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Original Article

Short-term Toxicity of High Dose Rate Brachytherapy in Prostate Cancer Patients with Inflammatory Bowel Disease

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Abstract

Aims: Inflammatory bowel disease (IBD) has historically been considered a risk factor for increased bowel toxicity in patients receiving pelvic external beam radiotherapy. The risk is reduced in intensity-modulated radiotherapy compared with three-dimensional conformal radiotherapy. The effect of brachytherapy has been less extensively researched. Despite the increased dose to the gross tumour volume and decreased dose to organs at risk, previous studies have recommended avoidance of low dose rate (LDR) brachytherapy in patients with IBD, due to increased bowel toxicity. We investigated the effect of high dose rate (HDR) brachytherapy in IBD.

Materials and methods: Eleven IBD patients across four different sites (in the UK and Spain) who received HDR brachytherapy, between 2012 and 2015, were followed for up to 12 months. Acute bowel and urinary toxicity data were collected and recorded.

Results: The median length of follow-up was 6 months (range between 6 weeks and 12 months). Five patients had Crohn's disease and six patients had ulcerative colitis. Only one patient (with Crohn's disease) had active disease at the time of treatment. This patient reported no bowel toxicity. Of the remaining patients, two suffered grade 1 diarrhoea (at 6 weeks and 6 months); three suffered grade 1 proctitis (at 6 weeks and 6 months). There was no grade $\geq$2 bowel toxicity. The most severe toxicity was grade 2 urinary frequency in one patient (at 6 weeks).

Discussion: This small, prospective case series suggests that, in the short term, HDR brachytherapy is safe and well tolerated in IBD patients. Therefore, IBD should not automatically disqualify patients from, at least, HDR brachytherapy. The reason why these results differ from previous LDR studies possibly reflects the benefit of inverse planning, which more readily achieves rectal dose constraints in HDR brachytherapy.

Keywords: Brachytherapy; high dose rate; inflammatory bowel disease; low dose rate; prostate cancer; toxicity

Introduction

In the UK, prostate cancer is the most common cancer in men, with an incidence of about 40 000 cases per year. Early and locally advanced prostate cancers are amenable to external beam radiotherapy (EBRT), via three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT). However, brachytherapy has become an increasingly acceptable alternative, for both patients and clinicians alike. The 5 year prostate-specific antigen progression-free survival for prostate cancer treated with a high dose rate (HDR) brachytherapy boost is >90% (low risk disease), >85% (intermediate risk disease) and >65% (high risk disease) [1]. Brachytherapy monotherapy and combining EBRT with a brachytherapy boost have each shown superior biochemical outcomes to EBRT alone [2]. Given these outcomes between brachytherapy and EBRT [3,4], there are a number of possible reasons for preferring brachytherapy over EBRT. The major advantage is that brachytherapy results in minimal dose to the rectum and permits safe dose escalation, compared with EBRT. The logistical advantage of brachytherapy is the avoidance of prolonged treatment times (up to 7.5 weeks in EBRT). Further advantages of HDR brachytherapy include: (i) use of

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a temporary radioactive source, thereby obviating radioprotection concerns; (ii) using after-loading catheters, which can implant prostate, bladder and seminal vesicles, enabling the treatment of more advanced disease; (iii) exploiting hypofractionation in a low α/β tissue, which is radiobiologically more efficient than either low dose rate (LDR) brachytherapy or conventional fractionated EBRT [5].

In this study, we investigated the short-term clinical toxicity of brachytherapy in prostate cancer patients with inflammatory bowel disease (IBD), i.e. Crohn's disease and ulcerative colitis. Previous studies have shown significant bowel toxicity after EBRT in IBD [6]. During 3D-CRT, exposure of organs at risk (OAR) to a low dose 'bowel bath' is associated with an exacerbation of bowel toxicity, such as loose stool and proctitis. IMRT alleviates bowel toxicity, primarily by maximising conformity, and secondarily (with the help of image-guided radiotherapy) by minimising the overall 'bowel bath' to OAR. Theoretically, brachytherapy delivers a higher radiation dose to a smaller gross tumour volume, specifically mitigating dose to relevant OAR, namely bowel. It follows that brachytherapy should further improve bowel toxicity in IBD patients (compared with 3D-CRT and IMRT), by harmonising optimal conformality and image-guided radiotherapy [7]. However, toxicity results from previous LDR brachytherapy studies have been inconsistent. Early studies in 1998 and 2006 suggested that LDR brachytherapy was safe in patients with a history of controlled IBD [8,9], but a more recent 2013 study revealed significant bowel toxicity in IBD patients [10]. In this study, we specifically investigated the short-term clinical toxicity of HDR brachytherapy in IBD.

For prostate cancer patients *without* IBD, the main HDR brachytherapy toxicities are predominantly urinary, rather than bowel. The short-term toxicities include urinary symptoms (dysuria, urinary frequency and urgency) up to 12 weeks and, rarely, urinary clot retention (requiring catheterisation). The long-term toxicities include urethral stricture and impotence [1,7,11,12]. Therefore, the aim of this study was to investigate both gastrointestinal and genitourinary short-term toxicities in a group of patients with IBD, treated with HDR brachytherapy.

Materials and Methods

Eleven patients undergoing brachytherapy for prostate cancer between 2012 and 2015, who also had IBD, were identified from the prospective databases of four brachytherapy centres: Sussex Cancer Centre/Mount Vernon Centre for Cancer Treatment (three patients) and Leeds Teaching Hospitals NHS Trust (five patients) in the UK and Cruces University Hospital in Spain (three patients).

Eligible patients had to have localised or locally advanced prostate cancer suitable for brachytherapy and histologically confirmed IBD (Crohn's disease or ulcerative colitis). IBD could be 'active' or 'quiet' during brachytherapy and any previous abdominal surgery was recorded. Indications for HDR brachytherapy included stage T1b–T3b disease and any Gleason score. Exclusion criteria were distant metastasis, prostate volume >60 ml, poor baseline International Prostate Symptom Score (IPSS) and contraindications to lithotomy or general/spinal anaesthesia.

HDR brachytherapy techniques are well established. Leeds Teaching Hospitals NHS Trust and Cruces University Hospital use ultrasound planning. Sussex Cancer Centre and Mount Vernon Centre for Cancer Treatment use computed tomography planning. In the UK centres, HDR monotherapy was administered, delivering 19 or 20 Gy in one fraction. In Cruces University Hospital, two of the three patients received 37.5 Gy IMRT followed by 15 Gy HDR brachytherapy boost; the third patient received 19 Gy in one fraction HDR monotherapy. The main OARs are the bowel (specifically rectum), urethra and bladder.

Acute gastrointestinal and genitourinary toxicity (CTCAE 4.0) data were prospectively collected, for up to 12 months, in the outpatient follow-up clinic.

Results

Patient characteristics are displayed in Table 1. Eight patients (73%) were on long-term androgen deprivation therapy. The first follow-up appointment was 6 weeks after brachytherapy. Subsequent follow-up appointments were at 6 and 12 months. The median follow-up time was 6 months (range between 6 weeks and 12 months).

Relevant IBD characteristics are displayed in Table 2. Only one patient (9%) had active disease (Crohn's disease) at the time of brachytherapy treatment. This patient reported no gastrointestinal or genitourinary toxicity.

The gastrointestinal and genitourinary toxicities are displayed in Table 3. In summary, two patients (18%) reported grade 1 diarrhoea. One of these had ulcerative colitis, without abdominal surgery (at 6 months); the other had Crohn's disease, with abdominal surgery carried out in 2006 (at 6 weeks). Three patients (27%) reported grade 1 proctitis. Two of these had ulcerative colitis with no surgery (at 6 weeks and 6 months). The third patient had Crohn's disease with surgery carried out in 2006 (at 6 weeks). In our study, only one patient reported both grade 1 diarrhoea and proctitis (at 6 weeks). This patient also had the largest prostate volume, at 52 ml. There was no reported grade ≥2 gastrointestinal toxicity.

The most severe toxicity was grade 2 urinary frequency in one patient (9%) (at 6 weeks). The most common toxicity was grade 1 urinary urgency in seven patients (64%). Six patients (55%) reported grade 1 urinary frequency, two patients (18%) reported grade 1 cystitis and another two patients reported grade 1 urinary retention. There was no reported grade ≥3 genitourinary toxicity.

Discussion

Patients with both IBD and prostate cancer treated with brachytherapy form a rare subset. There has been a reluctance to recommend radiotherapy for patients with IBD, due to the perceived risk of further aggravating underlying

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