Management of muscle–invasive bladder cancer

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Cancer that has invaded the detrusor muscle can be associated with a high degree of morbidity and mortality. Radical treatments are required, including cystectomy, radiotherapy and chemotherapy. These treatments can cause short–term and long–term consequences for patients. In this article the authors describe the current treatment approaches to muscle–invasive bladder cancer.

Bladder cancer can be clinically classified by stage as either non–muscle invasive (NMIBC) or muscle invasive (MIBC) based on the involvement of the detrusor muscle (Figure 1). Approximately 20% of bladder tumours are muscle invasive at presentation, requiring radical treatment.

Tumour grade is also a well–established predictor of disease progression and bladder cancer specific mortality.1,2 High–grade bladder tumours present a significant risk in terms of disease recurrence, local invasion and metastasis, and are responsible for the high degree of morbidity and mortality associated with bladder cancer.3 High–risk NMIBC can progress to MIBC, and the prognosis is thought to be poorer for progressive disease compared to primary MIBC.4

In the UK, the majority of bladder cancers are transitional cell carcinomas, but there are variants, such as squamous cell carcinoma, adenocarcinoma and small cell cancer, which require different treatment strategies.5

TREATING MUSCLE INVASIVE BLADDER CANCER
NICE has recently published guidelines for the management of bladder cancer.6

The patient should be reviewed in clinic following discussion and review of histology and staging radiology results at the uro–oncology MDT. A thorough assessment of the patient’s cardiac and respiratory function and exercise tolerance...
should be made, and renal function (eGFR) should also be assessed. These assessments will help inform both the patient and the clinical team about the risks posed by major surgery and the potential for chemotherapy.

Patients should be counselled by the bladder cancer team (comprising the urologist performing cystectomy, a clinical oncologist and a nurse specialist) with regard to their treatment options, which include radical cystectomy (RC) with an ileal conduit or neobladder formation, or radical chemoradiotherapy (CRT). Both treatment options may be preceded by neoadjuvant chemotherapy (NAC), which has shown a 5% improvement in survival at 5 years. At the present time, there are no randomised controlled trials comparing the effectiveness of radical cystectomy and CRT. The patient should have the opportunity to discuss surgery and bladder sparing options in detail, including the risks of each procedure.

More advanced cases may be offered palliative radiotherapy, which can ease symptoms such as bleeding and pain. Metastatic disease is managed with systemic chemotherapy.

**RADICAL CYSTECTOMY**

RC has long been considered the standard method of care for MIBC. It usually includes the complete surgical removal of the bladder and prostate in males and the bladder, uterus and part of the vagina in females. Pelvic lymphadenectomy is also performed and may provide both diagnostic and therapeutic benefit. Two randomised clinical trials – the LEA study in Germany and SWOG (South West Oncology Group) – are evaluating the extent of lymph node dissection required and the impact on cancer control.

RC is associated with significant morbidity and mortality. However, improvements in technique and perioperative care have reduced the 90-day mortality rate to 2.1% of patients. Overall complication rates, when collected meticulously and prospectively, are approximately 60%. The procedure carries a significant risk of bleeding requiring blood transfusion. In addition, infection in the surgical wound, chest or pelvis can occur. Other complications, including small bowel anastomotic leak, uretero-ileal anastomotic leakage, rectal injury, deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, and disease recurrence, must all be discussed with the patient.

Recent trials with laparoscopic and robotic RC have also been described. These techniques appear to have similar morbidities, oncological and functional outcomes as open approaches. Blood loss and transfusion rates are lower with minimally invasive surgery, but operative times may be longer than for open surgery. The experience of the operator is an important factor, as with all surgical procedures.

Figueroa et al demonstrated that elderly patients (>70 years) with few comorbidities recovered following RC with clinical and functional results similar to younger patients. Contemporary surgical series (without NAC) have shown 5-year overall, recurrence-free and cancer-specific survival rates of 57.9%, 69.5% and 71.2%, respectively.

**URINARY DIVERSION**

Following removal of the bladder during RC, a ileal conduit or neobladder reconstruction is formed. Ileal conduit is the most commonly used method of urinary diversion in the UK (80%) and involves anastomosing the ureters to an isolated piece of distal ileum. The distal end is then mobilised and brought out as stoma on the right side of the abdomen (Figure 2).

Patients who require an ileal conduit need to be aware of the associated
complications (Table 1), which are relatively frequent in the longer term (over 15 years’ follow-up) with ureteric obstruction reported in 14%, stoma problems in 24%, bowel problems in 24%, UTIs in 20% and metabolic derangement (severe metabolic acidosis) in 1%. Renal insufficiency developed in 27%, although in this elderly, comorbid population it is difficult to determine how much of this is attributable to the diversion.14

Metabolic complications are less common with an ileal conduit than a neobladder, as the conduit does not act as a storage reservoir for urine. The absorption of acid and chloride can result in the development of a hyperchloremic metabolic acidosis. Although this can occur with an ileal conduit, it is more common in neobladders and can be managed with sodium bicarbonate, 1g once daily. The loss of the terminal ileum can result in the malabsorption of vitamin B12 and iron, which may cause macrocytic anaemia and neurological symptoms, although this is rare.

The most common neobladder procedure performed in the UK is Studer pouch reconstruction (Figure 3). This involves using a section of small bowel between 45–60cm long, which is detubularised and reconstructed into a globular shape, forming a new reservoir that replaces the existing bladder. The ureters are implanted into this new reservoir, which is then anastomosed on to the urethra, utilising the patient’s pelvic floor sphincter mechanisms to provide a continent reservoir. For younger patients, neobladder formation is increasingly offered to patients at the time of RC. It has the advantage of not requiring a stoma and 90% of patients are continent by day and 70–80% by night. The disadvantages are that it requires a larger segment of small bowel than an ileal conduit (60cm in the Studer neobladder versus 15cm for an ileal conduit). As such, the rate of metabolic complications is proportionately higher. In more recent studies, intermittent self-catheterisation is required in a minority of patients (10%), with higher rates observed in women.15 For any radical cystectomy procedure, patients also need to be aware of the risks of impotence, incontinence or urinary retention, and female patients aware of the risk of vaginal shortening.

Zippe et al found that fewer than 50% of female patients were able to have successful vaginal intercourse postoperatively and most female patients described reduced satisfaction with their sexual lives following surgery.16 In males, RC can be performed with nerve sparing techniques during the prostatic dissection to preserve sexual function. In females the procedure can be performed with preservation of the vagina.

### CHEMOTHERAPY
RC achieves excellent local control; however, many patients will present with clinically advanced and likely micro-metastatic disease. As a result, there is a role for NAC prior to patients undergoing RC. There is an associated morbidity with NAC which can result in a delay before definitive surgical treatment can be performed, although accelerated chemotherapy regimes have been developed to shorten the time to definitive treatment.

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**Table 1. Potential complications following ileal conduit formation**

<table>
<thead>
<tr>
<th>Early</th>
<th>Late</th>
<th>Metabolic</th>
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<tbody>
<tr>
<td>Ileus</td>
<td>Stomal stenosis</td>
<td>Hyperchloremic metabolic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>acidosis</td>
</tr>
<tr>
<td>Bowel obstruction</td>
<td>Para-stomal hernia</td>
<td>Macrocytic anaemia</td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>Uretero-ileal stenosis</td>
<td></td>
</tr>
<tr>
<td>Ischaemia of conduit</td>
<td>Skin excoriation</td>
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Figure 2. Ileal conduit formation is the most commonly used method of urinary diversion in the UK, and involves anastomosing the ureters to an isolated piece of distal ileum, which is then mobilised and brought out as stoma on the abdomen (reproduced with permission from Macmillan Cancer Support)

Figure 3. Neobladder formation involves using a section of small bowel reconstructed into a globular shape, forming a new reservoir that replaces the existing bladder. The ureters are implanted into this new reservoir, which is then anastomosed on to the urethra, utilising the patient’s pelvic floor sphincter mechanisms to provide a continent reservoir (reproduced with permission from Macmillan Cancer Support)
NAC (prior to RC) is predominantly used in patients with operable muscle-invasive tumours, with the purpose of treating micro-metastatic disease already present at the time of diagnosis.

The administration of NAC may be preferable to postoperative treatment as tumour downstaging through chemotherapy may enhance resectability, metastatic disease may be treated as early as possible, and chemotherapy may be better tolerated than in the adjuvant setting.

Adjuvant chemotherapy is used mostly to prevent recurrence in patients with either advanced disease or where there is regional lymph node involvement.

Currently, the body of evidence supporting preoperative chemotherapy is much stronger than the evidence supporting postoperative chemotherapy. As such, preoperative cisplatin-based combination chemotherapy followed by RC represents a standard therapeutic option for patients with MIBC who are fit for chemotherapy.

**EXTERNAL-BEAM RADIATION THERAPY (EBRT)**

Radiotherapy involves the use of ionising radiation to cause fatal damage to neoplastic cells. A typical course of radical radiotherapy takes either 4 or 6.5 weeks.

Radiation therapy as a single curative modality for MIBC has inferior local control rates compared to radical cystectomy, with 5-year survival between 30-60% depending on the stage. Radiotherapy outcomes can be improved with concurrent chemotherapy or with combined carbogen and nicotinamide administration. When combined with chemotherapy, although local relapse rates can be reduced, there is no benefit in terms of survival, mortality or quality of life.

Smith et al identified no survival advantage following the addition of preoperative radiation therapy to RC when compared to RC alone in a prospective randomised trial.

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Late</th>
</tr>
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<tbody>
<tr>
<td>Bladder</td>
<td>Dysuria, frequency, urgency, radiation induced cystitis, incontinence</td>
<td>Haematuria, reduced bladder volume</td>
</tr>
<tr>
<td>Bowel</td>
<td>Diarrhoea, cramps, radiation enteritis/proctitis, incontinence</td>
<td>Chronic enteritis</td>
</tr>
<tr>
<td>General</td>
<td>Fatigue, skin inflammation</td>
<td>Subcutaneous fibrosis, sexual dysfunction</td>
</tr>
<tr>
<td>Vaginal</td>
<td>Irritation, bleeding, discharge, pain</td>
<td>Shrinkage, adhesions</td>
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*Table 2. Early and late side-effects with external beam radiotherapy*

The best results with EBRT are seen in patients with solitary bladder lesions and without carcinoma *in situ* or evidence of upper tract obstruction.

EBRT is associated with side-effects. Up to half of patients will complain of lower urinary tract symptoms, including dysuria and urinary frequency, during EBRT treatment. This tends to be resolved several weeks after treatment. In addition, 15% of patients report bowel side-effects secondary to EBRT.

Radiotherapy can cause early side-effects that come on during the course, but can settle after 4 to 6 weeks, or late and often lasting adverse effects (Table 2).

Although the 5-year survival rates are better with RC, this may be because patients with significant comorbidities are more likely to be given radical radiotherapy, whereas patients who are stronger and have better general health are put forward for surgery. A staging effect may be another possible factor, as staging is more accurate following surgery. Management following either RC or EBRT according to NICE guidance is given in Table 3.

**CONCLUSION**

Treatment for MIBC is associated with significant morbidity. Patients need to be counselled extensively prior to commencing treatment, and healthcare professionals need to be aware of the long-term sequelae.

<table>
<thead>
<tr>
<th>Following radical cystectomy</th>
<th>Following radical radiotherapy</th>
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<tr>
<td>Monitor upper tracts annually for hydronephrosis, stones, cancer</td>
<td>Rigid cystoscopy 3 months after completion of radiotherapy</td>
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<tr>
<td>Monitor eGFR annually</td>
<td>Then cystoscopy every 3 months for first 2 years</td>
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<tr>
<td>CT chest/abdomen/pelvis to assess for local and distant recurrence at 6, 12 and 24 months post-cystectomy</td>
<td>Then cystoscopy every 6 months for the next 2 years</td>
</tr>
<tr>
<td>Then annual cystoscopy thereafter</td>
<td></td>
</tr>
<tr>
<td>Monitor annually for metabolic acidosis, vitamin B12 and folate deficiency</td>
<td>Upper tract imaging annually for 5 years</td>
</tr>
<tr>
<td>Male patients: urethral washings and annual urethroscopy for 5 years</td>
<td>CT chest/abdomen/pelvis to assess for local and distant recurrence at 6, 12 and 24 months post radiotherapy</td>
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*Table 3. Follow-up after treatment for muscle-invasive bladder cancer according to NICE guidance*
Declaration of interests
Jo Cresswell has received an honorarium from Prostrakan as an invited speaker and from Abbott as a member of an advisory panel.

REFERENCES