Radiotherapy - What Dose Is Safe: Improved Oncological Outcomes Vs. Local Toxicity?

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Citation

A Zilm, M Lloyd, J Miller, K Moretti, D Spernat. *Radiotherapy - What Dose Is Safe: Improved Oncological Outcomes Vs. Local Toxicity?*. The Internet Journal of Surgery. 2013 Volume 30 Number 2.

Abstract

Radiotherapy dose escalation has demonstratively improved progression-free survival and overall survival in prostate cancer patients. However, with ever increasing radiation doses the risk of concomitant injury to adjacent organs similarly increases. These risks are mitigated through improved technology and targeted therapy such as 3D conformational radiotherapy (3D CRT) and intensity modulated radiation therapy (IMRT).

Colovesical and prostato-vesical fistulae are known complications of colonic biopsy post-radiotherapy in prostate cancer patients. However, spontaneous formation of colo-prostatic fistulae post external beam radiotherapy without prostate or bowel biopsy has not been previously reported. Herein we report two cases of spontaneous colo-prostatic fistula that were managed at our tertiary referral centre in the last two years.

Neither of these patients had undergone any procedure, urethral or rectal, since their radiotherapy. Both patients had had only one transrectal ultrasound (TRUS) prostate biopsy prior to radiotherapy. Both patients presented with urine leak per rectum (PR). The fistulae were diagnosed on CT cystogram. Neither case spontaneously resolved with simple catheter diversion, and therefore required diverting colostomy and concomitant ileal conduit urinary diversion.

Both patients recovered well at 6 month follow-up and have an improved quality of life despite double stomas. We believe that these cases serve as an important lesson to the potential complications of ever increasing radiotherapy dosing while attempting to improve oncological outcomes.

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in Australian men and is the second most common cause of cancer deaths in Australian men. Around 20,000 new cases are diagnosed in Australia every year (1). Moreover, one in six men is diagnosed with prostate cancer. Treatment options include radiotherapy, radical prostatectomy, active surveillance or a 'watch and wait' approach. With increased prostate cancer screening and detection of prostate cancer the number of men treated with radiotherapy is expected to increase dramatically (2).

Radiotherapy may be delivered by external (EBRT) or internal (Brachytherapy) radiation sources. In external beam radiotherapy a radiation beam is delivered from outside the body to the target tumour through two- or three-dimensional beam arrays using linear accelerators (2). External beam radiotherapy is a flexible non-invasive outpatient therapy that can be used to treat patients with organ confined or locally advanced disease (3). Neoadjuvant androgen deprivation has been demonstrated to improve the efficacy of external beam radiotherapy (EBRT).

Similarly radiotherapy dose escalation has markedly improved progression free survival and overall survival in patients with localised prostate cancer. Unfortunately with conventional external beam radiotherapy a relatively large portion of the rectum and bladder receive the dose of radiation prescribed to the prostate and the risk of concomitant injury to these adjacent organs increases (4).

Advances in delivery technique such as 3-dimensional simulation (3D CRT) and intensity modulated radiation therapy (IMRT) have reduced the risk of normal tissue toxicity and have allowed for higher radiation doses to be delivered compared with conventional methods. Through increased target specificity new technology has permitted escalation of external beam doses to 75-81 Gy (4). Unfortunately, even with the use of new and improved

delivery systems dose escalation is not entirely without risk.

Brachytherapy can be used as the primary treatment modality (monotherapy) or in combination with conformal EBRT and/or androgen deprivation in the treatment of prostate cancer. Monotherapy is most often reserved for use in patients with low-risk prostate cancer. Conversely, high-dose rate brachytherapy in combination with EBRT and androgen deprivation is typically reserved for use in patients with high-risk prostate cancer.

The combination of high-dose rate brachytherapy (HDRB) and external beam radiotherapy has been shown to be the most effective form of dose escalation (5) and is therefore reserved for high risk patients. D'Amico et al. have described a risk stratification model which separates patients with prostate cancer into low, intermediate and high-risk groups. The following criteria are used by this group to identify high-risk prostate cancer patients: PSA > 20 ng/ml, biopsy Gleason Score 8-10, or clinical stage ≥ T2c (6).

High-risk patients are obviously at a greater risk of developing an adverse pathologic outcome or a biochemical recurrence. A recent study by Savdie et al (7) also found HDRB to have both durability and the potential for treatment efficacy compared with radical prostatectomy in high-risk patients. Patients that received HDRB performed better than was predicted by nomogram, whereas patients undergoing radical prostatectomy performed as well as predicted.

Radiotherapy may result in acute and chronic genitourinary and gastrointestinal complications. These complications may have a significant impact on the patients' Quality of Life (QoL). Chronic radiation injuries are often notoriously difficult to treat and add an extra burden to the cost of healthcare. The most common complications of prostate cancer treated with radiotherapy are gastrointestinal and genitourinary injuries (2) and the most important risk factor for tissue injury is the radiation dose delivered (8).

Acute radiation injury is said to occur within 90 days of treatment. Acute radiation injuries include rectal bleeding, irritative symptoms and faecal incontinence. Late or chronic radiation injury occurs within months to years of treatment. Chronic radiation injuries include urethral and ureteric strictures, bladder scarring, bowel perforation and fistulation. The risk of urethral stricture disease may be as high as 20% of patients with HDR brachytherapy and external beam boost (7). The overall incidence of chronic radiation injury to the bowel after radiotherapy to the pelvis is 1-5% (9). Rectal complication rates of 8-10% have been reported with 3D CRT. This is a reduction compared with those seen with conventional techniques such as EBRT. Several studies have shown a decreased rectal dose with IMRT compared with the 3D conformational technique, with an associated decrease in chronic gastrointestinal morbidity (10).

Formation of rectovesical fistulae following bowel or bladder biopsy post-radiotherapy in patients with prostate cancer has been previously reported in several studies and is considered to be a known complication. Similarly, spontaneous vagino-colonic fistulae have been reported with HDR brachytherapy. However, the spontaneous formation of rectal-prostatic fistulae post external beam radiotherapy in the absence of prostate or bowel biopsy has not been previously reported.

Herein we report two cases of spontaneous recto-prostatic fistula formation in patients with prostate cancer following treatment with external beam radiotherapy. Both patients were managed at our tertiary referral centre in the last two years. We believe that these cases serve as an important lesson to the potential complications of ever- increasing dose escalation in radiotherapy while attempting to improve oncological outcomes.

CASE REPORTS

Case 1:

A 62-year-old man with high-risk, localised adenocarcinoma of the prostate was referred to our tertiary referral centre in 2005 at the age of 54 years with a PSA of 20. A transrectal ultrasound-guided prostatic biopsy confirmed Gleason score 7 adenocarcinoma of the prostate. There was no perineural invasion. Staging scans were clear. On MRI the capsule was noted to be intact and there was no evidence of seminal vesicle invasion. In 2006, after staging, the patient was treated with external beam radiotherapy and neoadjuvant androgen deprivation (Androcur) for high risk prostate cancer. His treatment was complicated by severe radiation proctitis which resolved after treatment.

Two years later the patient represented with urine leakage per rectum associated with intermittent rectal urgency, perianal pain and excoriation, and fecaluria. There was a palpable defect at the anterior rectal wall on digital rectal examination. A CT cystogram demonstrated gas within the bladder and a 1cm rectovesical fistula, tracking from the prostate to the rectum.

The patient was initially managed conservatively with broad-spectrum intravenous antibiotics and simple urinary diversion via indwelling urinary catheter (IDC). The fistula did not resolve with these conservative measures and consequently the patient was admitted for an elective diverting colostomy and concomitant ileal conduit for urinary diversion. The patient remained in hospital for almost two months post-operatively. His recovery was complicated by a small bowel obstruction secondary to adhesions. He underwent re-look laparotomy, division of adhesions and a small bowel resection. His post-operative recovery was uneventful; he was discharged to a rehabilitation hospital shortly after the operation and eventually returned home.

Case 2:

A 72-year-old man referred to our tertiary referral centre with a PSA of eight in January 1998. Transrectal ultrasound guided prostatic biopsy confirmed Gleason 6 adenocarcinoma of the prostate. At that time there was no metastatic disease on staging scans. He was commenced on neoadjuvant hormonal therapy and subsequently completed seven weeks of external beam radiotherapy, receiving 66Gy in 33 fractions.

During the course of his radiotherapy treatment he developed a mild cystitis which resolved on completion of treatment. His PSA remained within normal range until 2002. In 2002, the patient suffered a biochemical relapse and was commenced on maximum androgen blockade with Goserelin and Bicalutamide. The patient remained asymptomatic for almost 10 years after initial diagnosis. Unfortunately, after this period, he developed bladder failure and required a long-term suprapubic catheter. He also required prolonged treatment with antibiotics for recurrent urinary tract infections.

In 2011, the patient presented with pneumaturia, faecal material in his suprapubic catheter (SPC) and urine leak per rectum. A CT cystogram was performed and showed a recto-prostatic fistula. As the fistulae failed to heal with conservative diversion in December 2011 the patient was re-admitted for an elective ileal conduit urinary diversion and end colostomy. On rigid cystoscopy he was noted to have a tight and fibrotic urethra, slough overlying the left side of bladder neck/prostate region and fecal material in bladder. There were no post-operative complications and the patient was discharged on day 10 post-operatively.

Both patients made a good recovery by their 6 month follow-up and reported a significant improvement in their quality of life despite double stomas.

DISCUSSION

Careful planning and the development of new, more specific radiation delivery systems has significantly reduced the risk of developing serious complications during and after radiotherapy treatment. Unfortunately, a large number of patients continue to sustain permanent injuries to their bladder and bowel during and after radiotherapy. Managing radiation injuries such as fistulation can be very challenging and may require radical surgical intervention.

Moreover, radiotherapy is often reserved for patients who are not suitable for radical prostatectomy because of their medical comorbidities, advanced age and BMI. New radiation delivery systems minimise radiation-induced injury to surrounding tissues; however, they do not remove the risk entirely. Understanding the nature and extent of radiation therapy complications will help to improve our understanding of the pathophysiology of radiation injury. We believe that these cases serve as an important lesson to the potential complications of ever-increasing radiotherapy dosing while attempting to improve oncological outcomes.

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