Treatment of rectal cancer after previous prostate cancer: A single institution experience

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Abstract. Clinical guidelines typically recommend a combination of chemotherapy, radiotherapy and surgery for the management of newly diagnosed rectal cancer. However, standard-of-care treatment may be high risk or not feasible after prior treatment for prostate cancer. Very few case reports describe outcomes or treatment options in this instance. The aim of the present retrospective study was to determine local treatment patterns and outcomes in patients with this diagnosis. The study population consisted of patients with rectal cancer who were treated at Westmead Hospital (Western Sydney, Australia) between January 2008 and January 2020, and had a background of previously treated or synchronous prostate cancer. A review of electronic medical records was conducted and a descriptive analysis was performed. In total, 15 (6.4%) male patients with rectal cancer had a synchronous or previously treated prostate cancer. Stage II, III and IV rectal cancer was recorded in 60.0, 26.7 and 13.3%, respectively. Overall, 8 patients had previously received definitive intent radiotherapy and did not receive neoadjuvant radiotherapy for their rectal cancer. After a median follow-up time of 2.4 years, 25.0% had experienced loco-regional recurrence and the overall survival rate was 87.5%. A total of 3 patients with higher-stage disease underwent neoadjuvant chemotherapy without radiotherapy, resulting in three R0 resections and no recurrences, at the time of data cut-off. At the centre in the present study, prior prostate cancer affected treatment decisions for newly diagnosed rectal cancer. Neoadjuvant chemotherapy was well tolerated and is an option for patients with stage III disease. Outcomes in patients who did not receive neoadjuvant radiotherapy were acceptable but with high rates of loco-regional recurrence. These findings provide some guidance for other clinicians when making decisions regarding treatment of this challenging disease.

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Introduction

Colorectal cancer is the third most common malignancy in Australia and prostate cancer is the most common malignancy among males (1,2). Prostate and colorectal cancer are also the second and third highest causes of cancer-related mortality in Australia, respectively, behind lung cancer (2). A rise in the incidence of both colorectal cancer and prostate cancer in Australia has occurred over time. This has been attributed to a number of factors, including rising obesity, reduced fibre intake, increased consumption of alcohol and red/processed meat, reduced exercise and increased screening rates (3-5).

Previous cohort studies and three subsequent meta-analyses have found an increase in the risk of rectal cancer, but not colon cancer, following prostate radiotherapy (6-10). This increased risk was only observed when patients were treated with external beam radiotherapy (EBRT) and not with brachytherapy (6,8,10). Notably, this association does not appear to work in reverse, with lower rates of prostate cancer observed in multiple European and Asian cohort studies of patients who have undergone rectal cancer treatment (10-13). There may also be poorer outcomes amongst this cohort of patients with rectal cancer who have previously been treated for prostate cancer (7). A Canadian Registry case-control analysis of 171 patients with prior radiotherapy for prostate cancer found a reduced 5-year survival outcome (42 vs. 62%; P<0.0001) and an increased risk of needing a permanent stoma (14).

The management of rectal cancer in patients who have undergone prior treatment for prostate cancer is challenging. Firstly, prior high-dose radiotherapy is considered a contraindication to neoadjuvant radiotherapy, a treatment with benefits such as improved local control and a trend towards improved overall survival (15). Secondly, prior radiotherapy or prostatectomy may alter the pelvic tissues and lead to higher rates of surgical complications at the time of rectal cancer resection (15). These issues may also pertain to patients who have previously undergone surgery or radiotherapy for other pelvic cancer types, including ovarian and uterine cancer, which are known to be associated with a higher risk of second primary colorectal cancer (16,17).

There has been prior research examining operative outcomes of patients with a background of prior prostate

radiotherapy who have then undergone rectal cancer surgery, but these studies were limited by small patient numbers. An analysis of the Swedish Cancer Registry data of 59 patients found that the anastomotic leak rate after anterior resection was 20% (18). Smaller retrospective case-control reviews have reported prior prostate cancer radiotherapy is associated with increased surgical morbidity, increased rates of anastomotic leakage or definitive stomas, higher relapse rates and reduced rates of overall survival (19-21).

The medical treatment of these patients has not been examined closely and there are limited guidelines to aid treatment plans. One single-centre report of 12 patients with synchronous or metachronous prostate and rectal cancer has been published along with another case series of 3 patients (22,23). There are even fewer reports of the medical management of these patients and the use of neoadjuvant or adjuvant chemotherapy in this cohort. The present study therefore reports on a single-centre retrospective case series of patients who underwent treatment for rectal adenocarcinoma and had a prior history of prostate cancer. The primary aim of this study is to report on the chemotherapy used for these patients and the outcomes or complications experienced during their treatment. Secondary outcomes examined include surgical morbidity, rectal cancer recurrence and overall survival rate.

Patients and methods

Patients. The present study was conducted at Westmead Hospital, a tertiary centre in Western Sydney, New South Wales, Australia. The hospital's cancer-specific electronic medical record system was queried for patients who met the study's inclusion and exclusion criteria. Patients were considered for inclusion if they were aged >18 years, had a diagnosis of rectal or rectosigmoid cancer (ICD codes C19.0-C21.9) between January 1, 2008, and January 1, 2020, and also had a diagnosis of prostate cancer (ICD code C68.0-9), either on the same date or prior to the rectal cancer diagnosis. Cases of stage I-IV disease, as defined by the American Joint Committee on Cancer 7th edition (AJCC-7), were included for review (24). History of other primary cancer sites (e.g., the lungs or breasts) were not considered for inclusion into the study due to an expected low patient numbers and the low likelihood of significantly affecting rectal cancer treatment decisions.

Patients were excluded if they had a diagnosis of rectal or prostate cancer other than rectal adenocarcinoma (e.g., neuroendocrine carcinoma or mucosal melanoma). Patients were also excluded if they had <6 months of available follow-up data.

Data collection. Patient files were reviewed for data regarding the diagnosis, histopathology, treatment and follow-up of both rectal and prostate cancer. Past medical history was also reviewed for evidence of prior prostate cancer that was not recorded as a primary or secondary diagnosis. Date of diagnosis was defined as the date of the first positive biopsy result. Follow-up data was recorded until the date of the last recorded follow-up visit or the date of death. Tumour response was assessed by the AJCC-7 Tumour Regression Grading (AJCC-TRG) criteria (24). Chemotherapy toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) (25). The cut-off for data analysis was April 20, 2020. Patients were not excluded from the case series on the basis of missing data.

Table I. Clinical characteristics of the patient cohort.

Clinical characteristics	Value
Median age (range), years	74.0 (56.4-91.3)
Male, n (%)	15 (100.0)
Stage, n (%)	
II	9 (60.0)
III	4 (26.7)
IV	2 (13.3)
Location of primary rectal tumour, n (%)	
Low	6 (40.0)
Mid	6 (40.0)
High	3 (20.0)
Histology - adenocarcinoma, n (%)	15 (100.0)
Timing of prior prostate cancer, n (%)	
Prior	12 (80.0)
Concurrent	3 (20.0)
Mean time from prostate cancer radiotherapy to rectal cancer (range), years	7.6 (1.9-12.1)
Treatment intent, n (%)	
Curative	12 (80.0)
Palliative	3 (20.0)
Prior chemotherapy, n (%)	0 (0.0)

Statistical analysis. Due to the low number of patients anticipated to be included in the analysis, data regarding survival and recurrence are reported as percentages to provide an accurate description of outcomes at this hospital rather than an indirect (e.g., Kaplan-Meier) estimation of these outcomes. Overall mortality was defined as death from any cause from the date of rectal cancer diagnosis. Recurrence-free survival was defined as the time from diagnosis to death or recurrence, at any site, of rectal adenocarcinoma.

Ethics. The research project was reviewed by Westmead Hospital Human Research Ethics Committee and received approval to proceed on July 10, 2020 (approval no. 2005-09 QA).

Results

Patient inclusion. A total of 384 patients with a diagnosis of rectal adenocarcinoma were identified. Reasons for exclusion are detailed in Fig. S1. In total, 235 (61.2%) patients were male, and 6.4% (15/235) of the male patients had a prior or synchronous diagnosis of prostate cancer (Table I). The median age at diagnosis was 74.0 years. The majority (80.0%; 12/15) of patients were diagnosed with either low or mid-rectal primary rectal tumours and 13.3% (2/15) of cases were metastatic at the time of diagnosis, 50.0% (1/2) of which were reported as oligometastatic disease. A total of 86.7% (13/15) of tumours were stage II-III. Of the two metastatic tumours identified, one carried a KRAS

Table II. Outcomes of patients undergoing surgery for rectal cancer after prior prostate cancer treatment.

Clinical characteristic	Patients								
	1	2	3	4	5	6	7	8	9
Age, years	81	62	82	77	71	74	75	70	69
Primary tumour location	Low rectal	High rectal	Mid rectal	Low rectal	Low rectal	Mid rectal	Rectal	Mid rectal	Low
TNM staging	T3N0M0	T2N1M0	T4bN2aM0	T4bN1N0	T3N0M0	T4bN0M0	T3N0M0	T3N1M0	T3N2M1
Prior prostatectomy	N	N	N	N	N	N	N	N	Y
Prior radiotherapy	Y	Y	Y	Y	Y	Y	Y	Y	N
Neoadjuvant radiotherapy	N	N	N	N	N	N	N	N	N
Neoadjuvant chemotherapy (cycles, n)	N	N	FOLFOX (12)	FOLFOX (6)	N	N	N	N	XELOX (4)
Surgery type	APR	APR	Exenteration	APR	ULAR	Exenteration	APR	LAR	ULAR
Positive margins	N	N/A	N	N	N	N	N	N	N
Tumour regression score	N/A	N/A	3	2	N/A	N/A	N/A	N/A	0
Permanent stoma	Y	N	Y	Y	N	Y	Y	N	N
Adjuvant chemotherapy	N	Y	N	Y	Y	Y	N	Y	Y
Recurrence	N	N	N	N	Local	N	Regional	N	N
Disease-free survival, years	2.8	7.2	1.0	0.5	3.3	2.0	4.2	2.0	3.5
Deceased	N	N	N	N	Y	N	N	N	N

Y, yes; N, no; FOLFOX, fluorouracil, leucovorin and oxaliplatin; XELOX, capecitabine and oxaliplatin; TNM, Tumor-Node-Metastasis; APR, abdominoperineal resection; ULAR, ultra-low anterior resection; LAR, laparoscopic anterior resection; N/A, (data) not available.

mutation and one was KRAS wild-type. The histopathology reported on all cases confirmed adenocarcinoma and no patients had known cancer syndromes. No mismatch-repair deficiencies in tumours were identified by immunohistochemistry, although the results were unavailable for 40.0% (6/15) of patients.

Overall, 20.0% (3/15) of patients were diagnosed with synchronous rectal and prostate adenocarcinoma. Of the remainder of patients with a prior diagnosis of prostate cancer, 4 had received a prostatectomy and 8 had received radiotherapy for prostate cancer. No cases of metastatic prostate cancer or treatment for metastatic prostate cancer prior to a diagnosis of rectal adenocarcinoma were identified. No patients had received prior chemotherapy for prostate cancer or other malignancies.

Among the 12 patients treated with curative intent, there were no distant recurrences; 3 patients (25.0%) had loco-regional recurrence, 2 patients (16.7%) were treated effectively with curative intent repeat resection and 1 patient (8.3%) died 3 years after their initial diagnosis from complications of unresectable local recurrence.

Outcomes of patients with prior radiotherapy for prostate cancer. In total, 8 patients received radiotherapy of ≥66 Gy for the prior diagnosis of prostate cancer. All patients received EBRT, and no cases of rectal cancer after prior brachytherapy were identified. These patients had marked variations from standard-of-care treatment to account for this. The treatment and outcomes of these patients are documented in Table II. The mean time from the diagnosis of prostate cancer to the diagnosis of rectal adenocarcinoma was 7.7 years, and 87.5% (7/8) of the tumours were located in the mid-low rectum.

None of the 8 patients had neoadjuvant radiotherapy. Despite this, no patients had a positive surgical margin. Only 1 patient was noted to have significant complications post-surgery (anastomotic leak, sepsis and delayed wound healing). In total, 2 patients underwent pelvic exenteration for either stage IIC or IIIC disease. Exenteration was required in the patient with stage IIC disease due to the extent of the primary tumour (T4b) involving the seminal vesicles. In the patient with stage IIIC disease, there was also evidence of a colovesical fistula that necessitated extensive surgery. No reports of significant adhesions or excessive bleeding were identified. Data on volume of estimated blood loss was not collected.

All patients with an indication for adjuvant chemotherapy were well enough to receive adjuvant treatment, although 5-fluorouracil was the only treatment prescribed (either oral or intravenous). No patients received any platinum chemotherapy in the adjuvant setting. No unexpected gastrointestinal toxicity in the context of a history of high-dose EBRT for prostate

cancer was observed. No patients required admission or dose reduction for diarrhoea or colitis.

Overall, 50.0% (4/8) of patients required a permanent stoma. Mean and median patient follow-up time was 2.8 and 2.4 years, respectively. A local relapse was experienced by 25% (2/8) of patients; 1 patient was treated with palliative intent radiotherapy and chemotherapy. The other patient with locoregional recurrence was treated with repeat resection without evidence of further recurrence, at the time of data cut-off. Overall survival rate at the time of data cut-off was 87.5% (7/8). The 1-year all-cause mortality rate was 0.0%.

Experience with neoadjuvant chemotherapy. Neoadjuvant chemotherapy was administered to 3 patients, who received either 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX) or capecitabine/oxaliplatin (XELOX) for up to 12 cycles over 6 months (Table II). Neoadjuvant chemotherapy was administered to patients with more advanced disease (at least stage IIIC). The patient with oligometastatic stage IV disease exhibited a radiological response to chemotherapy. All three patients underwent resection of the primary lesion and any oligometastatic disease. The degree of tumour response, assessed by AJCC-TRG criteria, was variable between the three cases (grade 0, 2 and 3. However, a R0 resection was achieved in all 3 cases and no patient had disease recurrence at the time of data cut-off. No grade three gastrointestinal toxicity was observed in the setting of prior radiotherapy. A single patient had a dose reduction for thrombocytopenia and neuropathy.

Treatment in patients with prior prostatectomy. A total of 4 patients were identified who had undergone a prostatectomy prior to their diagnosis of rectal adenocarcinoma. The mean time between the diagnosis of their prostate and rectal cancer was similar to those who had previously had radiotherapy alone (7.5 vs. 7.7 years).

A single patient was managed with curative intent short-course neoadjuvant radiotherapy, ultra-low anterior resection (ULAR) and adjuvant capecitabine, without recurrence 3 years after surgery. Among the other 3 patients, a 91-year-old patient received palliative radiotherapy alone for rT3N0 disease. An 81-year-old patient was diagnosed with synchronous T3N0 rectal adenocarcinoma and unresectable intra-abdominal sarcoma so was therefore also managed with palliative intent. Finally, a 77-year-old patient presented with advanced *de novo* metastatic disease and was managed with palliative intent. Their subsequent respective overall survival times ranged from <1 month to 2.1 years (Table III).

Management of synchronous prostate and rectal adenocarcinoma. Concurrent rectal and prostate adenocarcinoma was diagnosed in 3 patients (Table IV). All 3 patients had Gleason 7 (3+4) disease of the prostate, node-negative rectal adenocarcinoma, and were treated with curative intent (26). A 56-year-old patient with T2aN0 low rectal adenocarcinoma was treated with 78 Gy radiotherapy to the prostate and 46 Gy concurrent with capecitabine chemoradiotherapy to the rectum, before proceeding to an ULAR. After 3 years, the patient developed a local recurrence of rectal cancer that was re-resected before developing recurrent metastatic rectal adenocarcinoma and dying almost 5 years after their initial diagnosis. A 65-year-old patient with T2aN0 mid-rectal adenocarcinoma received short-course radiotherapy (25 Gy) before proceeding to an abdominoperineal resection and resection of the involved prostate gland. The patient did not experience any recurrence and died 10 years later from lung adenocarcinoma. Finally, a 74-year-old patient with high-rectal T4aN0 adenocarcinoma proceeded with upfront surgery but was considered too frail post-operatively for adjuvant chemotherapy or radiotherapy. The patient remained recurrence-free after 1 year of follow-up.

Table III. Treatment outcomes for patients with palliative intent management.

	Patient details		
Clinical characteristic	10	11	12
Age at diagnosis, years	91	81	77
Tumour stage	IIA	IIA	IV
Prior prostatectomy	Yes	Yes	Yes
Radiotherapy	16 Gy/4#	25 Gy/5#	No
Surgery	No	No	No
Chemotherapy	No	No	No
Cause of death	Rectal cancer	n/a	Rectal cancer
Overall survival, years	1.1	2.1	0.1

Gy, Gray; #, radiotherapy fractions; n/a, not applicable.

Discussion

This case series reports on the management of a subset of patients with rectal adenocarcinoma in conjunction with a diagnosis of either synchronous or previous prostate adenocarcinoma. Often, these patients will be unable to receive standard-of-care management for rectal cancer. To the best of our knowledge, only two prior case series of 3 and 12 patients, respectively, have been identified and there are no recommendations around the management of these patients (22,23). This is reflected in the heterogeneous treatments received.

In terms of the chemotherapy decisions made for the patients in the present study, notably, 3 patients with stage IIIC-IV disease had 3-6 months of 'neoadjuvant' intent chemotherapy with up to 12 cycles of FOLFOX or four cycles of XELOX in place of chemoradiotherapy. Although the patient number in this analysis is too low to comment on efficacy, no marked surgical morbidity was observed and all 3 patients remained recurrence-free at the time of data cut-off. The depth of treatment response was observed to vary, although measuring response to neoadjuvant therapy in rectal cancer is known to be subject to significant inter-observer variability (27). Overall, these data provide some confidence for the use of neoadjuvant chemotherapy alone in patients with more advanced rectal adenocarcinoma, but further evaluation is needed.

Table IV. Treatment and outcomes for patients with synchronous prostate and rectal adenocarcinoma.

	Patient details		
Characteristic	13	14	15
Age, years	56	65	74
Primary tumour location	Low rectal	Mid rectal	High rectal
Tumour stage	IIA	IIA	IIB
Gleason score	7 (3+4)	7 (3+4)	7 (3+4)
Neoadjuvant treatment	RT (25#/46 Gy) concurrent capecitabine	RT (25#[a])	N
Surgery type	ULAR	APR	LAR
Prostate cancer treatment	RT (39#/78 Gy)	Prostatectomy	Active surveillance
Complications	N	N	Ileus, high output stoma
Permanent stoma	N	Y	N
Adjuvant treatment	Capecitabine	N	N
Recurrence	Local (resected)	N	N
Cause of death	Rectal cancer	Lung cancer	n/a
Overall survival, years	4.4	9.8	1.0

RT, radiotherapy; ULAR, ultra-low anterior resection; APR, abdominoperineal resection; LAR, laparoscopic anterior resection; n/a, not applicable. [a]Gy data unavailable.

Patients with lower stage disease (stage IIA-IIIA) who had received prior high-dose radiotherapy to the prostate did not receive neoadjuvant radiotherapy for their rectal cancer and proceeded to surgical resection. No patients received adjuvant platinum-based chemotherapy, which is consistent with the high average age of the patients in this analysis and the lack of significant overall survival benefit in lower stage colorectal adenocarcinoma. The patients who had an indication for adjuvant chemotherapy received 5-flurorouracil alone and there were no reports of early cessation of treatment due to gastrointestinal side effects despite having prior high-dose radiotherapy. This provides further confidence for the use of adjuvant 5-fluorouracil-based chemotherapy despite the patient's history of high-dose radiotherapy to the prostate and surrounding tissues, and Westmead Hospital will continue to utilise this treatment.

However, the instances of loco-regional recurrence (25.0%) were higher than reported in the original trials of neoadjuvant chemoradiotherapy (28). In addition, the present case series found higher rates of permanent stomas (50.0%) compared to prior reports of 35-41% (18-20). One patient died 3 years after their original surgery from complications of loco-regional recurrence. This patient initially had T3N0M0 (stage IIA) rectal adenocarcinoma and underwent curative intent surgery with negative margins and was administered adjuvant capecitabine without neoadjuvant radiotherapy due to a prior history of 74 Gy given to the prostate 13 years prior. It is unclear from these few cases which specific risk factors predispose these patients to loco-regional recurrence. The present study did not compare outcomes with patients who received standard-of-care therapy at Westmead Hospital. These findings could form the basis for additional research in this area, likely requiring a multi-centre collaboration for sufficient patient numbers for statistical analysis. Patients should be counselled on the likely inferior outcomes compared to standard-of-care treatment.

The selection of patients for neoadjuvant chemotherapy vs. upfront surgery is challenging. At Westmead Hospital, patients with stage IIIC disease or higher received 3-6 months of neoadjuvant chemotherapy, whilst those with stage IIIA disease or lower received upfront surgery without neoadjuvant treatment. There were no patients with stage IIIB disease to review. Given the efficacy of neoadjuvant chemotherapy in higher stage disease, we would also consider 3-6 months of neoadjuvant chemotherapy in stage IIIA-B disease of good performance status, given the known benefit of oxaliplatin-based chemotherapy in stage III colorectal adenocarcinoma in the adjuvant setting. However, the decision about neoadjuvant treatment and length of therapy should be guided by the clinical context, response on imaging and surgical feasibility. Given the incomplete pathological response in some patients, we would still consider adjuvant chemotherapy after neoadjuvant treatment, and we would not consider chemotherapy without surgery as a potential treatment option in stage III rectal adenocarcinoma.

One patient was initially diagnosed with colorectal adenocarcinoma invading the prostate. Distinguishing rectal cancer from prostate cancer can be challenging. In this patient, magnetic resonance imaging and a separate prostate biopsy identified a second prostatic malignancy. Histopathological features to distinguish prostate cancer and rectal adenocarcinoma include the presence of columnar cells with basal nuclei and dirty necrosis, respectively. Immunohistochemistry may identify prostate-specific antigen in prostate cancer, or caudal-type homeobox 2 and cytokeratin in colorectal adenocarcinoma (29).

Prior prostatectomy itself was not found to influence treatment decisions significantly, and the treatment decisions were primarily dictated by the overall clinical status of the patient. These patients had a high mean age and the majority did not proceed with curative intent therapy due to co-morbidities. Patients with synchronous prostate and rectal cancer received

heterogenous treatments; however, the number of patients identified was too small to draw further conclusions.

No cases of rectal cancer after prior prostate brachytherapy were reported. Although this is consistent with a previous report that the increased risk of rectal cancer does not extend to brachytherapy patients, it could also reflect lower rates of patients undergoing brachytherapy at our institution (30). It has previously been acknowledged that EBRT is associated with a higher risk of rectal adenocarcinoma (6,8,10). In the present case series, there was insufficient access to the radiotherapy treatment database to assess any relationship between the prior radiotherapy field and the location of the rectal cancer. All patients in this case series had at least stage IIA rectal adenocarcinoma. This selection bias may be due to lower stage disease being managed by the surgical team without referral to the Cancer Care Centre and inclusion into the hospital oncology database. Alternatively, cases of rectal cancer may be diagnosed late or initially misdiagnosed as symptoms of prior prostate cancer therapy. The hospital database does not contain information on the delay in diagnosis so no comment can be made on the potential effect of this on the patients.

The prevalence of prior prostate cancer was 2.1% amongst all patients with rectal cancer at this institution, which is slightly lower than other population-based studies that found a prevalence of 3.3-10.8% (14,20). This could reflect the weakness of a retrospective file review reliant upon accurate documentation of a patient's past medical history. No statistical analysis could be performed on the data due to the low patient numbers, which is a limitation of the present study; therefore, optimal treatment in these patients could not be reported. However, it is not expected that a randomised trial would be able to recruit sufficient numbers to be able to provide prospective data to guide management. In that setting, experience-based medicine provides a guide to the clinician and this case series adds to the existing experience in the literature, with a specific focus on the use of neoadjuvant and adjuvant chemotherapy at Westmead Hospital.

In conclusion, different treatment approaches are usually required in patients diagnosed with rectal adenocarcinoma in conjunction with a prior or synchronous diagnosis of prostate cancer, with limited data to guide treatment decisions. At Westmead Hospital, 8 patients with lower stage disease (stage IIA-IIIA) proceeded to resection without neoadjuvant radiotherapy and loco-regional recurrence rates were high (25.0%). Platinum-based neoadjuvant chemotherapy was utilised in 3 patients with higher stage (stage IIIC-IV) disease without evidence of recurrence at the time of data cut-off. Adjuvant 5-flurorouracil was well tolerated in patients with a history of high-dose EBRT to the prostate. Further research into this cohort of patients is required to better understand their optimal treatment and the role of neoadjuvant chemotherapy.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Authors' contributions

JM gathered and interpreted the data. JM and MW reviewed the data together. JM wrote the initial draft of the manuscript and MW reviewed the initial draft. Both authors read and approved the final manuscript. JM and MW confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The project was reviewed by the Westmead Hospital Human Research Ethics Committee and received approval for publication, approval number 2005-09.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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