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Original Article

Defining Bowel Dose Volume Constraints for Bladder Radiotherapy Treatment Planning

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Abstract

Aims: Increases to radiotherapy dose are constrained by normal tissue effects. The relationship between bowel dose volume data and late bowel toxicity in patients with muscle-invasive bladder cancer treated with radical radiotherapy was assessed.
Materials and methods: The bowel was contoured retrospectively on radiotherapy plans of 47 patients recruited to the BC2001 trial (CRUK/01/004). The relationship between bowel volume at various dose levels and prospectively collected late bowel toxicity was explored.
Results: Fifteen per cent and 6% of patients experienced grade 1 and grade 2 or more late bowel toxicity, respectively. The mean bowel volume was significantly less at doses $\geq$50 Gy in those treated with reduced high dose volume radiotherapy compared with standard radiotherapy. The probability of late bowel toxicity increased as bowel volume increased ($P \leq 0.05$ for dose levels 30–50 Gy). No grade 2 or more late bowel toxicity was observed in patients with bowel volumes under the thresholds given in the model that predict for 25% probability of late bowel toxicity.
Conclusions: There is a dose volume effect for late bowel toxicity in radical bladder radiotherapy. We have modelled the probability of late bowel toxicity from absolute bowel volumes to guide clinicians in assessing radical bladder radiotherapy plans. Thresholds predicting for a 25% probability of late bowel toxicity are proposed as dose volume constraints.

Key words: Bladder radiotherapy; bowel constraints; dose escalation; radiotherapy planning

Introduction

Radical radiotherapy is an alternative to cystectomy for the treatment of localised muscle-invasive bladder carcinoma, as part of a multimodality approach to bladder preservation, with surgery reserved for the salvage of local failure. Although there have been no reports of randomised data comparing the two approaches, despite attempts [1], modern series combining endoscopic resection, systemic neoadjuvant platinum-based chemotherapy and conformal radiotherapy techniques suggest comparable survival rates to surgery [2–4]. More recently, improved outcome with the addition of concomitant chemotherapy or carbogen and nicotinamide has been shown [5,6].

A strategy to improve outcome from the bladder-sparing approach is to escalate the radiotherapy dose [7,8], but the development of dose-escalation studies has been hampered by a number of factors. First, the traditional clinical target volume for the maximum prescribed dose was the whole bladder [9]. However, after either brachytherapy or localised partial bladder external beam radiotherapy, <10% of local disease relapse has been observed at a site distant to the tumour within the bladder [10,11]. This observation led to a number of studies using the technique of reduced high dose volume bladder radiotherapy with encouraging results [12–14]. Reducing the volume treated to a high dose has the potential to allow for dose escalation within normal tissue constraints.

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Second, the magnitude of variation in size, shape and position of the bladder during a course of radiotherapy has necessitated a large planning target volume (PTV) margin of 1.5–3.0 cm, with the aim of avoiding geographical miss at treatment delivery, but with the consequent irradiation of large volumes of surrounding normal tissues [15–19]. With the recent development of image-guided individualised adaptive radiotherapy techniques, a reduction in treatment volumes is possible [20–27]. A consequent reduction in the volume of surrounding normal tissue receiving high doses of radiation is associated with lower acute and late toxicity rates [28] and therefore may facilitate target dose escalation.

Finally, for the development of safe dose-escalation studies, normal tissue dose constraints, particularly at doses of radiation higher than traditionally used for bladder radiotherapy, are required for estimates of toxicity and to allow the comparison of the relative merits of radiotherapy plans. There is evidence of dose volume relationships for bladder, rectum and bowel toxicity [29]. Previous reports suggest that the risk of global injury to the whole bladder $\geq$ grade 3 is $\leq$6% after a dose of 64 Gy, whereas a 5–10% risk of focal bladder injury $\geq$ grade 3 is observed after about 20% of the bladder receives 70–75 Gy [30,31]. The dose volume relationship for the rectum has been well established in the literature, with sufficient late toxicity data for rectal dose constraints [32,33]. However, there are limited dose volume data available to guide clinicians on dose constraints for bowel other than rectum [34].

The aim of this study was to assess the relationship between bowel dose volume data and prospectively collected late bowel toxicity data in a cohort of patients from a single centre treated within the National Cancer Research Institute Bladder Cancer Trial: BC2001 (ISRCTN 68324339, CRUK/01/004).

Materials and Methods

Patient Population and Treatment Allocation

Between August 2001 and March 2008, 55 patients with localised muscle-invasive transitional cell carcinoma of the bladder (T2-T4a N0 M0) were randomised from a single centre (The Royal Marsden NHS Foundation Trust, Sutton, UK) within the BC2001 multicentre phase III study. The trial had a partial 2 $\times$ 2 factorial design to compare standard whole bladder radiotherapy (SRT) with reduced high dose volume radiotherapy (RHDVRT) with and without concurrent chemotherapy (5-fluorouracil [5-FU] iv at 500 mg/m^2/24 h for 5 days in each of weeks 1 and 4 of radiotherapy and mitomycin 12 mg/m^2 iv on day 1 of radiotherapy). Patients were excluded from the bowel dose volume constraints analysis if there were no late toxicity data available (6 months or more after radiotherapy), if the superior slice of the planning computerised tomography scan was less than 1 cm above the PTV, compromising adequate dose volume assessment of surrounding bowel and if a two-phase radiotherapy technique was used (as composite dose volume data from separate planning computed tomography scans are difficult to assess accurately).

Initial Radiotherapy, Follow-up and Toxicity Data Collection

Details of radiotherapy treatment planning and delivery methods are described in Huddart *et al.* [14]. In brief, patients had planning computed tomography with an empty bladder. For patients allocated SRT, the PTV was the outer bladder wall plus the extravesical extent of tumour with a 1.5 cm margin. Three-dimensional conformal radiation therapy was used to encompass the PTV in the 95% isodose. For RHDVRT patients, two PTVs were defined: PTV1 as for the SRT group and PTV2 as gross tumour volume (i.e. tumour seen on magnetic resonance imaging/computed tomography with guidance of a surgical bladder map) plus a 1.5 cm margin; three-dimensional conformal radiation therapy was used with the aim of delivering 100% of the reference dose to PTV2 and 80% of the reference dose to PTV1. The dose prescribed for this patient cohort was 64 Gy in 32 fractions and this was delivered in a single phase, daily over 6.5 weeks. Patients were followed-up at 6, 9 and 12 months and annually for 5 years after the completion of radiotherapy. The Radiation Therapy Oncology Group (RTOG) toxicity assessment was used to assess baseline symptoms and to prospectively collect late toxicity data at each follow-up appointment.

Retrospective Bowel Assessment

Retrospectively, the radiotherapy planning scans were assessed between April and September 2009. All bowel segments proximal to the rectosigmoid junction and within 2 cm of the PTV were outlined as ‘other bowel’ (OB) by a single observer (FMcD). The rectosigmoid junction was identified on the computed tomography scan at the level the bowel turns anteriorly, close to the inferior level of the sacroiliac joints. The absolute volume of OB in cubic centimetres at various dose levels on the plan was recorded.

Statistical Analysis

The Mann-Whitney U test was used to compare treatment groups in terms of worst late bowel toxicity experienced at any time point and the volume of OB at each dose level. Logistic regression was used for each dose level separately to predict the probability of any grade RTOG late bowel toxicity from OB volume at that dose level. Sets of recommended dose constraints were derived, taking as constraints the volume at which the predicted probability of RTOG late bowel toxicity reached a fixed limit (separate sets of constraints derived for 20, 25, 30 and 40% probabilities). The number of constraints missed by each patient was assessed compared with the worst reported RTOG late bowel toxicity.