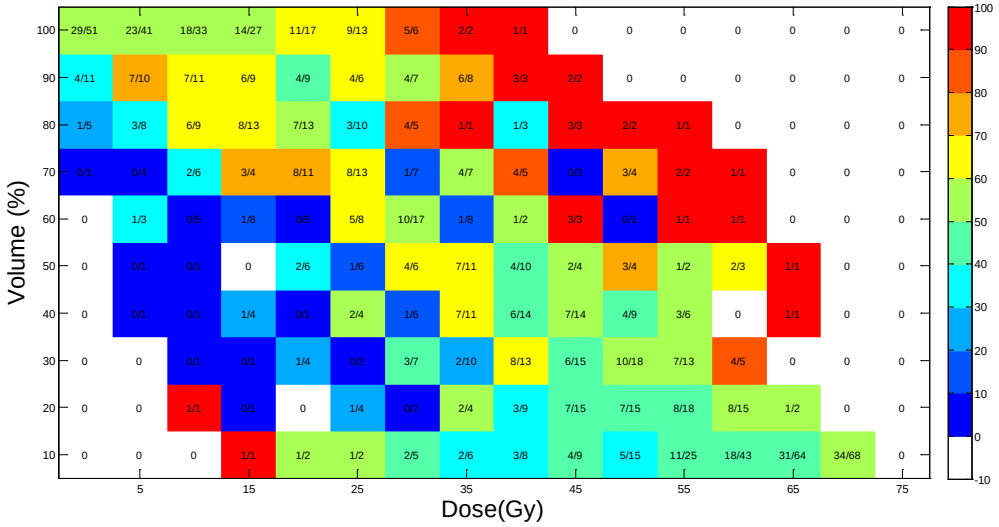

Figure A3: Atlas of complication incidence (ACI) relating the anal canal with control-like rectal toxicity described using LENT/SOMA.

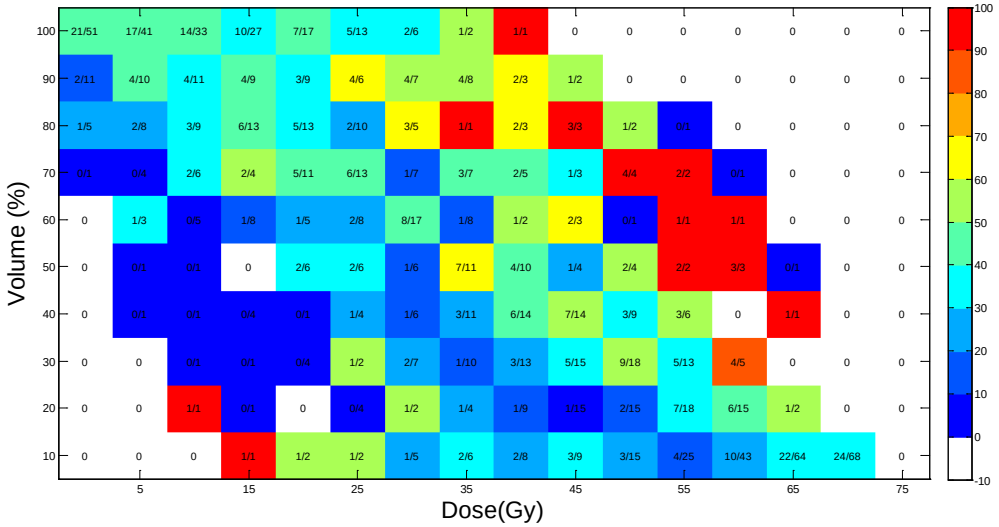

Figure A4: Atlas of complication incidence (ACI) relating the anal canal with Grade 2 rectal bleeding described using LENT/SOMA.

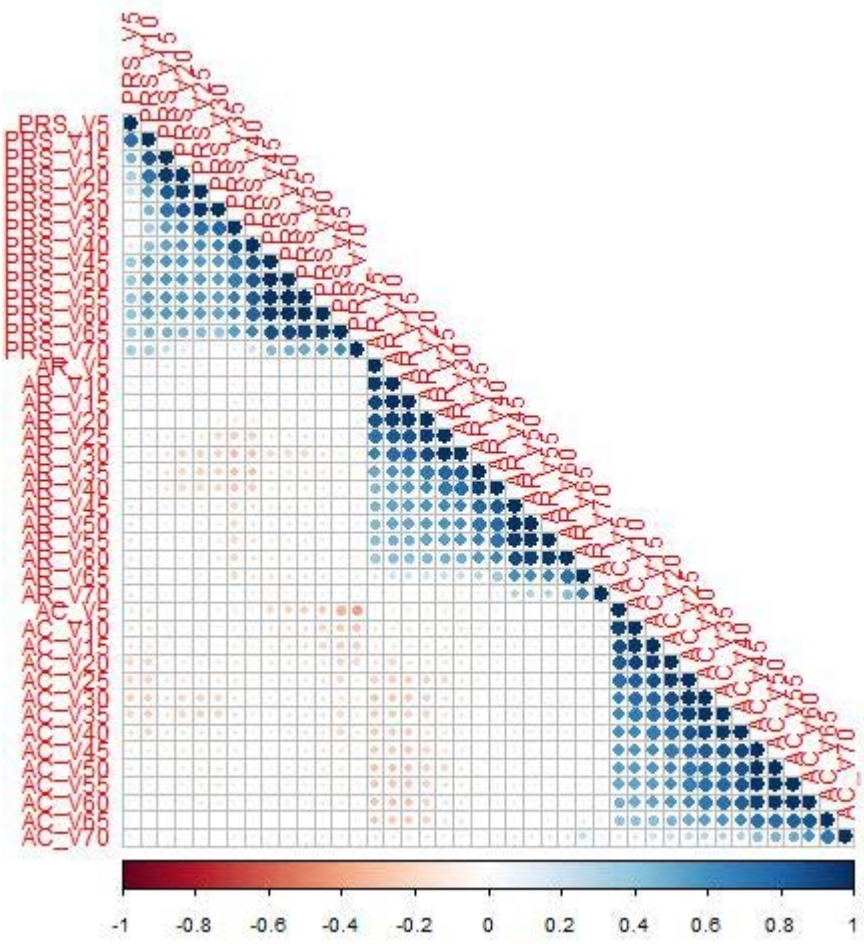

Figure A5: Correlation matrix for dosimetric parameters of the PeriRectal Space (PRS), Anorectum(AR) and Anal Canal (AC).