ABSTRACT

Objective

Complications are an undesired side effect of any treatment and radiotherapy is no different. The aim of this study was to quantify the burden of these side effects in a tertiary referral urology department.

Patients and methods

A prospective study of all urology admissions in a six-month period to a public urology department at a tertiary hospital was performed. Patients admitted with complications due to radiotherapy were included in the study. Data obtained included patient demographics, radiotherapy details, complication type and the management required.

Results

A total of 1198 patients were admitted; 921 (77%) were elective and 277 (23%) were emergency admissions. 13 out of 921 (1.4%) of elective admissions and 20 out of 277 (7.2%) of emergency admissions were due to radiotherapy complications. Radiotherapy complications was the fourth most common reason for emergency admission, ahead of acute urinary retention. 21 patients accounted for these 33 admissions. 39 separate complications due to radiotherapy were diagnosed, with some patients having multiple complications. The median time to onset of complication was four years, IQR (1-9). The surgical intervention rate was 67%. The commonest procedures were washout with/without clot evacuation or diathermy in theatre (15.8%) and urethral dilatation/bladder neck incision (15.8%). Two urinary diversions and two cystoprostatectomy & urinary diversion was performed.

Conclusion

Radiotherapy complications are consequential and account for a significant proportion of a tertiary urology department's emergency workload. These complications generally occur years after radiotherapy and frequently require surgical intervention.

INTRODUCTION

Radiotherapy is an important part of the modern multidisciplinary approach to urological cancer. It is used in both primary and adjuvant settings, and the palliative benefits of radiation are well recognised. Until

recently, up to 60% of prostate cancer patients and 58% of bladder cancer patients received at least one course of radiotherapy during their lifetime (1) (2). This rate will have diminished with the advent of active surveillance for prostate cancer and more modern approaches to managing bladder cancer. Despite these changes in the management of some urological cancers, radiotherapy will continue to play an integral role.

The main disadvantage of radiotherapy is the damage to normal tissues that can occur during treatments. The degree of radiation-induced injury depends on total radiation dose, dose per fraction, volume of tissue irradiated, method of delivery, as well as patient factors and comorbidities (3) (4). Specific urological complications of radiotherapy include radiation cystitis, ureteric stricture, ureteric fistula, urethral stricture, urethral fistula, infertility and erectile dysfunction (5). These complications can be challenging to manage; patients tend to be older and frequently require surgical intervention, the outcome of which is compromised due to poor wound healing (6). Additionally, the true incidence of radiation-related complications may be understated when compared with outcomes reported in randomised controlled trials (RCTs). This is because these side-effects often occur late and outside the follow up period (7) (8).

The aim of this study was to assess all urological admissions to our institution related to the side effects and complications of radiotherapy. Our objective is to define the common radiotherapy complications presenting to urology departments, the specific treatments needed and report the burden these complications place on our healthcare system.

METHODS

Patient population

A prospective study of all patients admitted to a tertiary urology department from November 2015 to May 2016 was performed. Institutional ethics board approval was obtained prior to collection of data. Subjects included those who were admitted with a complication of radiotherapy. Radiotherapy complications were defined according to the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) toxicity criteria (9).

Data collection

Data obtained included: age, sex, American Society of Anaesthesiologists (ASA) score, co-morbidities, medications, smoking status, primary malignancy treated by radiotherapy, radiotherapy type (external beam radiation therapy (EBRT), intensity-modulated radiation therapy (IMRT), image guided radiation therapy (IGRT) or brachytherapy), dose in Gray (Gy) and fraction, number of admissions, type of admission (elective or emergency), complication and intervention. An emergency admission was defined as any admission that was unplanned, unpredictable and at short notice because of clinical need. Length of stay and total bed days, including total intensive care unit (ICU) bed days, were noted. In terms of absolute costs, patients treated at our institution may choose to use their private insurance within a public hospital setting. The cost incurred for all patients utilising private insurance was also documented.

Complication classification

Complications were divided into sub-categories (cystitis, fistula, stricture, bladder neck stenosis, lymphocoele). Data on management was divided into non-operative and operative. Routine postoperative care was provided to patients who underwent surgical intervention and each patient was followed up for a minimum of 30 days. Unless otherwise stated, data is represented as median (interquartile range); N represents the number of patients included in the analysis.

RESULTS

Admission data and admissions due to radiotherapy complications

There were 1198 admissions; 921 (77%) were elective and 277 (23%) were emergency. 33 (2.9%) of total admissions were due to radiotherapy complications. 13 (1.4%) of elective admissions and 20 (7.2%) of emergency admissions were due to radiotherapy complications. Radiotherapy complications was the fourth most common reason for an emergency admission and was a more common emergency admission reason then acute urinary retention. Table 1 lists the admission reasons of all emergency admissions during the study period.

Radiotherapy patient demographics and clinical data

The median age of the patients in this cohort was 79 years, IQR (71 – 82); 19 (90.5%) were male and 2 (9.5%) were female. 52.4% of patients were on some form of anticoagulation/antiplatelet therapy. Prostate cancer was the primary malignancy in 15 patients, urothelial cancer for 4 patients and non-urological cancers for 2 patients. Of the 15 patients with prostate cancer, 4 patients underwent a radical prostatectomy prior to radiotherapy. The main mode of radiation therapy was EBRT (61.9%). The median dose was 2 Gy per fraction, IQR (2) and the median number of fractions was 34.5, IQR (31.8 – 37.5). The median overall dose of radiation was 70 Gy, IQR (65.8 – 75). The median time from treatment to admission for complication was 4 years, IQR (1 – 9). Table 2 summarises the demographic and clinical data of these patients.

Urological admissions, radiotherapy complication type & management

During the 33 admissions, 39 separate radiotherapy complications were managed. Radiation cystitis was the commonest complication and accounted for 51.2% of admissions. Strictures (6 ureteric, 3 urethral) were the next most common and accounted for 23.1% of admissions. There were 4 cases of bladder neck contracture and 1 case of a pelvic lymphocoele. In the case of the radiotherapy-related lymphocoele, the patient had undergone a radical prostatectomy without lymph node dissection and subsequently developed a lymphocoele as a result of adjuvant radiotherapy. Fistulae accounted for a total of 5 presentations in 3 patients. There were 3 presentations with prostatic-rectal fistulae amongst 2 patients (one patient represented with the same issue). There was 1 case of perineal-vesical fistula and 1 case of ureteric-iliac artery fistula found in the same patient.

Two-thirds of the radiotherapy complications required surgical intervention. Seven (18.4%) of these were emergencies and nineteen (81.6%) were elective. The commonest emergency procedure performed was endoscopic bladder washout and diathermy for radiation cystitis. The commonest elective procedure performed was urethral dilatation/bladder neck incision (15.8%). Of the patients that required bladder neck incision, 50% had never undergone a radical prostatectomy. Major operations included two urinary diversions, and two cystoprostatectomy and diversion. The indication for urinary diversion in one patient

was a prostatic-rectal fistula, and severe bilateral radiation induced strictures in the second. The indication for both cystoprostatectomy and diversion was intractable radiation cystitis requiring repeated blood transfusions. Figure 1 shows the cystoprostatectomy specimen from one of the patients. The mean length of admission was 6.8 days. Radiotherapy complications accounted for a total of 226 bed days, of which 15 were ICU bed days. Radiotherapy complication data and treatment is summarised in Table 3.

DISCUSSION

Radiotherapy is an invaluable resource and an integral part of the multimodal treatment of patients with cancer, however there are significant drawbacks associated with its use, in particular, radiation induced damage to normal tissues and the resulting side effects and complications. In this study, we demonstrated that over a six-month period, radiotherapy complications account for nearly two percent of elective admissions and over seven percent of emergency admissions. Indeed, radiotherapy complications was the fourth most common cause of emergency admissions and accounted for more admissions than acute urinary retention. The presentations of the radiotherapy complications varied and a wide spectrum was seen, including cystitis, stricture, stenosis, fistula and lymphocoele. Comparable wide variations of complications have been reported and up to 43 potential complications post-radiotherapy for prostate cancer have been catalogued (10). Frequently these complications required surgical intervention and an operative rate of 67% was noted. Similar surgical intervention rates for patients with urinary adverse events after radiotherapy for prostate cancer have been reported (10) (11) (12).

Radiation induced haemorrhagic cystitis was the most common complication and accounted for 70% of the presentations. Haemorrhagic cystitis is challenging to manage as radiation causes ischaemia in the bladder mucosa, which ulcerates and bleeds (13) (14) (15). All patients underwent a washout and continuous irrigation initially on the ward. This was unsuccessful in 28.6% of patients, and endoscopic washout and diathermy was needed. Two patients with severe intractable haemorrhagic cystitis required a cystoprostatectomy and ileal conduit diversion. Our findings are in keeping with data from Meyer *et al,* who similarly noted that patients with complex radiotherapy complications required urinary diversion (16). Strictures were the next most common complication; ureteric strictures were more common than urethral. The six presentations of ureteric strictures were managed with regular JJ stent changes. None of these patients had evidence of metastatic nodal disease which could be a cause of ureteric obstruction. One patient with long bilateral strictures and renal deterioration despite ureteric stenting underwent colonic

conduit urinary diversion. Short urethral strictures can be managed with endoscopic dilatation and internal urethrotomy, but have a high recurrence rate. Urethroplasty may have a higher success rate, but this is limited by radiation damage to normal urethra (17). All three patients had relatively short bulbar urethral strictures and were managed with endoscopic urethral dilatation.

Urinary fistula were the most difficult complication to manage and were the most incapacitating of all the complications encountered (18) . In our cohort, these patients underwent urinary and faecal diversion or, due to other factors, were simply diverted via suprapubic catheter and/or continence aids. At a later date if the patient desired, a fistula repair was attempted. This approach is in keeping with data reported by Lane *et al,* who described treating 22 men with recto-urethral fistulas following primary radiotherapy for prostate cancer (19). No patient in this cohort underwent artificial urinary sphincter (AUS) placement for postprostatectomy stress urinary incontinence (SUI) or had an AUS complication due to radiotherapy in the time period, but it is worth noting that radiotherapy too may increase the complexity of AUS placement (20) (21).

It is well documented that radiotherapy injuries can remain asymptomatic for a long time. Pellerin *et al* studied 39 cases of genitourinary complications following abdominopelvic radiotherapy and found that the mean latent period was 3.5 years for bladder complications and 4 years for ureteric complications, with fistula formation occurring up to 14 years after radiotherapy (22). Faris *et al* looked at urinary diversions after radiation for prostate cancer and noted that the average time between radiation treatment to presentation was 4.6 years (23). We noted a similar figure, with a median time since treatment of 4 years. The long latent time until onset of symptoms of radiotherapy complications may be why some authors have reported higher short term satisfaction rates for radiotherapy over surgery for prostate cancer (24) (25).

There does not appear to be any literature examining the cost burden of radiotherapy complications. We examined the burden of radiotherapy complications by looking at the length of stay, total bed days and ICU bed days. We were unable to calculate the cost of patients belonging to the public sector. However, within the private sector, there were five private patients with nine admissions amongst them. The total cost for these nine admissions was $20803.65 AUD, which averages to be $2311.52 AUD per admission or $520.10 AUD per bed day.

One of the major criticisms of radiotherapy literature is that there is no true equivalence to the Clavien system of complications adopted for surgery. RTOG uses restrictive and limited classifications with little granular value when considering impact on individual patients. Therefore, comparing complications of

surgery and radiation remains problematic. Limitations of the study include the inability to capture patients that may have presented at other hospitals. Also, some cases may be managed initially by consultations in a delayed emergency setting, or in an outpatient setting by urologists, general practitioners or even radiation oncologists. These cases would be missed by our study criteria. Furthermore, the period studied is short and may not reflect the true number of urological complications secondary to radiotherapy; more longitudinal data is desirable and is being collected.

CONCLUSION

Radiotherapy is an extremely useful treatment modality for patients with cancer, however the side effects are significant. In our institution, radiotherapy complications made up a small but important portion of elective and emergency admissions. Multiple different complications were noted that frequently required surgical intervention. In addition, the time from onset of radiotherapy to complication tends to be long, occurring several years after radiotherapy.

CONFLICTS OF INTEREST

None

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FIGURE LEGENDS

Figure 1. Cystoprostatectomy performed for intractable radiation cystitis

Figure A. Note the radiotherapy skin marking in the suprapubic area. The patient had radiotherapy for prostate cancer and was suffering from radiation induced haemorrhagic cystitis that was transfusion dependent. Figure B shows the excised bladder with clot removed; it was abnormally thickened, oedematous and showed all the hallmarks of radiation cystitis. Incidentally, Gleason score 3+3=6 prostate cancer was found in the prostate.

TABLES AND TABLE LEGENDS

Table 1. Emergency admission data

	Total, N (%)
Total	277 (100)
Renal/ureteric calculi	90 (32.4)
Non-radiation induced haematuria	70 (25.2)
UTI/urosepsis/pyelonephritis/renal abscess	24 (8.6)
Radiotherapy complications	20 (7.2)
Acute urinary retention	17 (6.1)
Epididymitis/prostatitis	15 (5.4)
Ureteric obstruction	11 (3.9)
Testicular trauma/torsion/pain	7 (2.5)
Post-operative pain	6 (2.1)
Perinephric/retroperitoneal haemorrhage/AML/kidney rupture	6 (2.1)
Wound dehiscence/infection	2 (0.72)
Scrotal cellulitis	2 (0.72)
Renal cyst/pain/mass	2 (0.72)
Perineal abscess	2 (0.72)
Penile fracture/injury	2 (0.72)
Nephrostomy tube related	1 (0.36)

N; number. %; percentage. UTI; urinary tract infection. AML; angiomyolipoma.

Table 2. Radiotherapy patient demographics and clinical data

	Total, N (%)
Patients	21
Age, median (IQR)	79 (71 – 82)
Male	19 (90.5%)
Female	2 (9.5%)
ASA	
2	4 (19%)
3	14 (66.7%)
4	3 (14.3%)
Anticoagulant/antiplatelet agents	
None	10 (47.6%)
Aspirin	3 (14.3%)
Clopidogrel	2 (9.5%)
Warfarin	2 (9.5%)
Rivaroxaban	3 (14.3%)
Aspirin + apixaban	1 (4.8%)
Co-morbidities	
Diabetes	4 (19%)
Long-term steroid use	3 (14.3%)
Previous androgen deprivation therapy	10 (47.6%)
Primary malignancy	
Prostate	15 (71.4%)
Prior radical prostatectomy	4 (26.7%)
Gleason 3+3	1 (6.7%)
Gleason 3+4	3 (20%)
Gleason 4+3	6 (40%)
Gleason 4+5	4 (26.7%)
Gleason 5+4	1 (6.7%)
Urothelial	4 (19%)
T2	2 (50%)
T3	1 (25%)
T4	1 (25%)

Non-urological	2 (9.5%)
Rectal	1 (50%)
Cervical	1 (50%)
Radiotherapy modality	
EBRT	13 (61.9%)
IMRT	4 (19%)
Brachytherapy	1 (4.8%)
Combination therapy	2 (9.5%)
Unknown	1 (4.8%)
Gray, median (IQR)	2 (2)
Fraction, median (IQR)	34.5 (31.8 – 37.5)
Time since treatment, years , median (IQR)	4 (1 – 9)

N; number. IQR; interquartile range. %; percentage. EBRT; external beam radiotherapy. IMRT; intensity-modulated radiotherapy.

Table 3. Urological admissions and radiotherapy complications

	Total, N (%)
Total admissions	33
Complications	39
Radiation cystitis	20 (51.2%)
Strictures	9 (23.1%)
Ureteric	6 (15.4%)
Urethral	3 (7.7%)
Fistula	5 (12.9%)
Prostatic-rectal	3 (7.7%)
Perineal-vesical	1 (2.6%)
Ureteric-iliac artery	1 (2.6%)
Bladder neck contracture	4 (10.2%)
Pelvic lymphocoele	1 (2.6%)
Management	
Non-operative	13 (33.3%)
Operative	26 (66.6%)
Emergency operations	7 (18.4%)
Washout ± clot evacuation ± diathermy	6 (15.8%)
Nephrostomy tube insertion	1 (2.6%)
Elective operations	19 (81.6%)
Urethral dilatation/bladder neck incision	6 (15.8%)
Stent changes	5 (13.2%)
Conduit diversion	2 (5.3%)
TURP	2 (5.3%)
SPC insertion	1 (2.6%)
TURBT	1 (2.6%)
Cystoprostatectomy and diversion	2 (5.3%)
Mean length of stay	6.8 days
Length of stay, days median (IQR)	1 (0 – 11)
Total bed days	226
Total ICU bed days	15

TURP; transurethral resection of prostate. SPC; suprapubic. TURBT; transurethral resection of bladder tumour. N; number. IQR; interquartile range. %; percentage.

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