

Case Study

Squamous Cell Carcinoma of the Bladder and the Challenges of Treatment for Rarer Histological Variants

Benjamin Eastwood¹ and Jeremy Crew MA, MD, BChir, FRCS(Urol)²¹Medical Sciences Division, University of Oxford, UK²Nuffield Department of Surgical Sciences, University of Oxford, UKKeywords:
Bladder, squamous cell carcinoma, cystectomy.

Key Learning Points**Jeremy Crew**

Bladder cancer is a common cancer and in many cases the treatment is relatively straight forward and the outcome is good. However, the reported case represents a more aggressive form of the disease necessitating a decision to treat the patient aggressively with major surgery with bladder removal (cystectomy) and ileal conduit formation. One of the more important parts of this surgery is preparation of the patient to ensure they understand the potential complications and the impact of the ileal conduit (the stoma). Such surgery has a 90-day mortality of 3% and a complication rate of between 30-60%.

Where possible alternatives to radical surgery must be discussed with the patient. For transitional cell cancer such alternative may include radiotherapy or multimodal therapy as stated in the report. However, in the case reported the histology was a rarer variant of bladder cancer, squamous cell carcinoma. This histological variant carries a worse prognosis as the cancer behave more aggressively. In addition, squamous cell carcinoma is resistant to radiotherapy making this not a viable treatment option. For patients with this variant the mainstay of treatment remains radical cystectomy as described.

The case reports a female patient. Recent data shows that stage for stage female have a worse prognosis than males. The exact reason for this is unclear but contributing factors include the thinness of the female bladder and the high incidence of aggressive variant pathologies such as SCC. Another possibility for the worse outcome is a delay in diagnosis of the bladder cancer. As the report suggests the differential diagnosis includes urinary infections. Historically there was a delay in diagnosing bladder cancer in female patients due to misdiagnosis and treatment for presumed urinary infections. In order to address this the cancer 2 week-wait criteria were altered to included recurrent urinary tract infections. Although no data is presently available it is hoped that this has reduced to time to diagnosis and improved the prognosis in female patients with bladder cancer.

The patient reported did well from her surgery and has a good prognosis with a 5-year cancer specific survival of about 60%. The fact that she has rheumatoid arthritis is a concern going forward as loss of hand function may impact on her ability to manage her stoma.

Introduction

Bladder Cancer (BC) is the 9th most common cancer worldwide and the 10th most common in the UK in terms of incidence.¹ It is more common in men, accounting in the UK for 4% of all new male cancer cases and only 2% in women.² Due to differences in aetiology, progression, and treatment, BC can be divided broadly into non-muscle-invasive bladder cancer (NMIBC, T1) and muscle-invasive bladder cancer (MIBC, T2-4-); often considered separate entities that are stratified during transurethral resection of a bladder tumour (TURBT) which may be curative for NMIBC.³ Patients in whom BC is suspected are investigated with a CT urogram, flexible cystoscopy, and TURBT if the prior findings are positive. For MIBC T2-3, radical cystectomy (RC) often with neo-adjuvant chemotherapy

(NAC) is the gold-standard treatment, although variations are discussed in this article. Trimodal therapy (TMT) involving maximal TURBT + chemoradiotherapy is a regimen designed to spare the bladder and is developing an evidence base as an oncologically equivalent treatment.^{4,5} MIBC T4 has by definition invaded adjacent structures, and therefore RC is often not possible nor adequate and palliation is offered. BC 10-year mean survival with current best treatment is 50%, with 1-year mean survival ranging from 95% for NMIBCs to 35% for MIBC T4.⁶

Case

Ms SM, a usually well 76-year-old lady, phoned her GP with painless visible haematuria. She was afebrile and otherwise well but was prescribed pivmecillinam for a

suspected UTI. Three days later, she presented to A&E “in the worst agony of [her] life” due to urinary retention.

Her symptoms improved after catheterisation, but four hours later her pain and bleeding returned, and she was admitted to Urology. On admission, she reported no history of fevers, night sweats, or weight loss, and indeed no other symptoms.

Her past medical history includes interstitial cystitis confirmed by cystoscopy 20 years prior to the current admission for which she received urethral dilation and cystodistention. She had a Dukes’ A stage caecal adenocarcinoma 25 years prior treated by right hemicolectomy with endoscopic surveillance every 5 years, and a 30-year history of rheumatoid arthritis (RA) which is well-managed with methotrexate (15mg/week) and folic acid (5mg/week). She has no known allergies, is not anticoagulated, and takes no other medications.

Ms SM was never a smoker nor alcohol consumer. She worked as a teacher and since being retired volunteers for a charity. She lives at home with her husband and usually has no difficulties with activities of daily life and maintains a healthy weight. There was no relevant family history, no recent sexual history, and no history or evidence of trauma.

Differentials: UTI, Urolithiasis, Pyelonephritis, Bladder Cancer

Investigations: Basic Observations were stable and in-range (HR 78, RR 16, BP 123/72, T 36.6). Abdominal examination revealed mild suprapubic discomfort on deep palpation and the bladder was percussed up to the umbilicus. Bladder scan revealed a post-void residual volume over 500mL. Bladder washing via 3-way catheter identified old, dark haematuria but no clots and soon started draining clear fluid. Urine dip was negative for nitrites but positive for leukocytes. MSU culture was negative. Blood counts were normal (Hb 131 WCC 8.45 Pl 209).

She was discharged with catheter in situ as she failed a trial without catheter (TWOC) with a post-void residual volume of 301mL. Follow-up was done according to the haematuria investigation protocol, involving a CT urogram with contrast and flexible cystoscopy.

CTU identified no upper urinary tract pathology but noted circumferential bladder wall thickening more pronounced posteriorly. Flexible cystoscopy identified this to be a large (4cm) bladder tumour.

TURBT maximally resected the tumour, which was confirmed on histology as pure muscle-invasive SCC. The case was referred to MDT after a CT thorax for complete staging.

Diagnosis: Muscle-invasive squamous cell carcinoma of the bladder currently confined to the muscularis propria (T2) with no evidence of nodal spread (N0) or metastatic disease (M0).

Treatment: RC with ileal conduit formation

The day after her operation, Ms SM was able to walk around her room with assistance but uncomfortable, unable to keep food down, vomiting green liquid due to post-operative bowel immobility. She has since made a full recovery and is at home adjusting to life with a urostoma.

Discussion

Management of BC can be considered as prevention, diagnosis, surgical and medical interventions, and supportive care.

Prevention can be optimised by reducing exposure to risk factors. For all BCs, a positive effect could be expected by encouraging smoking cessation, with half of all BCs attributable to smoking.⁷ By briefly advising patients

who smoke that giving it up could have a great benefit to their health, a Cochrane systematic review found that 1 to 3 more of every 100 patients would go on to quit than would otherwise.⁸

The histological variants of BC have different sets of risk factors. Most western BCs are Transitional/Urothelial Cell Carcinomas (TCCs, ~90-95%) with Squamous Cell Carcinomas (SCCs, 2-5%) being the most common of a handful of rarer malignancies.⁹

SCC has a unique causative factor in schistosomiasis infection and is therefore much more common in areas of the world where the parasite is endemic, such as the Middle East, South-East Asia, and South America. It is therefore subdivided into bilharzia (an alternative name for the causative parasite *Schistosoma haematobium*) associated SCC (B-SCC) and non-bilharzial SCC (NB-SCC), which not only have different geography but also a different typical patient. B-SCC has a marked male dominance (5:1 M:F) and presents most commonly in the fifth decade, while NB-SCC does not display such a male dominance (3:2 M:F) and presents most commonly in the seventh decade.⁹

Other important risk factors historically have been occupational exposure in the rubber, dye, and metalwork industries to known bladder carcinogens such as 2-naphthylamine, which was once widely used in dyes but has since been phased out due to its carcinogenicity.³ It is also a component of tobacco smoke, and is thought to specifically target the bladder because it is conjugated first by the liver and excreted in the urine, but reactivated to carcinogenic 2-aminonaphthol by beta-glucuronidase enzymes in the bladder.¹⁰

Causes of chronic bladder inflammation such as chronic cystitis, cyclophosphamide therapy, recurrent UTI, and indwelling catheters have a weak association with BC, but are typically associated with SCC.^{3,11} Reduction in unnecessary catheterisation is already a recognised objective in healthcare for the prevention of catheter-associated UTIs, and widespread adoption of this practice could help to minimise long-term risks such as BC.¹²

A good occupational, travel, medical, and social history are therefore all important in raising suspicion for BC. As this case demonstrates, it is worth remembering that the most common BC patient (male smoker) is not the same as the typical NB-SCC patient.

Staging and grading of a bladder tumour is an important part of diagnosis for guiding the treatment plan and providing a prognosis. The American Joint Committee on Cancer’s TNM system is widely used for describing BC, whereby the local invasiveness of the tumour is indicated by T0-4 (Figure 1) as determined by TURBT and histological examination, and the spread of the cancer is indicated by the number of positive regional nodes (N0-3) or distant metastases (M0-1) which are identified from staging CT scans. Each tumour is also classified as high- or low-grade based on extent of differentiation on microscopy and each TNM combination can be assigned to a numerical stage 0-IV. For BC, the numerical stage simply reflects the T number, with the exceptions of T4aN0M0 being stage III and any cancer with nodal or metastatic spread being stage IV.¹³

Haematuria investigation protocols are regional guidelines which encourage investigation of these potential BC cases, because BC can present with no other symptoms. Frank (visible) haematuria is a greater cause for concern in this regard than microscopic (dipstick) haematuria, and is the presenting sign in 66% of patients with urological

malignancies.¹⁴ A UK prospective cohort study found that one in twelve women over 60 years old presenting with frank haematuria had a urological malignancy, the vast majority being bladder cancers.¹⁵ It is important to note that this study was done in an emergency department on patients whose GPs had already ruled out UTI.

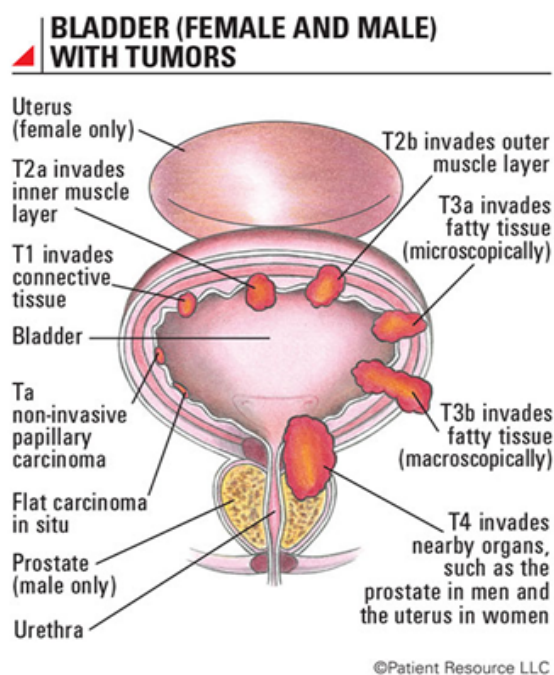


Figure 1 Illustration of T0-4 notation in describing bladder tumours. T4 tumours are also subdivided into T4a and T4b. T4a tumours have spread to the prostate in men or to the uterus and/or vagina in women, while T4b tumours have spread to the pelvic wall or abdominal wall. Image reprinted with permission from Patient Resource LLC. © 2020 Patient Resource LLC.

UTI is a challenging differential diagnosis in elderly patients, as the gold-standard for diagnosis is often considered to be bacteriuria identified by urine culture in the context of the clinical syndrome of UTI.^{16,17} However, elderly patients, and particularly elderly women, often have asymptomatic bacteriuria, making urine cultures an unhelpful tool for differentiating between UTI and other, more sinister causes of urinary symptoms. The urine dipstick for nitrites and leukocyte esterase is also a non-specific test for the same reasons.¹⁸ In the case of Ms SM, a 'trial-of-treatment' approach was used, but this has concerning implications both in terms of antimicrobial custodianship and the risk of coincidental regression of symptoms delaying the true diagnosis.

In this sense, one could argue that she was fortunate her symptoms got worse, and perhaps she should have been referred for investigation regardless. On the other hand, investigation of haematuria in hospital involves invasive procedures such as flexible cystoscopy, which carry their own risks and would perhaps not be reasonable to establish as part of a first-line investigation. However, there is potential value in proactively investigating patients who arouse suspicion as almost 80% of GP-referred/two-week-wait BC diagnoses are caught early at stage I-II but 20% of all bladder cancers are only diagnosed after A&E admission and 50% of those cases are late at stage III-IV.¹⁹

After the diagnosis is made, surgical and medical interventions have two important facets: minimising likelihood of progression or recurrence and optimising

urinary and sexual quality of life (QoL). Standard RC in males involves removal of the bladder, prostate, seminal vesicles, and distal ureters; in females it involves the bladder, entire urethra and adjacent vagina, uterus, and distal ureters, although there are variant procedures to spare certain structures, the risks and benefits to be weighed up on an individual patient basis.²⁰ RC is the basis of gold-standard therapy for MIBC, but by its very nature has a huge potential to impact on QoL, as well as a significant risk of long-term complications associated with urinary diversion, which occur in more than half of patients.⁵ This impact was reflected in a retrospective cohort study in the USA which found that only 42% of patients opted for cystectomy and that increasingly more would be willing to try chemotherapy alone despite its inferior oncologic prognosis.²¹

A bladder-sparing alternative to RC is trimodal therapy, which involves TURBT + chemoradiotherapy, and preserves normal urinary system anatomy and function, removing the need for urinary diversion. The current best evidence to compare these approaches is synthesis of large-scale observational studies as no RCTs have yet compared TMT to RC head-to-head, although the SPARE trial is attempting to do so.⁴ The current studies do suggest that oncological outcomes in carefully selected patients can be similar, and therefore TMT may be a viable option to preserve QoL for a handful of patients.²²

Although the overwhelming majority of BC data exists only for TCC, this data has been extrapolated to guide surgical treatment of variant histologies with success, but vastly differing responses to chemotherapy prove the need for more specific evidence which has not yet been established due to the rarity of the disease.²³ This has implications for the use of both NAC and TMT, which are not currently routinely offered for non-TCC BC.⁹

There is of course no certainty that further investigation would result in uncovering of an effective regimen for NAC or TMT in non-TCC patients, but there is great potential for a significant therapeutic benefit, with a 2016 systematic review demonstrating a hazard ratio of 0.84 (95% CI 0.76-0.93) favouring overall survival of BC with NAC compared to surgery alone.²⁴ The authors noted that their result included mostly TCC patients, but remained significant when a trial including 50% SCC patients (Khaled et al. 2014)²⁵ was included. However, that study itself did not show any benefit to the use of NAC, and therefore is not good evidence to support the practice, but the authors also called for further investigation into the use of TMT and NAC in bladder SCC.

Arguably one of the most important parts of undergoing RC for patients is the accompanying urinary diversion. The most commonly used method is the formation of an ileal conduit, whereby a small part of the ileum forms a connection between the ureters and the abdominal wall, where a stoma is connected. Alternative methods which are rarely used include plumbing the ureters directly into the bowel, carrying with it an increased risk of ascending infection; and directly attaching the ureters to the abdominal wall, which is much less suitable due to the small size of the ureters. Formation of a neobladder is a common technique in which the piece of ileum is used to construct a replacement bladder in an arrangement consistent with the original anatomy.

Making the decision to opt for one method or the other often depends on patients' personal preference but can be constrained by which options are offered at their treatment centre. Neobladders require training of the urinary sphincters and learning a technique called 'abdominal

voiding', where increased intra-abdominal pressure is used to expel urine rather than detrusor contraction. Patients need to be trained to self-catheterise in case they are unable to void, while some experience urinary leakage that persists despite best efforts.²⁶ Urostomy is generally more easily managed but may be unfavourable due to several reasons such as cosmetic concerns, particularly but not exclusively in younger patients.

For many patients, their appointment with the stoma nurse is a memorable experience, as it was for Ms SM. A suitable site for the stoma is located based on how the patient sits, moves, and how their abdominal skin folds. The patient can ask questions and a set of equipment is taken away for the patient to familiarise themselves with. A discussion about treatment would be incomplete without mentioning the importance of appointments such as these in improving patients' experience of such a major procedure.

A final point of discussion for this case is the management of her rheumatoid arthritis. It is common for patients on methotrexate for RA to have their weekly dose held surrounding the date of their surgery. As an immunosuppressant with poor wound healing among the myriad side-effects, it makes logical sense to avoid such a medication in the peri-operative period, although a survey of the literature suggests that there is no consensus on whether such a practice has a grounding in evidence. The majority of evidence comes in the form of retrospective cohort studies, and many of those investigate surgeries related to the rheumatoid disease such as joint arthroscopies, rather than unrelated pathologies. One systematic review assesses the state of the literature for perioperative management in bariatric surgery but found such limited evidence that it could not provide recommendations other than to avoid most immunosuppressive agents in post-operative infection.²⁷ Higher-quality prospective or interventional evidence is required on this topic as it has a potentially significant impact on patient management. For example, a patient with RA may have more difficulty mobilising post-surgery if their condition is not well-controlled, which can affect their bowel motility, QoL, and activities of daily life. More complex patients with multiple co-morbidities should be advised on a case-by-case basis by a rheumatologist, which could be done during the MDT meeting that proves itself consistently to be a vital component of modern patient management.

Conclusions

Although radical cystectomy is the mainstay of treatment for muscle-invasive bladder cancers, transurethral resections and advances in chemoradiotherapy may allow more patients to avoid radical cystectomy. More primary evidence is needed to facilitate similar advances in the treatment of non-TCC histologies. As with many cancers, early diagnosis improves prognosis significantly, and a thorough history, combined with a keen suspicion and vigilance in following up haematuria cases would help in early identification of as many BC cases as possible.

Abbreviations

BC = bladder cancer
BP = blood pressure
(N)B-SCC = (non-)bilharzial associated squamous cell carcinoma
CT(U) = computed tomography (urogram)
Hb = haemoglobin

HR = heart rate
NAC = neo-adjuvant chemotherapy
M:F = male-to-female ratio
MDT = multi-disciplinary team
MSU = mid-stream urine
Pl = platelet count
QoL = quality of life
RA = rheumatoid arthritis
RC = radical cystectomy
RR = respiratory rate
SCC = squamous cell carcinoma
SPARE = Selective bladder Preservation Against Radical Excision
T = temperature
TCC = transitional (urothelial) cell carcinoma
TNM = tumour grade/nodal spread/metastases
TMT = trimodal therapy (TURBT + chemoradiotherapy)
TURBT = trans-urethral resection of a bladder tumour
UTC = urothelial (transitional) cell carcinoma
UTI = urinary tract infection
WCC = white cell count

Conflicts of interest

None.

Funding

None.

Consent

The patient has consented to the publication of this case study.

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