Radiotherapy and Oncology 103 (2012) 347–352

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Dose-response of anal cancer

The dose–response of the anal sphincter region – An analysis of data from the MRC RT01 trial

Florian Buettner [a,*], Sarah L. Gulliford [a], Steve Webb [a], Matthew R. Sydes [b], David P. Dearnaley [c], Mike Partridge [a]

[a] Joint Department of Physics, Institute of Cancer Research, Surrey; [b] Cancer Group, MRC Clinical Trials Unit, London; [c] Academic Unit of Radiotherapy, Institute of Cancer Research, Surrey, UK

ARTICLE INFO

Article history:
Received 27 June 2011
Received in revised form 15 February 2012
Accepted 4 March 2012
Available online 18 April 2012

Keywords:
Prostate cancer
Radiotherapy
Anal sphincter
Dose–effect relation

ABSTRACT

Purpose: Most studies investigating the dose–response of the rectum focus on rectal bleeding. However, it has been reported that other symptoms such as urgency or sphincter control have a large impact on quality-of-life and that different symptoms are related to the dose to different parts of the anorectal wall. In this study correlations between the 3D dose distribution to the anal-sphincter region and radiation-induced side-effects were quantified.

Materials and methods: Dose–surface maps of the anal canal were generated. Next, longitudinal and lateral extent and eccentricity were calculated at different dose levels; DSHs and DVHs were also determined. Correlations between these dosimetric measures and seven clinically relevant endpoints were determined by assessing dosimetric constraints. Furthermore, an LKB model was generated. The study was performed using the data of 388 prostate patients from the RT01 trial (ISRCTN 47772397).

Results: Subjective sphincter control was significantly correlated with the dose to the anal surface. The strongest correlations were found for lateral extent at 53 Gy ($p = 0.01$). Outcome was also significantly correlated with the DSH and the mean dose to the anal surface.

Conclusions: The dose to the anal sphincter region should be taken into account when generating treatment-plans. This could be done using shape-based tools, DSH/DVH-based tools or an NTCP model.

Many attempts have been made to assess the dose–response of the rectum by quantifying correlations between specific aspects of the dose delivered to the rectum and late rectal complications. Usually the dose delivered to the rectum is described by measures such as the mean dose, the volume V_d receiving more than a threshold dose d or the equivalent uniform dose which can be derived from dose–surface histograms (DSHs) or dose–volume histograms (DVHs). Univariate or multivariate statistical analysis can be used in order to find correlations between these summary measures and late complications and get a better insight into the dose–response relationship of the rectum.

While the majority of studies have focussed on high-grade rectal bleeding as endpoint, it is also desirable to take other endpoints such as loose stools, urgency and incontinence into account which have a major impact on the quality-of-life of patients [1,2]. Correlations between dose–volume factors and these non-bleeding endpoints as well as bleeding endpoints were investigated in several studies [3–6]. Some studies have assessed correlations between the dose to the anal-sphincter region and late toxicities and reported evidence that endpoints such as faecal leakage are correlated more strongly with the dose to the anal-sphincter than to the dose to the entire anorectal wall [5,7–9]. However, in these studies no dosimetric constraints were assessed and only little data on establishing threshold doses exist [4]. More recently, it has been suggested that some incontinence-related symptoms are related to different anatomic and pathophysiological substrates [10]: urgency and incontinence were related to a lower anal resting pressure as well as a lower tolerated rectal pressure. Furthermore, urgency was significantly correlated with the dose to the anal wall as well as to the dose to the rectal wall while incontinence was significantly correlated with the dose to the anal wall only. In a recent review on radiotherapy-related faecal incontinence, Maeda et al. [11] show that correlation between rectal dose–volume parameters and incidence is equivocal and conclude that an analysis of the spatial distribution of radiation-dose to the rectum could yield better insights into links between the dose to the rectum and faecal incontinence.

When quantifying correlations between DVH-data and late rectal toxicity several difficulties can occur. First, there are strong correlations between different summary measures such as V_{50} and V_{60} so that it is hard to single out the summary measure with the strongest correlation. When quantifying correlations between constraints derived from these measures and outcomes, multiple tests

* Corresponding author.
E-mail address: florian.buttner@icr.ac.uk (F. Buettner).

0167-8140/$ - see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.radonc.2012.03.002

Table 1
Number of patients free of the respective symptom before treatment who reported each grade of toxicity.

	Rectal bleeding	Proctitis	Sphincter control (subj.)	Stool frequency	Sphincter control management	Loose stools	Rectal urgency
Grade 0	202	207	322	209	366	204	154
Grade 1	105	95	39	106	15	73	67
Grade 2	54	86	18	29	0	41	67

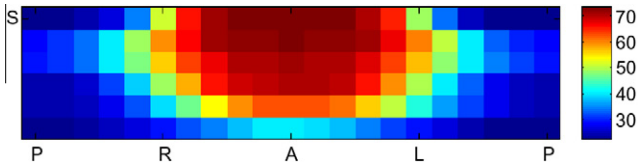

Fig. 1. Normalised DSM of a typical patient treated to 64 Gy with conformal radiotherapy. The dose in Gy is shown by different colours, as shown in the colour-bar. P = posterior, R = right, A = anterior, L = left, S = superior.

are performed. As it is difficult to perform an appropriate multiple-testing correction, often no correction is performed at all so that significance levels are over-estimated [12]. Second, all spatial information is lost when using DVHs or DSHs. Tucker et al. [13] have suggested the use of cluster models which are based on the hypothesis that the complication probability depends on the size of clusters of damaged tissue. More recently, Gianolini et al. [14] suggested the extraction of spatial features from dose–surface maps (DSMs) and testing correlations with rectal toxicity.

The primary aim of this study is to quantify correlations between the 3D dose distribution to the anal surface and clinical outcome by explicitly taking spatial information into account.

In addition to this spatial analysis a DVH analysis was also performed and cutpoints for DVHs (i.e. dose–volume constraints) as well as mean-dose constraints for the anal sphincter were assessed and mean-dose based normal tissue complication probability (NTCP) models were derived.

Materials and methods

Patient cohort

The study was performed with data from the MRC RT01 multicentre randomised controlled trial (ISRCTN 47772397). In this trial 843 prostate cancer patients were treated with 3D conformal radiotherapy, 421 with a prescribed standard dose of 64 Gy, 422 with an escalated dose of 74 Gy. Further details about the implementation of the trial can be found in Sydes et al. [15]; results were published in Dearnaley et al. [16]. Only 388 patients were eligible for dosimetric analysis, as the planning data were only available for a subgroup of patients [17]. Previous analyses of these data were performed with focus on the relations between dose, rectal volume and late effects on sexual function [18] as well as a variety of late rectal toxicities [17]. Furthermore correlations between late rectal toxicities and the spatial distribution of dose to the rectal wall were assessed [19]. In the present analysis of the dose response of the anal sphincter region, seven clinically-relevant rectal toxicity endpoints (including patient and clinician reported outcomes) were considered separately (Table 1). Only patients who were free of the respective symptom before treatment were considered and all patients had a minimum follow-up of 2 years. Toxicity was defined as the highest grade reported during the follow-up. In a conventional DVH-analysis of the original trial a three-grade scheme was used for all toxicities to bring together the different grading schemes [17]. This common grading scheme was also used in this analysis. The number of patients who reported each grade of toxicity is listed in Table 1.

Characterisation of the spatial distribution

The rectum was outlined from the anus taken at the level of the ischial tuberosities or 1 cm below the planning target volume, whichever was more inferior, up to the rectosigmoid junction; the anal canal was defined as the caudal 3 cm of the rectum [7,8,20,21]. Dose–surface maps (DSMs) were generated by virtual unfolding of the anal canal (Fig. 1). These DSMs reflect the dose delivered to the surface of the anal wall and are a well-known tool for analysing radiation-induced rectal toxicity as well as organ motion [13,22–27]. They are constructed by virtually unfolding the rectum following the same algorithm as in a previous study [19]. The algorithm works as follows: at every CT slice the contour was cut at its posterior-most location and the dose at 21 equidistant points was determined by interpolation. In order to facilitate inter-patient comparisons, the maps were normalised in the longitudinal direction by interpolation to maps of 21×21 pixels. This was implemented using in-house software Guiness [18].

Binary DSMs were generated by thresholding the primary maps at 29 doses between 15 and 71 Gy (Fig. 2(b)). At each dose level an ellipse was fitted to the largest dose–cluster (shown in red in Fig. 2(b)). Lateral and longitudinal extents were quantified by projecting the axes of the ellipse to the main axes of the DSMs (shown in light blue in Fig. 2(b)). The irregularity was described by the eccentricity of the ellipse.[1] Furthermore DSHs were derived from the DSMs by determining the fraction of the DSMs receiving at least a certain threshold dose.

Statistical analysis

Correlations between seven clinically relevant endpoints and the geometrical measures as well as conventional DVHs, dose–surface histograms (DSHs), mean dose and maximum dose were quantified. This was done by evaluating Wilcoxon rank-sums for cutpoints for all geometrical and volumetric measures. The Wilcoxon rank sums were standardised to mean zero and standard deviation of one. Hence, for a test statistic of 1 the strength of the correlation between a cutpoint and outcome is one standard deviation away from what is expected under the null-hypothesis of independence. In order to determine the statistical significance of the different cutpoints the distribution of standardised test statistic $\mathbf{T}^{\star}$ was determined using a permutation test. $\mathbf{T}^{\star}$ was calculated for 10,000 permutations and the p-values were calculated as proportion of permuted statistics that exceeded the observed statistic. The randomisation of the patients into the 64 Gy and the 74 Gy arm of the trial was taken into account by only allowing permutations within each arm. In order to correct for multiple testing a step-down algorithm [28] was applied, taking advantage of the dependence structure between the cut-points. The same framework was used in a previous analysis and further details on the method can be found in Buettner et al. [19].

[1] The eccentricity of an ellipse can be thought of as a measure for how far the shape of the ellipse deviates from a circle.