Progress in the management of solid tumours

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Bladder cancer

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Summary

Bladder cancer is the fourth most common cancer in England and Wales. The most common presenting symptom is macroscopic haematuria. The management options for superficial and invasive bladder cancer depend on the stage at presentation. Most superficial bladder cancers are managed by transurethral resection and cystoscopic follow-up. The prognosis for patients with invasive bladder cancer is less good. The roles of chemical, radiotherapeutic and surgical intervention are discussed

Keywords: bladder cancer, haematuria

Each year in England and Wales, 8000 men and 3000 women develop cancer of the bladder; it is the fourth most common cancer after lung, colorectal and prostate/breast cancer.¹ In the developed world, transitional cell carcinoma (rather than squamous or adenocarcinoma) is responsible for most bladder carcinoma. About 25% of newly diagnosed cancers are muscle invasive (T2–T4); the remainder are superficial (70%), classified as limited to the mucosa (pTa), lamina propria (pT1) or being *in situ* changes (Tis, 5%).

Its aetiology is heavily dependent on chemical exposure from smoking and occupation, although genetic polymorphisms for certain enzymes involved in detoxification affect susceptibility. These include *N*-acetyl transferase, one of the cytochrome P450s (CYP 2D6) and glutathione transferase M1.² Squamous metaplasia induced by stones, strictures and infection by *Schistosoma haematobium* is a risk factor in the development of squamous carcinoma.

Nonrandom chromosomal deletions have been reported in bladder cancer. These include losses from chromosome 9 found in early stage disease.³ Deletions of 17p (including mutations in p53) and 13p (Rb) are associated with advanced bladder cancer.^{4,5} Overexpression of several oncogenes has been described including ras, myc and *c-erbB-2*. Although ras mutations are not associated with any particular stage,⁶ overexpression of *c-erbB-2* and epidermal growth factor receptor are associated with muscle invasion.⁷

Presentation

The most common symptom is painless macroscopic haematuria; irritative symptoms such as frequency, urgency and pain signify the presence of carcinoma *in situ* (cis) or invasive bladder cancer. Less common complaints are loin pain from ureteric obstruction, lymphoedema due to metastatic disease and nonspecific symptoms from metastatic disease.

MICROSCOPIC HAEMATURIA AND SCREENING

Five to ten per cent of patients over 50 years of age with microscopic haematuria detected by urine strips have bladder cancer; microscopic haematuria should therefore be investigated. However, it does not follow that widespread screening will improve health. Screening patients who have been occupationally exposed is carried out by regular cytological testing of urine.

Diagnosis

Open access haematuria clinics in which patients can be seen and assessed without delay have been set up, but we do not yet know if they have survival benefit.⁸ A full history is taken, including potential exposure to carcinogens, and physical examination is performed; intravenous urography to image the upper tract (or kidney–ureter–bladder plus ultrasound) and flexible cystoscopy under local anaesthesia are carried out. Investigations include blood tests, and a midstream sample of urine for culture and cytological examination. An intravenous urogram is important because it may detect upper tract tumours or dilatation caused by muscle invasion growth into the intramural ureters.

Staging

Once the diagnosis is established, a careful cysto-urethroscopy and examination under anaesthetic are performed; this includes taking bladder washings and mucosal biopsy distant from the primary tumour to determine whether there are changes of carcinoma *in situ*. A soft mass may be palpable which disappears after resection (T1), irregularity signifies superficial invasion (T2) while

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Figure Diagram illustrating the pathological staging of bladder tumour from resected specimens: Tis, carcinoma in situ; Ta, no lamina propria invasion; T1, invasion through lamina propria but confined within the submucosa; T2, invasion of the superficial muscle; T3, deep muscle involvement; T4, involvement of adjacent organs (refer to box 1 for details of TNM classification)

TMN classification of bladder cancer	
Tis	pre-invasive carcinoma (carcinoma in situ)
Ta	papillary non-invasive carcinoma showing no lamina propria invasion
T1	tumour invading beyond the lamina propria but confined within the submucosal tissue
T2	tumour invading the superficial muscle
T3a	tumour invading the deep muscle
T3b	tumour invading through the bladder wall
T4a	tumour infiltrating the prostate in men and uterus or vagina in women
T4b	tumour fixed to the pelvic wall and/or abdominal wall
N1	single ipsilateral regional lymph node involvement
N2	contralateral or bilateral or multiple regional lymph node involvement
N3	fixed regional lymph nodes as a fixed mass separated from the tumour within the bladder
N4	juxta-regional lymph node involvement
M1	distant metastases

Box 1

invasion into deep muscle produces a mobile mass (T3). Fixation suggests involvement of adjacent organs or the pelvic wall (T4).

Initial assessment must include a thorough transurethral resection to include underlying detrusor muscle. Histopathological staging and grading will detect whether lamina propria or detrusor is involved (figure). Computed tomography of the pelvis and abdomen is performed in patients with invasive tumours to define local invasion, lymph node enlargement and assess resectability. However, recent endoscopic surgery may result in over-staging owing to oedema. The bladder tumour is then assigned an appropriate TNM stage (box 1).

Management of superficial bladder cancer (pTa, pT1 and Tis)

Most superficial carcinomas are managed by transurethral resection followed by regular cystoscopic follow-up. The survival rate is excellent. However, 60% to 70% of tumours recur⁹ and 5% of pTa and 25% of pT1 tumours progress to invasive or metastatic cancer.¹⁰ Features associated with future progression include size, multi-focality, high grade, invasion of the lamina propria (pT1), lymphatic invasion, associated carcinoma *in situ* and expression of epidermal growth factor receptor.⁷ For instance, patients with a pT1G3 lesion are at very high risk of progression.¹¹

FOLLOW-UP

Two factors define the risk of future recurrence in a new tumour; firstly, whether it is solitary or multifocal, and secondly, whether at the first three-month follow-up cystoscopy it has recurred.¹² Three groups can be defined¹³ and their corresponding management plans are outlined in box 2.

INTRAVESICAL THERAPY

The most commonly used agents include mitomycin C, doxorubicin (adriamycin) and epirubicin. Bacillus Calmette Guérin (BCG) is an immunotherapeutic agent which produces more local side-effects,¹⁴ including cystitis, but systemic toxicity is a major disadvantage and can have serious consequences.

Intravesical treatment in newly diagnosed low-risk patients (Group 1)

Many urologists do not use intravesical agents at all in such patients. Two large trials have suggested that a single instillation of intravesical chemotherapy immediately after transurethral resection is worthwhile and reduces recurrence by up to 50%.^{15, 16}

Intravesical therapy in high risk tumours (Groups 2 and 4) and recurrent tumours
BCG immunotherapy may provide superior protection from recurrence, albeit

The three proposed prognostic groups, their relationship to risk of recurrence and a recommended management plan		
Prognostic groups	Cystoscopic findings	Management plan
Group 1	Solitary tumour at presentation; no tumour recurrence at three months (20% risk of recurrence at one year)	followed up safely by annual flexible cystoscopy
Group 2	Solitary tumour at presentation; tumour recurrence at three months; multiple tumours at presentation; no tumour recurrence at three months (40% risk of recurrence at one year)	followed up three monthly by flexible cystoscopy for the first year, then annually if no recurrence
Group 3	Multiple tumours at presentation; tumour recurrence at three months (90% risk of recurrence at one to two years)	three monthly rigid cystoscopic assessment under general anaesthesia

Box 2

at the price of more side-effects. Given the systemic side-effects, most European urologists would opt for a trial of intravesical chemotherapy first and reserve BCG for refractory multifocal disease.

Intravesical therapy and cis

Without intravesical therapy, 60% of patients with diffuse symptomatic *cis* progress to muscle invasion and one third are dead within five years.¹⁷ These patients must receive intravesical treatment. BCG is the treatment of choice¹⁸ and maintenance therapy may be beneficial. The poor prognosis of nonresponders should be remembered as many will require early cystectomy.

T1G3 TUMOURS

Such patients must not be followed by flexible cystoscopy as they require regular washings and biopsy; 30–50% progress to muscle invasion and within three years a third will have metastasized.¹¹ Many urologists recommend early cystectomy, particularly if the tumour was multifocal and accompanied by *cis* as it will provide an excellent cure rate.¹⁹ Studies have not convincingly demonstrated that intravesical treatment improves survival.

Radiotherapy in T1 disease is generally thought to have a poor outcome, although five-year survival rates of about 60% are quoted by some authors.²⁰ Surprisingly, a complete or incomplete response to radiotherapy had no impact on survival.

Management of invasive bladder cancer

Patients with tumours just invading detrusor muscle have a 50% five-year survival whereas those whose tumours have invaded beyond the detrusor muscle have a 10% five-year survival. The outlook for patients with metastatic disease remains poor. At the time of diagnosis, 50% of muscle-invasive tumours have occult metastases, which will manifest themselves clinically within 12 months; few such patients survive more than two years. Similarly, patients with local nodal metastases have poor survival rates of 10–20% after cystectomy and pelvic lymphadenectomy.²¹

Treatment options include radical cystectomy, radiotherapy and chemotherapy – either alone or in combination. Radical cystectomy is the ‘gold-standard’. For those who would not tolerate radical treatment, transurethral resection may give temporary relief from haematuria.

STANDARD CURATIVE TREATMENTS

For those with T2 and T3a, these include:

- radical cystectomy followed by ileal conduit diversion, bladder reconstruction or continent diversion
- radical curative radiotherapy, surgery being reserved for nonresponders
- initial low-dose radiotherapy followed by planned cystectomy some weeks later.

The operative mortality of cystectomy has decreased and ranges from 0.4–3%^{22,35}, even in selected elderly patients.²³ Nerve-sparing cystectomy can preserve potency in 50% of men²⁴ and the bladder can now be reconstructed.^{25,26}

NOVEL APPROACHES

More experimental forms of treatment include:

- extensive transurethral resection followed by systemic chemotherapy for patients with T2 tumours
- initial systemic chemotherapy to ‘down-stage’ the tumour followed by cystectomy or radiotherapy (so-called neo-adjuvant treatment) for patients with extensive T3 or T4 tumours.

PALLIATIVE TREATMENTS

These include palliative radiotherapy, transurethral resection to diminish haematuria, and general expert palliative care.

CYSTECTOMY

This operation involves an anterior exenteration with inclusion of perivesical and pelvic nodes. The ureters are anastomosed to an ileal conduit or to a reservoir constructed from bowel which may be connected to the urethra or to the abdominal wall as a continent diversion. Some patients require removal of the urethra.

Five year survival after radical cystectomy alone or in combination with radiotherapy or chemotherapy						
Ref	Ta/ cis	T1	T2	T3a	T3b	T4/ N+
24		73%		52%		
35		75%	63%	50%	15%	21%
22		88%		40%		
21		75%	54%			36%

Box 3

Short-term morbidity

Thromboembolic complications can be reduced by the use of prophylactic subcutaneous heparin and compression stockings and the patient should receive prophylactic systemic antibiotics starting at anaesthetic induction. Peri-operative physiotherapy is essential. It is often six days before the gastro-intestinal tract recovers sufficiently for the patient to receive oral nutrition, if this is delayed, an early decision to provide parenteral nutrition should be taken.

Complications include small bowel obstruction (3–5%), anastomotic breakdown (<1%, but more common after radiotherapy), urinary leakage (2%) and intra-abdominal abscesses.

Late outcome of cystectomy

Box 3 shows survival after cystectomy, the survival of patients with advanced tumours or positive nodes is poor regardless of treatment. The selection of patients who will benefit from radical surgery is difficult.

URINARY DIVERSION

Ileal conduit

For many years, the ileal conduit has been the standard urinary diversion; it results in an incontinent stoma. Improvements in collecting appliances have increased acceptability; nevertheless, body image is altered. Late studies of the ileal conduit diversion have shown that 10–20% develop upper tract dilatation.

Bladder reconstruction and continent diversion

Recent changes in technique have meant that some patients can be offered reconstruction which avoids an ileal conduit. The underlying principle is the formation of a large capacity, low pressure urinary reservoir made of bowel to which the ureters are attached. In some patients the reservoir is attached to the urethra just proximal to the sphincter which controls continence (orthotopic bladder replacement), though patients may be required to self-catheterise. In others, a continent reservoir is constructed. The decision to perform such procedures must be taken seriously and patients must be counselled by both surgeon and specialist nurse. The advantages and potential complications of both need to be compared with the ileal conduit for the patient (box 4). Important features also include the stage of the tumour and the dexterity, health and motivation of the patient.

Orthotopic bladder replacement is contraindicated in those at high risk of urethral recurrence. Risk factors include multifocal tumours or those invading prostate or widespread cis. The single most important predictor is prostatic involvement.

In general, the outcome of bladder replacement is good. Day-time continence is obtained in over 90%, though sphincter function may require several months to recover and it is important that patients are warned about this. Other significant complications include mucus production, recurrent urinary infection, difficulty in self-catheterisation and intermittent diarrhoea (especially when long ileal segments have been used).

Ileal conduit urinary diversion or bladder reconstruction?		
	Ileal conduit	Reconstruction
Pros	<ul style="list-style-type: none">• simple to perform• well documented results• low complication rate	<ul style="list-style-type: none">• no stoma appliance required• avoids skin problems• better body image and sense of control• no adverse effect on follow up of bladder cancer
Cons	<ul style="list-style-type: none">• stoma appliance• skin irritation• complication of stoma (stenosis, hernia)• urinary tract infection	<ul style="list-style-type: none">• urinary tract infection• pouch-related problems: mucus formation, self-catheterisation difficulties, urinary leakage, rupture of the reservoir, (? risk of malignancy), metabolic consequences• bowel-related problems: intermittent diarrhoea/steatorrhoea, malabsorption (vitamin B12)

Box 4

Metabolic and mechanical consequences of urinary diversion

Hydronephrosis developing in the first year is usually due to an ischaemic ureteric stricture. Late dilatation may be due to stenosis, tumours or malfunction of the conduit or reservoir. Metabolic consequences such as hyperchloraemic acidosis are uncommon unless the loop is too long. However, continent diversions involving large segments of bowel have a significantly higher risk, particularly in patients with decreased renal function (glomerular filtration rate < 40 ml/min). Use of an ileocolic segment for either a continent cutaneous or an orthotopic reservoir removes a portion of the terminal ileum, thus increasing the risk of vitamin B12, bile salt and fat malabsorption.²⁷ The risk of colon cancer in patients with ureterosigmoidostomy is significantly increased,²⁸ but the risk in reconstructed bladders is as yet unclear.

RADIOTHERAPY

This can be used as definitive radical treatment or in combination with planned cystectomy. Techniques include external beam treatment and interstitial radium or iridium wire treatment. About 30% of invasive tumours can be cured by external beam radiation therapy alone.²⁹ Clinical understaging of the tumour may account for some of the apparently poor results of radiotherapy.

Of the 50% who fail to respond after radical radiotherapy, only a small proportion appear to be offered salvage surgery in most series. However, in those selected, about 30% to 40% survive in the long term. Trials of radical radiotherapy and 'flash' radiotherapy combined with cystectomy have not shown a clear difference, but most series showed a survival advantage for surgery.³⁰

Complications of radiotherapy

These are closely related to the dose and result from damage to rectum and bladder and small bowel. Chronic small bowel complications occur in 5-8% of patients given 5000 cGy.

SYSTEMIC CHEMOTHERAPY

Chemotherapy in the management of muscle-invasive bladder cancer can be considered as follows:

- sole treatment (monotherapy)
- as an adjuvant to conservative surgery (partial cystectomy or endoscopic resection)
- in the adjuvant or neo-adjuvant setting, being given in addition to cystectomy or radiotherapy with the aim of destruction of occult micrometastases.

In nonrandomised trials of multidrug regimens, response rates were higher than in single-agent studies. Cisplatin-containing protocols seem to be most effective. The two most widely used regimens are MVAC (methotrexate, vinblastine, doxorubicin/adriamycin and cisplatin) and CMV (cisplatin, methotrexate and vinblastine). MVAC has been extensively reported. It has an overall response rate of 40-72%, with 13-36% being complete.

Systemic chemotherapy as monotherapy

Overall response rates of 60-70% with complete response rates of the order of 30% have been observed. Response rates of primary tumours are better than those of metastatic lesions.³¹

Conservative surgery combined with chemotherapy

Partial cystectomy or endoscopic resection plus chemotherapy has been shown by some to provide good cure rates in selected patients.³² The results of nonrandomised studies of chemotherapy and radiotherapy are not encouraging; the proportion of patients remaining tumour-free in the bladder being no greater than one would expect from conventional radiotherapy.

The role of adjuvant chemotherapy in T2-T4a bladder cancer

Randomised trials of non-cisplatin-containing chemotherapy given in addition to conventional radical treatment have failed to demonstrate an advantage, but Skinner claims to have demonstrated an advantage for the adjuvant use of chemotherapy.³³ The results of the recent large MRC/EORTC trial of systemic chemotherapy plus/minus conventional treatment have shown no benefit for chemotherapy.

Chemotherapy for the metastatic disease

Metastatic bladder cancer is generally regarded as incurable, but response rates to MVAC have been encouraging.³¹ However, most series have reported

Key points

- haematuria clinics and flexible cystoscopy will reduce delays in diagnosis and allow investigation at a single visit. It is uncertain whether this will improve survival
- a targeted cystoscopic follow-up policy based on the number of tumours at presentation and the presence or absence of tumour at the three-month cystoscopy should reduce unnecessary cystoscopies
- a single instillation of intravesical epirubicin or mitomycin C immediately following transurethral resection in newly diagnosed patients reduces recurrence rate by 50%
- intravesical BCG may be more effective than intravesical chemotherapy, but at the price of side-effects
- orthotopic bladder replacement is possible in many patients undergoing cystectomy
- patients with refractory carcinoma *in situ* or with T1G3 tumours should undergo early cystectomy

complete response rates of only 10–15%. Memorial Sloan-Kettering continues to report durable remissions with MVAC. However, their long-term survivors have had nodal, rather than visceral metastases and remissions were 'consolidated' by aggressive surgical resection. Others, while confirming the activity of MVAC, have failed to replicate the response rates observed at Memorial Sloan-Kettering.³⁴

Patients in primary health care

Early referral of patients with significant haematuria will allow prompt diagnosis. Awareness that carcinoma *in situ* produces symptoms of dysuria and irritative symptoms accompanied by only minimal haematuria should help in selecting such patients for urgent referral. Routine examination of urine using dipstick test as well as a mid-stream sample for culture and cytological examination should be performed on patients with urinary symptoms suggestive of haematuria or urinary infection.

One development which is likely to occur is the use of nurse-practitioner-run assessment clinics. There is no doubt that the initial history, examination and investigation of patients with haematuria can be organised on a protocol basis and can be run effectively by nurse practitioners. Indeed, some centres are now employing nurse practitioners in diagnostic flexible cystoscopy.

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