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Original Article

Searching for Optimal Dose–Volume Constraints to Reduce Rectal Toxicity after Hypofractionated Radiotherapy for Prostate Cancer

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Abstract

Aims: Late rectal toxicity is a major concern for prostate cancer patients treated with radiotherapy. Rectal dose–volume constraints, set as guidelines to reduce its incidence, vary among institutions. From a group of patients uniformly treated with hypofractionated radiotherapy, we correlated the incidence of late rectal toxicity with rectal dose–volume rectal constraints as described in three randomised trials for prostate cancer.

Materials and methods: Favourable-risk prostate cancer patients received a dose of 66 Gy in 22 fractions without hormonal therapy. Toxicity was prospectively assessed using Common Toxicity Criteria v3. The whole or part of the rectum and rectal wall were contoured as an organ at risk for all patients. The rectal constraints of the RTOG 0126, RTOG 0415 and the PROFIT trials were used to correlate with late rectal toxicity.

Results: The median follow-up time was 58 months. Late rectal toxicity was 62, 20 and 18% for grades 0, 1 and 2/3, respectively. No statistically significant correlation was found between late rectal toxicity and the rectal constraints used in the three trials. The number of patients violating the recommended constraints was similar for the group with grade 2/3 toxicity and the group without any toxicity. Analysis derived from the actual dose–volume histogram dose parameters of this group of patients did not show a relationship between dose to volume of the rectum and late rectal toxicity that could generate a guideline of dose constraints.

Conclusion: For this group of patients, despite the use of recognised dose–volume constraint guidelines of three trials, we were unable to establish a relationship between these constraints and the late rectal toxicity registered. Further studies on the correlation of dosimetric parameters with rectal toxicity, particularly for hypofractionated regimens, are required. Non-dosimetric factors may also be involved in the risk of late rectal toxicity.

Key words: Dose–volume constraints; DVH; late rectal toxicity; prostate cancer; radiotherapy

Introduction

Late rectal toxicity is a major concern in curative radiation treatment for localised prostate cancer, particularly with hypofractionated regimens [1–3]. Dose–volume histograms (DVH) have been used as a tool to help predict the likelihood of late toxicity and several studies have reported a correlation between DVH parameters and the incidence of late rectal complications [4–18]. However, there are significant differences in two key areas throughout published studies. First, rectal constraints, set as guidelines to reduce the incidence of late rectal toxicity, vary among studies. Constraints suggested in published studies include, but are not limited to, $V_{40\ Gy}$ (volume of the rectum receiving at least 40 Gy) < 75% [19] or <60% [20], $V_{60\ Gy}$ < 45–50% [4] or 60% [5] or no cut-off value according to Boersma *et al.* [18], $V_{70\ Gy}$ < 25% [11] and even limiting the absolute volume of the rectum receiving more than the prescribed dose to under 15 cm^3 [21]. Each of these DVH constraints was generated based on the toxicity data of a different institution using standard fractionation. Additionally, there remains controversy in how the rectum should be outlined. Whereas some investigators contour the entire rectum, including the cavity [4,20,22,23], others contour only the rectal wall [5,12,17,18]. There is also variation in the length contoured, with some investigators outlining the organ from the anal verge up to the recto-sigmoid junction

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[12,22–24], others considering 11 cm of the rectum as the final volume [6,11], and yet others limiting the length to a few millimetres below and above the planning target volume (PTV) [21,25]. In summary, there is currently no established consensus on dose–volume rectal constraints and on how much rectal volume to contour.

In an attempt to better understand the relationship between the dose delivered to a rectal volume and the probability of late rectal toxicity, we analysed the data from a group of prostate cancer patients with long-term follow-up consistently treated with curative hypofractionated radiation therapy alone and correlated defined rectal constraints, as described in three randomised trials for prostate cancer, to the development of rectal toxicity in such patients. The aim of this study was to validate them and to determine which rectal constraint parameter would have better predicted the late rectal toxicity found in our group of patients.

Materials and Methods

Between October 2002 and April 2004, 71 patients with favourable-risk prostate cancer were treated in our centre with hypofractionated radiation therapy. The clinical outcomes and technical details of this programme are reported elsewhere [26]. Briefly, each patient received a total dose of 66 Gy in 22 fractions (3 Gy/day), prescribed to the isocentre, using a five-field three-dimensional conformal radiotherapy technique with 18 MV photons. According to the linear quadratic formula, using an alpha/beta ratio equal to 3 Gy, 66 Gy in 22 fractions of 3 Gy is biologically equivalent to 78 Gy in 39 fractions of 2 Gy, or 79.2 Gy in 44 fractions of 1.8 Gy. All patients underwent treatment planning computed tomography using 5 mm slice thickness in the supine position. Daily localisation of the prostate was carried out using a transabdominal ultrasound system (BAT, Nomos Corporation, Sewickly, PA, USA). The PTV consisted of the prostate plus a 7 mm margin in all directions. The bladder, femoral heads and rectum were contoured as organs at risk. The field and multileaf collimator shielding were set to treat the PTV conformally (covered by a 95% isodose line relative to 100% at the isocentre). There were no predefined limiting dosimetric constraints for the rectum. None of the patients received hormonal therapy. Follow-up was every 4–6 months, during which the patients had a full clinical assessment, including a digital rectal examination and prostate-specific antigen measurement. Late rectal toxicity, considered to occur beyond 90 days after treatment, was prospectively assessed using the Common Toxicity Criteria v3 scoring system [27]. Patients with rectal bleeding who underwent any endoscopic therapy were considered to have grade 3 rectal toxicity. The highest grade documented at any time was considered as the final late rectal toxicity, even if the complication resolved later on. The date of the event was considered as the date of the first registration of that grade in the patient's medical records. Actuarial curves were generated from these data.

To consistently define the rectal volume and to avoid inter-observer variation, all patients had their treatment plans retrieved and the rectum re-contoured by a single investigator (BJ). The whole rectum and rectal wall were contoured for each patient, both from the anal verge to the sigmoid junction and also 18 mm above and below the prostate. DVHs were then re-generated based on these newly outlined rectal contours. Five patients were excluded from this analysis; in four patients the treatment plan could not be retrieved due to technical difficulties and one patient had had a previous abdomino-perineal resection. Therefore, the total number of subjects for this analysis was 66.

The resulting DVHs for our cohort of patients were compared with the rectal dose–volume constraints recommended by the following three prostate cancer trials: Radiation Therapy Oncology Group (RTOG) 0126 [28], RTOG 0415 [29] and the Canadian PROFIT trial [30]. These three trials were arbitrarily chosen because they were ongoing at our institution at the time of this analysis.

The RTOG 0126 is a phase III randomised trial for intermediate-risk prostate cancer patients comparing 70.2 Gy versus 79.2 Gy in daily fractions of 1.8 Gy with external beam radiation alone. The recommended rectal dose–volume constraints are that no more than 50, 35, 25 and 15% of the whole rectal volume should receive more than 60, 65, 70 and 75 Gy, respectively. Because our patients were treated with 3 Gy per day, the rectal dose–volume constraints of the RTOG 0126 were adjusted to a biologically equivalent dose (BED) using the linear quadratic equation with an alpha/beta ratio of 3 Gy. Thus, the adjusted RTOG 0126 rectal dose–volume constraints are that no more than 50, 35, 25 and 15% of the whole rectal volume should receive more than 48, 52, 56 and 60 Gy, respectively, for a 3 Gy/day regimen.

The RTOG 0415 is a phase III randomised trial for low-risk prostate cancer patients comparing conventionally fractionated 73.4 Gy in 41 fractions of 1.8 Gy with a hypofractionated regimen of 70 Gy in 28 fractions of 2.5 Gy. The recommended rectal dose–volume constraints in this trial for the hypofractionated arm is that no more than 50, 35, 25 and 15% of the rectal volume should receive more than 59, 64, 69 and 74 Gy, respectively. Again, using the linear quadratic formula, the adjusted RTOG 0415 rectal constraints are that no more than 50, 35, 25 and 15% of the rectal volume should receive more than 54, 59, 64 and 69 Gy, respectively, for a 3 Gy/day regimen.

The PROFIT trial compares the hypofractionated regimen of 60 Gy in 20 fractions of 3 Gy each with a conventionally fractionated dose of 78 Gy in 39 fractions of 2 Gy. The recommended rectal constraint for the hypofractionated arm is that not more than 50 and 30% of the rectal wall volume (as defined below) should receive more than 37 and 46 Gy, respectively. This constraint did not need BED adjustment, as the daily dose of 3 Gy was the same as we used in our group of patients.

The two RTOG studies use the whole rectum volume from the anal verge to the recto-sigmoid junction, and the PROFIT trial defines the rectum as the organ at risk as only the rectal wall to a length of 18 mm above and below the