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# Short-Term Toxicity of HDR Brachytherapy In Prostate Cancer Patients With Inflammatory Bowel Disease

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## INTRODUCTION

In the UK, prostate cancer is the most common cancer in men, with an incidence of approximately 40,000 cases per year. Early and locally advanced prostate cancers are amenable to external beam radiotherapy (EBRT), via 3D-CRT or IMRT. However, brachytherapy (BT) has become an increasingly acceptable alternative, for both patients and clinicians alike. The 5 year PSA progression free survival for prostate cancer treated with a high dose rate (HDR) BT boost is > 90 % (low risk disease), > 85 % (intermediate risk disease) and > 65 % (high risk disease) (1). BT monotherapy and combining EBRT with a BT boost have each demonstrated superior biochemical outcomes to EBRT alone (2). Given these outcomes between BT and EBRT (3, 4), there are a number of possible reasons for preferring BT over EBRT. The major advantage is that BT results in minimal dose to the rectum and permits safe dose escalation, compared to EBRT. The logistical advantage of BT is the avoidance of prolonged treatment times (up to 7.5 weeks in EBRT). Further advantages of HDR BT include: (i) use of a temporary radioactive source, thereby obviating radio-protection concerns (ii) employing after-loading catheters, which can implant prostate, bladder and seminal vesicles, enabling the treatment of more advanced disease (iii) exploiting hypo-fractionation in a low $\alpha/\beta$ tissue, which is radiobiologically more efficient than either low dose rate (LDR) BT or conventional fractionated EBRT (5).

In this study, we investigated the short-term clinical toxicity of BT in prostate cancer patients with inflammatory bowel disease (IBD) i.e. Crohn's Disease (CD) and Ulcerative Colitis (UC). Previous studies have demonstrated significant bowel toxicity following 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 IGRT) by minimising the overall 'bowel bath' to OAR. Theoretically, BT delivers a higher radiation dose to a smaller GTV (gross tumour volume), specifically mitigating dose to relevant OAR, namely bowel. It follows that BT should further improve bowel toxicity in IBD patients (compared to 3D-CRT and IMRT), by harmonizing optimal conformality and IGRT (7). However, toxicity results from previous LDR BT studies have been inconsistent. Early studies in 1998 and 2006 suggested that LDR BT 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 BT in IBD.

For prostate cancer patients *without* IBD, the main HDR BT 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 catheterization). The long-

term toxicities include urethral stricture and impotence (1, 7, 11, 12). Therefore, the aim of this study was to investigate both gastro-intestinal (GI) and genito-urinary (GU) short-term toxicities in a group of patients with IBD, treated with HDR BT.

**METHODS**

11 patients undergoing BT for prostate cancer between 2012 snd 2015, who also had IBD, were identified from the prospective databases of 4 BT centres: Sussex Cancer Centre/Mount Vernon Centre for Cancer Treatment (3 patients) and Leeds Teaching Hospitals NHS Trust (5 patients) in the UK, and Cruces University Hospital in Spain (3 patients).

Eligible patients had to have localised or locally advanced prostate cancer suitable for BT, and histologically confirmed IBD (CD or UC). IBD could be 'active' or 'quiet' during BT, and any previous abdominal surgery was recorded. Indications for HDR BT included stage T1b – T3b disease and any Gleason score. Exclusion criteria were distant metastasis, prostate volume > 60 ml, poor baseline IPSS score and contra-indications to lithotomy or general/spinal anaesthesia.

HDR BT 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 CT planning. In the UK centres, HDR monotherapy was administered, delivering 19 Gy or 20 Gy in 1 fraction. In Cruces University Hospital, 2 of the 3 patients received 37.5 Gy IMRT followed by 15 Gy HDR BT boost, and the third patient received 19 Gy in 1 fraction HDR monotherapy. The main OAR are the bowel (specifically rectum), urethra and bladder.

Acute GI and GU toxicity (CTCAE 4.0) data was prospectively collected, for up to 12 months, in the outpatient follow up clinic.

**RESULTS**

Patient characteristics are displayed in Table 1. 8 patients (73 %) were on long-term androgen deprivation therapy (ADT). The first follow up appointment was 6 weeks after BT. Subsequent follow up appointments were at 6 months and 12 months. Median follow up time was 6 months (range between 6 weeks and 12 months).

Relevant IBD characteristics are displayed in Table 2. Only 1 patient (9 %) had active disease (CD) at the time of BT treatment. This patient reported no GI or GU toxicity.

The GI and GU toxicities are displayed in Table 3. In summary, 2 patients (18 %) reported Grade 1 diarrhoea. 1 of these had UC, without abdominal surgery (at 6 months), and the other had CD, with abdominal surgery performed in 2006 (at 6 weeks). 3 patients (27 %) reported Grade 1 proctitis. 2 of these had UC with no surgery (at 6 weeks, and 6 months). The third patient had CD with surgery performed in 2006 (at 6 weeks). In our study, only 1 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 GI toxicity.

The most severe toxicity was Grade 2 urinary frequency in 1 patient (9 %) (at 6 weeks). The most common toxicity was Grade 1 urinary urgency in 7 patients (64 %). 6 patients (55 %) reported Grade 1 urinary frequency, 2 patients (18 %) reported Grade 1 cystitis, and another 2 patients reported Grade 1 urinary retention. There was no reported ≥ Grade 3 GU toxicity.

**DISCUSSION**

Patients with both IBD and prostate cancer treated with BT 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 mucosal inflammatory processes. A recently published systematic review of acute and late bowel toxicity in IBD patients receiving EBRT found that the mean rate of acute bowel toxicity ≥ Grade 3 was 15 % (range between 5 % and 29 %). For LDR BT patients, the mean rate of acute bowel toxicity ≥ Grade 3 was 7 % (6).

A previous cohort study demonstrated significant bowel toxicity using LDR BT as monotherapy (10). In that study, 13 prostate cancer patients were followed up for a median duration of 4.2 years. 3 patients had CD, and 10 patients had UC. 23 % developed ≥ Grade 3 GI toxicity within 12 months of LDR BT. Beyond 12 month follow-up, 15 % developed ≥ Grade 3 GI toxicity. 2 patients (15 %) required surgery following BT, for peri-anal fistulas (which developed at 6 months and 19 months following BT). Both of these patients had active UC at the time of BT treatment. GU toxicity was not recorded.

In previous studies, the type of IBD and a history of previous abdominal surgery do not appear to correlate with toxicity. The 2 patients who required surgery subsequent to LDR BT in the study described above had active UC at the time of BT. In this current study, the 1 patient with active CD (and rectal involvement) suffered no toxicities following HDR BT. Therefore, there remains insufficient evidence to associate active IBD at the time of BT with subsequent bowel toxicity.

Although this case series is too small to reach robust conclusions, it suggests that HDR BT is safe and well tolerated in patients with IBD, in the short-term. Bowel toxicity is minimal, while mild urinary toxicity is more common. It may be that bowel toxicity differs between HDR and LDR BT because of the technique; HDR uses real-time and inverse-planning techniques, which more reliably achieve and deliver doses within rectal dose constraints. Also, LDR BT might be compounded by seed migration (5). Whether or not these acute effects in any way predict late effects currently remains unanswered. Defining OAR constraints in prostate HDR BT has proved challenging. Varying dose prescriptions in BT monotherapy versus boost have confounded these definitions. Data from HDR BT in gynaecological malignancies, along with LDR BT have been informative. The proposed rectal dose constraint by GEC/ESTRO is a D2cc ≤ 75 Gy EQD2 (13).

We might intuitively expect the spectrum of radiotherapy bowel toxicity to progressively worsen from ‘no IBD/normal population’ to ‘quiet IBD’ to ‘active IBD’. However, bowel toxicity due to active IBD is an inflammatory process, whereas bowel toxicity due to radiotherapy is less well understood, and thought to represent an ischaemic/fibrotic process (14). Let us hypothesize that these are two mutually exclusive mechanisms, which bring about the same (bowel) toxicity through different pathophysiological pathways. This hypothesis is open to a prediction. If bowel toxicity in active IBD is a distinct pathophysiological process compared to bowel toxicity in radiotherapy, then patients with active IBD should experience no more bowel toxicity than patients without IBD (ischaemic/fibrotic process secondary to radiotherapy predominates in both populations, resulting in equivalent toxicity). However, if active IBD patients suffer worse radiotherapy bowel toxicity, then this suggests that there is some overlap/synergy between the ischaemic/fibrotic and inflammatory processes.

This leads to a second prediction. Drugs used to treat active IBD (e.g. anti-inflammatories, steroids, immunosuppressants or biologics) are effective by neutralising the inflammatory component of IBD bowel toxicity. If bowel toxicity in active IBD is a distinct pathophysiological process compared to

bowel toxicity in radiotherapy, then the use of these drugs in patients with active IBD should restore radiotherapy bowel toxicity to levels comparable to the normal population, barring idiosyncratic radio-sensitising effects (15). However, if there exists overlap/synergy between the pathways, then patients with active IBD should always suffer worse radiotherapy bowel toxicity compared to the normal population (provided their IBD affects the rectum/small bowel in the radiotherapy treatment field). Our data set is simply too small to explore these hypotheses at this time. However, survivorship is becoming an increasing priority for Oncologists (16). To successfully prevent/treat radiotherapy bowel toxicity in IBD patients, we must first understand the mechanisms involved. The concept of different pathophysiological pathways producing the same toxicity/symptoms is by no means a novel idea. As an analogy, we accept that emesis can be driven by central, peripheral or bowel receptor pathways i.e. the same symptom is produced by different mechanisms. This allows us to target our treatment to the underlying cause of the emesis (toxins, motion-sickness, bowel obstruction etc.), rather than the symptom per se. The same principle should apply to treating radiotherapy bowel toxicity in IBD.

Shortcomings of this study relate to the small sample size, and limitations of assessing complex symptomatology related to IBD using the CTCAE scoring system. Patient reported outcomes are recognised as more sensitive than physician scoring (17), and may have elicited more events. However, we feel confident that any major exacerbation of symptoms related to IBD or radiation toxicity would have been identified using the prospective CTCAE scores.

In summary, HDR BT should be considered for patients with a history of proven IBD who require radical non-surgical treatment for both localised and locally advanced prostate cancer. On the basis of the small dataset presented here, we have identified no excess in GI toxicity within the first year as a result of this approach.

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