Dose volume constraints to reduce rectal side-effects from prostate radiotherapy

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Each patient who receives external-beam radiotherapy has an individually optimised treatment plan. Based on a CT scan, this plan defines the dose distribution that will be delivered and the instructions to deliver it. The dose distribution is a delicate balance between ensuring that the tumour is covered by the prescribed dose and that the radiation dose received by surrounding healthy tissue is minimised. Advances in radiotherapy, including intensity-modulated radiotherapy and rotational techniques such as VMAT and RapidArc enable many degrees of freedom when optimising an individual treatment plan, making it possible to sculpt exquisite dose distributions.

However, it is not feasible to avoid healthy tissues and organs completely since they are often in close proximity to the target. The question then is what is the dose distribution which will result in the lowest risk of toxicity?

Whereas some organs are regarded as having a serial response, where the maximum dose to any small part of the organ governs the likelihood of toxicity, other organs are parallel in response. In this case the incidence of toxicity depends on the fraction of the organ receiving a specified dose. However, the reality is often more complex with a combination of responses. What is required for each organ is a comprehensive set of validated organ-specific treatment planning constraints which will minimise toxicity. This article considers some of the issues and findings in relation to rectal toxicity resulting from prostate radiotherapy.

Rectum is one of the most studied normal tissues. As such, there are a number of useful papers available. Recently, two review articles summarising the literature on rectal toxicity have been published. The first by Fiorino et al. was a summary of radiation-induced toxicity in the normal tissues of the pelvis. The second was the comprehensive report by the Quantec (Quantitative analysis of normal tissue effects in the clinic) group published in the red journal which comprised a number of introductory and discussion papers combined with reviews of individual organ toxicity. Rectum was one of the organs in the publication. The Quantec review summarises that “The volume of rectum receiving ≥60 Gy is consistently associated with the risk of Grade ≥2 rectal toxicity or rectal bleeding” while Fiorino concludes that “although the ‘high-dose’ region is the prevalent one in predicting the risk of rectal bleeding, a dose bath of around 40-50 Gy to large portions of the rectum has been reported to increase the incidence of bleeding, even when treating patients at relatively low doses (<70 Gy).”

Both these statements are related to rectal bleeding which is the most commonly-recorded rectal toxicity, although it is not the most prevalent. It is relatively easy to accurately record rectal bleeding and also in most cases to manage it. It is far harder to quantify toxicities, such as loose stools, rectal urgency or stool frequency. They are far more subjective and prone to confounding causes. However, they are also more likely to be reported by patients (if they are asked about them). Consequently, there are much less published data available, despite these being likely side-effects with the potential to influence patients’ quality of life.

Ideally, dose-volume constraints should be derived for clinically relevant endpoints from carefully collected clinical data. It is therefore important to ensure consistent definitions, treatment and reporting. For example, the delineation of the rectum on CT varies dramatically between the protocols of different prostate trials. The definitions vary from +/- 2cm crano-caudally from the clinical target volume to the more common definition extending from the level of the ischial tuberosities to the recto-sigmoid junction. The issue of whether or not to include rectal contents complicates matters further. Of course, this data is taken from the CT planning scan which is obtained to design the treatment plan. The rectum will naturally change over time so the treatment plan can, at best, be regarded as representative of the dose distribution to the rectum. Once the reporting of the treatment planning data has been standardised, it must be compared with the incidence of complications reported by the same cohort of patients. A number of toxicity reporting schemes have been published; however, it is not uncommon for protocols to modify these scales or generate new ones.

Data from the Medical Research Council RT01 trial (ISRCTN 47772397) have been used extensively by our group, to investigate the dose-volume response of rectum. This trial was a multicentre randomised trial comparing prescription doses of 64Gy and 74Gy for prostate radiotherapy. Treatment planning data were recovered for half of the patients treated in the trial (n=388) and combined with rectal toxicity recorded using data from a number of reporting schemes. Seven specific rectal toxicity endpoints were analysed: Rectal bleeding (RMH grading); proctitis (RTOG); Subjective sphincter control, management sphincter control and subjective stool frequency (all LENT/SOM); and rectal urgency and loose stools (both UCLA Prostate Cancer Index). The grading schemes were harmonised into a common grading scheme with three grades of toxicity: None; mild; or moderate & severe. Initially we tested two sets of published constraints those used by the CHHIP trial which were based on the literature available at the time of protocol development and a set proposed by Fiorino in a previous publication. The effect of applying dose-volume constraints was quantified using odds ratio which compared the odds of experiencing a specific toxicity if a treatment plan met the constraint compared with a plan that did not. A number of statistically significant results were observed with the results varying between endpoints. Figure 1 summarises incidence of any of the seven toxicities for the tightest volume constraint (of the two sets) at each dose level. Results are grouped according to the number of the constraints failed. Following on from this study, we derived dose volume constraints from the RT01 data for two separate definitions of toxicity. The first was the classic definition of maximum toxicity reported over the follow-up period. This definition can be sensitive to ‘short term blips’ in reporting which may occur as a result of a confounding causality. An alternative area under the curve metric, referred to as Integrated Longitudinal Toxicity (ILT), was considered where the duration and severity of toxicity were included. The dose volume constraints were derived using Receiver Operator Curve (ROC) analysis to find the point on the curve closest to the...
ideal point. For most toxicities, the derived constraints were similar regardless of the time dependence on reporting. However, the constraints differed between endpoints. A summary of the derived constraints is shown in figure 2. It can be seen that for stool frequency (which is one of the more subjective measures) using ILT produced a set of dose volume constraints where none was generated using the conventional definition.

It is important to consider an inherent weakness with conventional dose volume constraints, that is, that the spatial aspects of how the dose is distributed are completely ignored. Work by PhD student Florian Buettner has shown that by using a dose surface map of the rectum (figure 3) it is possible to quantify spatial aspects of the dose distribution. The dose distribution to the rectum resulting from prostate radiotherapy normally results in a high dose on the anterior wall with a gradient towards the posterior wall. The resultant dose surface map is essentially deformed concentric isodoses which can be quantified using the longitudinal and lateral extent of a specific dose level and the eccentricity (shape) of the isodose. A promising result from one study showed that rectal bleeding is associated with the lateral extent of individual doses in the range 35-60 Gy. In contrast, loose stools was related to longitudinal extent and eccentricity of individual doses in the region of 20-40 Gy.

The variation in techniques, definitions and toxicities which underpin the published literature result in different recommendations of dose volume constraints for the rectum. However, there is clear evidence that minimising the volume of rectum receiving doses as low as 30 Gy will reduce the incidence of a range of toxicities that are observed in modern clinical practice. A number of sets of dose-volume constraints have been proposed and consideration of them should be part of routine clinical practice.

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Further reading
The references within the two review articles referenced provide a comprehensive reading list on this subject.

Reference list

FIGURE 1
Summary of incidence of rectal toxicity, grouped according to the number of constraints failed from the group of lowest volume constraint at each dose level.

FIGURE 2
Rectal dose volume constraints derived from the RT01 data using peak and longitudinal definitions of rectal toxicity.

FIGURE 3
Rectal dose surface map. Annotation: I/A (inferior/anterior); P (posterior); L (left); R (right).