Bladder cancer

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Abstract

Urothelial carcinoma of the bladder is the most common malignancy affecting the urinary tract. This review examines the current standards in the diagnosis and management of this disease. Cystoscopy and urine cytology remain important tools in the diagnosis and follow-up of bladder cancer. Alternatives include photodynamic diagnosis, narrow band imaging and professional image enhancement which may improve detection of tumours. En-bloc resection using either laser or electrocautery shows promise in improving the quality of transurethral resection. For patients with muscle-invasive bladder cancer, robot-assisted radical cystectomy has been shown to be oncologically equivalent to open radical cystectomy; however, cost effectiveness remains to be determined. The mainstay of bladder preservation treatment in muscle-invasive cancer is trimodal therapy utilizing transurethral resection and chemoradiotherapy with equivalent outcomes to radical cystectomy in selected patients. Management of locally advanced and metastatic disease has rapidly advanced through the use of systemic immunotherapy agents targeting the PD-L1/PD-1 axis.

Keywords Bladder cancer; cystoscopy; en-bloc resection; narrow-banded imaging; photodynamic diagnosis; radical cystectomy; tri-modal therapy; urine markers

Introduction

Epidemiology and statistics

Bladder cancer is a malignancy affecting the urothelium of the bladder. Although this epithelial surface lines the bladder, it extends beyond this covering nearly all of the urinary tract. Bladder cancer is the most common malignancy of the urinary tract and accounts for approximately 3.2% of all cancer worldwide where it remains the seventh most commonly diagnosed malignancy in the male population.[1] It is a significant cause of cancer morbidity and mortality, accounting for an estimated 380,000 new cases and 150,000 deaths worldwide in 2008. In the UK, it is the ninth most common malignancy, with incidence being three times greater in men than in women. There were approximately 10,300 new cases of bladder cancer in the UK in 2013.[2]

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The incidence of bladder cancer increases with advancing age, and the majority of cases (80%) occur in individuals' aged over 65 years. Of note, in the UK, the incidence of bladder cancer has reduced by approximately 12% in the past decade. Despite this, the mortality rate from bladder cancer has not changed for over 20 years. Overall, it remains the seventh leading cause of cancer death in the UK, and accounts for around 5200 deaths in the UK each year. Of newly diagnosed bladder cancer cases, the 5- and 10-year survival rates are 53% and 50%, respectively in England and Wales (2010–2011).[2]

Aetiology

Causative risk factors for the development of bladder cancer can be broadly divided into inherited (genetic predisposition) and acquired (due to environmental exposure). The reality remains that one factor may not be solely responsible for the differing incidence and progression of this disease in different population groups, but rather the complex interaction between factors.

Tobacco smoking is the most important environmental risk factor for bladder cancer. It accounts for approximately 50% of bladder tumours, and smokers have a 2.5-fold increased risk compared to non-smokers. Tobacco smoke contains known urothelial carcinogens such as ß-naphthylamine and polycyclic aromatic hydrocarbons. These compounds are excreted through the kidneys and therefore exert a direct carcinogenic effect on the entire urinary system. Their likely dwell time in the bladder combined with urinary stasis increases exposure of these chemicals to bladder urothelium, resulting in an increased incidence of disease in the lower urinary tract compared to the upper tract. There is a latency period of approximately 20–30 years following the initiation of smoking to the development of bladder cancer. Smoking cessation results in an immediate risk reduction of bladder cancer of approximately 40% within 1–4 years;[3] reaching an age-adjusted baseline equivocal of non-smokers by approximately 20 years.

The second most common cause of bladder cancer is occupational exposure to urothelial carcinogens. Specifically, these include aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons; and are commonly found in industrial areas processing dyes, rubber, paint, metal and petroleum products. With greater occupational awareness and tighter regulations, exposure to these carcinogens is falling.

There remain other environmental influences, some known, others yet to be identified which have a limited role in the development of bladder cancer. Examples include exposure to arsenic in drinking water where large population based studies in Chile have been shown to increase the risk of bladder cancer.

Therapeutic strategies in medicine themselves can predispose individuals to bladder cancer, either as a consequence of medical treatment or through direct causation. External beam radiotherapy for pelvic malignancies can increase the risk of bladder cancer. Additionally, the cytostatic agent, cyclophosphamide, commonly used in the management of haematological malignancy has been associated with the development of squamous cell carcinomas of the bladder. Chronic inflammation is an established cause of bladder cancer, typically squamous cell carcinoma. This can develop secondary to chronic schistosomiasis haematobium infection, chronic cystitis, bladder calculi and indwelling urinary catheters.

Our understanding of the genetics that influence bladder cancer is growing. At present, the best-established risk factors for bladder cancer are genomic variations in the N-acetyl transferase enzymes (NAT1, NAT2) that are involved in the detoxification of extrinsic carcinogens. A slow NAT2 genotype (less effective) was found to increase the risk of bladder cancer if exposed to environmental factors such as tobacco. Furthermore, it has been shown that inherited mutations in the retinoblastoma tumour suppressor gene are associated with the development of bladder cancer. Increasing evidence has identified many other gene associations in bladder cancer, these have been linked to development, recurrence and progression risk, and while their definitive role remains unclear, it is hoped further research could tailor detection, prognostication and treatment strategies.

Pathophysiology

The principal histological sub-type of bladder carcinomas in the Western world is the urothelial or transitional cell carcinoma, accounting for 90% of cases. The remaining groups are comprised of squamous cell carcinoma (SCC) (5%), adenocarcinoma (2%) and other rare tumours (including sarcoma, small cell, and metastatic deposits). In countries where schistosomiasis is prevalent, SCC is more common, however; this trend is changing in favor of urothelial carcinoma with increasing environmental influences through globalization.

Bladder cancers tend to originate from the urothelial layer and stage migration is observed through direct invasion into the submucosa, lamina propria, muscularis layers and serosa. Bladder cancers have the ability to spread directly to adjacent pelvic structures, including the prostate, urethra, vagina, uterus and bowel. Lymphatic spread is seen through obturator, presacral, iliac and para-aortic lymph nodes. Haematogenous spread typically results in metastatic deposit to the liver, lungs, bones and adrenal glands.[4]

Classification

Staging of bladder cancer: The TNM (tumour, node, metastasis) classification, based on tumour depth, nodal or metastatic spread, is widely used to stage bladder cancer and guide management (Box 1).

Approximately 75% of patients will have disease confined to the mucosa (pTa, Tis) or lamina propria (pT1), which can be classified as non-muscle-invasive bladder cancer (NMIBC). (Figure 1). The remaining 25% of newly diagnosed bladder tumours invade the muscularis propria bladder wall (pT2) and are termed muscle invasive bladder cancer (MIBC).

Grading: The WHO classification of bladder cancer recognizes superficial bladder cancers as a heterogenous group consisting of urothelial papilloma (a benign lesion), papillary urothelial neoplasm of low malignant potential (PUNLMP) and low- and high-grade papillary cancer. The fourth edition[5] recognizes two new grades of non-invasive bladder lesions: urothelial proliferation of uncertain malignant potential and urothelial dysplasia. Urothelial proliferation of uncertain potential supplants the term hyperplasia and refers to thickened urothelium with no atypical features. Urothelial dysplasia is a difficult to interpret category to define, and refers to a lesion with cytological and architectural abnormalities believed to be preneoplastic but do not constitute carcinoma in situ (CIS). These lesions are usually seen in patients with previous urothelial malignancy and treatment. Muscle-invasive bladder tumours are high grade by definition however the classification of invasive tumours has changed remarkably reflecting the plasticity of urothelial malignancies.

The TNM Staging System for Bladder Cancer

Primary tumour (T)
Tx Primary tumour cannot be assessed
T0 No evidence of primary tumour
Ta Noninvasive papillary carcinoma
Tis Carcinoma in situ
T1 Tumour invades lamina propria
T2 Tumour invades muscularis propria bladder wall
  T2a Tumour invades superficial muscle
  T2b Tumour invades deep muscle
T3 Tumour invades perivesical tissue
  T3a Microscopically
  T3b Macroscopically
T4 Invasion of: prostate, uterus, vagina, pelvic and abdominal wall
  T4a Tumour invades prostate, uterus, or vagina
  T4b Tumour invades pelvis or abdominal wall

Regional lymph nodes (N)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Single regional lymph node metastases,
N2 Multiple regional lymph nodes metastases
N3 Common iliac lymh node metastases

Distant Metastasis (M)
Mx Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Box 1

Diagnosis

Haematuria remains the cardinal sign of urothelial malignancy, with some 70% of patients with bladder cancer presenting with painless haematuria. Others present with non-specific lower urinary tract symptoms (LUTS), including recurrent infections, frequency, urgency and nocturia. While it is less common for pTa and pT1 tumours to present with bladder pain, CIS might be suspected in patients presenting with non-specific LUTS resistant to treatment.

Non-specific LUTS can be found in a wide variety of urological disease and therefore a number of differential diagnosis may be suspected; including urinary tract infections, urinary calculi, renal and prostatic malignancy. Early suspicion and investigation may avoid a delay in diagnosis in some.

Urine cytology

Urine cytology allows for a non-invasive method for detecting malignant urothelial cells. It has good sensitivity and specificity

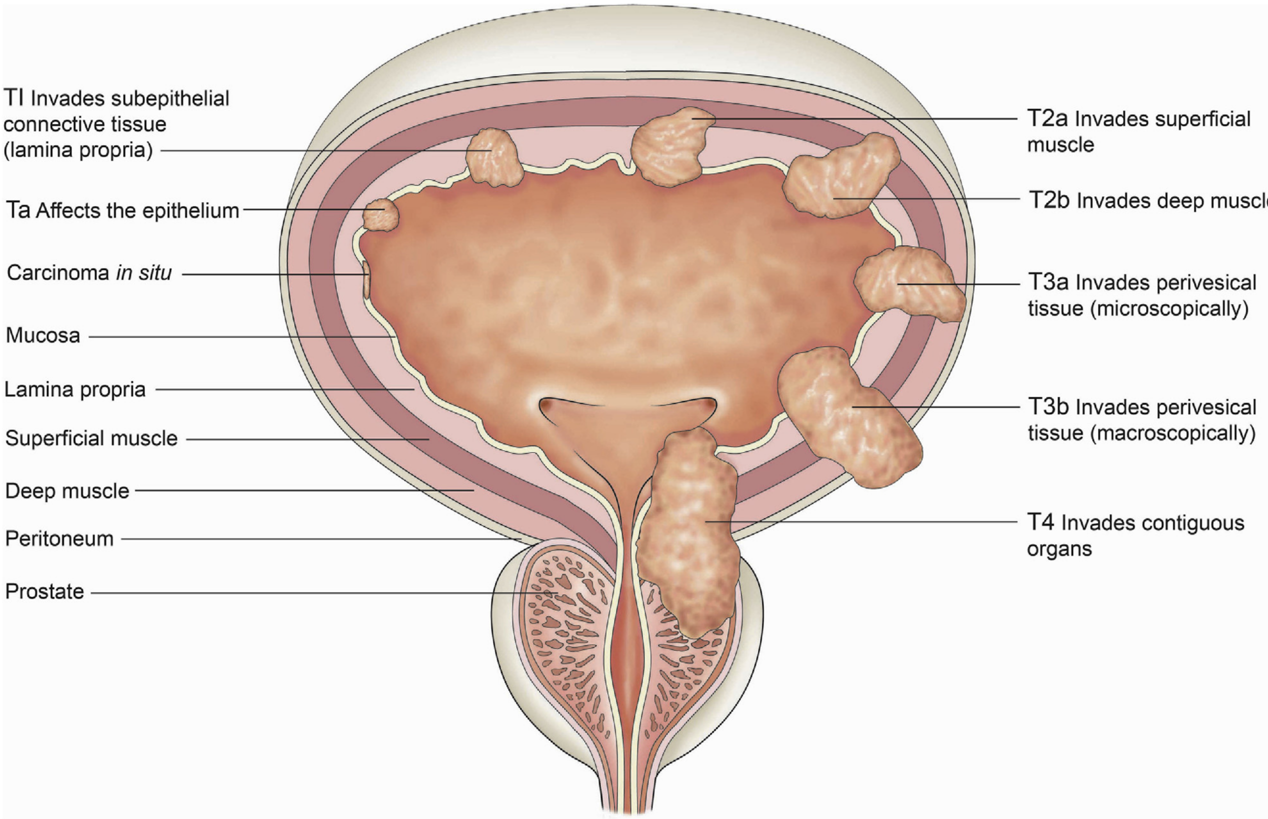

Figure 1 Local bladder staging according to the TNM staging criteria for bladder cancer.

for the detection of high-grade tumours and CIS (median sensitivity 64%), but a low sensitivity for low-grade tumours (median sensitivity 12%).[6] Thus, negative cytology does not exclude the presence of tumour. A number of urinary markers have been investigated, and aim to improving the sensitivity and specificity of current tests in conjunction to flexible cystoscopy or urine cytology. These include nuclear matrix protein-22 (NMP22), bladder tumour antigen (BTA), ImmunoCyst, microsatellite analysis and fluorescence in situ hybridization (FISH). Overall, these urinary markers perform better than cytology in relation to sensitivity but score lower in specificity and cost. Consequently these markers have not been adopted into routine clinical practice and the ideal non-invasive test is yet to be developed.

Urinary tract imaging

Transabdominal ultrasound is a useful screening tool in the investigation of visible and non-visible haematuria. It allows for identification of renal and larger intraluminal bladder lesions, in addition to evaluating for hydronephrosis secondary to an obstructing bladder tumour over the ureteric orifice or ureteric tumour. However, its use remains user dependent and reliant on whether the bladder is filled. In addition, a negative ultrasound does not exclude a bladder tumour, nor can it reliably confirm extra-vesical or metastatic spread.

Computed tomography (CT) urography is mandatory in the assessment of visible haematuria. It has a sensitivity of 95% and specificity of 83%[6] for upper tract urothelial lesions. Its role in bladder malignancy detection is poor, as a well-filled bladder is required to detect smaller lesions. When larger tumours are identified, extravesical spread used to detect papillary lesions in the urinary tract which can be seen as filling defects. This form of imaging can also give additional information including status of lymph nodes and distant metastasis. After the diagnosis of bladder cancer is made, staging is carried out by performing CT (thorax-abdomen-pelvis) scans.

Accurate pretreatment staging of bladder cancer is important in assessing the extent of disease and therefore guiding appropriate treatment. The current gold standard of transurethral resection of bladder tumour (TURBT) followed by CT imaging provides excellent staging specificity; however, CT is poor in evaluating the depth of tumour invasion. The consequence is a clinical understaging of MIBC, leading to adverse outcomes. Magnetic resonance imaging (MRI) has shown promise in assessing depth of tumour invasion when compared to CT. MRI facilitates better soft tissue differentiation, therefore greater accuracy in distinguishing NMIBC from MIBC (Figure 2). Further work is needed to evaluate the role of MRI in bladder cancer diagnosis, however it appears to overcome some of the pitfalls we associated with CT urography.

Cystoscopy

Direct visualization of the bladder with white light cystoscopy (WLC) remains the gold standard in bladder cancer diagnosis. This can be done in an outpatient setting under local anesthetic using a flexible cystoscope or under general anaesthetic with a larger caliber rigid scope. Flexible cystoscopy has a sensitivity of 98% and specificity of 94%.[6] Current urological haematuria clinic arrangements allow for flexible cystoscopy and ultrasound

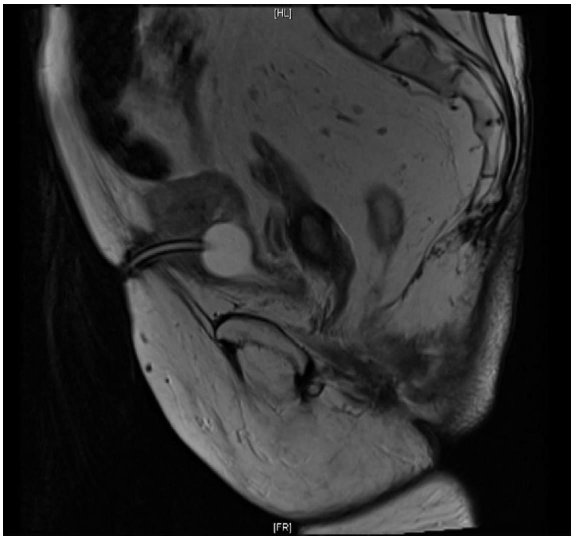

Figure 2 Multiparametric MRI scan of bladder demonstrating muscle-invasive bladder cancer.

imaging to be performed in one visit to allow for efficient diagnosis. When a tumour is seen by flexible cystoscopy, the next stage is to perform TURBT. This allows for both treatment with attempted clearance of all visible tumour, diagnosis through histopathological assessment and local staging by determining whether bladder detrusor muscle has been infiltrated by tumour.

Management

Non-muscle-invasive bladder cancer

A range of treatment options are used for bladder cancer, depending on the stage and grade of disease. The UK National Cancer Plan stipulates a timeframe of 31 days from diagnosis to treatment of all new cases of bladder cancer. TURBT is the first-line treatment for patients with NMIBC if the patient is considered fit for an anaesthetic. A complete resection is essential to achieving good prognosis and this can only be considered achieved when muscularis propria is present in the resected tissue. It has been shown that the quality of initial TURBT strongly determines patients' prognosis, rate of recurrence and overall treatment costs. Despite TURBT being the mainstay of treatment, there remain substantial drawbacks to its use, these include scattering and seeding of tumour tissue, thermal damage to the bladder and a relatively high rate of incomplete resections. In order to improve initial resection quality, lower complication rates and decrease recurrence rates the en-bloc resection technique (ERBT) has been developed in which the entire tumour is resected as a single specimen. ERBT can either be performed using monopolar/bipolar electrocautery (e-ERBT) or Tm:YAG/Ho:YAG lasers (l-ERBT). Both ERBT techniques have been shown to achieve a higher rate of complete resections while having a similar perioperative morbidity as compared to conventional TURBT. Nevertheless, it is not clear from the available small scale studies whether ERBT provides any benefit in recurrence rates compared to conventional TURBT and there is a lack of good quality randomized controlled trials (RCTs).

Another strategy to improve the quality of resection is to improve visualization of tumour deposits so that these can be resected fully. WLC is the gold standard for diagnosing bladder cancer and is currently used intraoperatively to identify tumours requiring resection; however, its use is operator dependent and may miss flat lesions such as CIS. A number of techniques have been developed to improve visualization of tumours during resection, these include photodynamic diagnosis (PDD), narrow-band imaging (NBI) and other novel methods.

PDD requires the preoperative intravesical instillation of 5-aminolevulinic acid (5-ALA) dye or the hexyl ester derivative hexaminolevulinate (HAL; Hexvix). This is absorbed by malignant cells and metabolized to protoporphyrin IX which emits a red fluorescence when exposed to blue light (380–480 nm), and background normal urothelium appears blue (Figure 3). A metanalysis has shown that PDD-guided biopsy is more sensitive than WLC for the detection of bladder cancer (93% vs 65%), particularly in patients with CIS. However, PDD has a lower specificity than WLC (81% vs 63%) which may be due to false positives caused by infection, inflammation or intravesicular bacillus Calmette-Guerin (BCG) treatment. PDD-guided TURB has been shown to reduce recurrence rates in the short and long term in an analysis of 15 randomized controlled trials; however, there was no effect on cancer progression rates or mortality.

In NBI, white light is filtered into to two wave-lengths (415 nm and 540 nm). These wavelengths are preferentially absorbed by haemoglobin, and therefore mucosal and submucoal vascular architecture of tumours is enhanced allowing for easier visualization. This technique requires no preoperative preparation, only requires an extra 3 minutes of operative time and has similar costs to WLC. A recent meta-analysis has shown a clear reduction in recurrence rates using NBI-guided TURB at 3 months, 1 and 2 years; however, there is currently no conclusive data regarding disease progression.

Other novel techniques include a professional image enhancement system (SPIES) which uses a number of image enhancement modalities to increase colour contrast, improve sharpness and add local adaptive brightness to improve visualization of darker regions. The system is currently being investigated in a large international trial. Other methods are being developed including optical coherence tomography, confocal laser endomicroscopy and ultraviolet autofluorescence with promising results however they do not yet have routine clinical application.[7]

Risk stratification: To facilitate treatment recommendations, NMIBC can be subdivided into three prognostic groups: low, intermediate and high risk. Management of these groups differs and treatment can be classified according to stage and grade of disease (see European Urology Association (EAU)).[8]

- Low-risk tumours (<3 cm, solitary, Ta, G1/G2) should have cystoscopic follow-up at 3 months following initial resection. If disease free at this stage, subsequent cystoscopy is recommended at 12 months and annually for 5 years thereafter.
- Intermediate-risk tumours (not part of adjacent groups) should have cystoscopy and cytology at 3 months. If clear, cystoscopy is recommended at 3–6 monthly intervals for 5 years, and then annually thereafter. These tumours have a high probability of recurrence (62%) and progression (17%) at 5 years and therefore adjuvant intravesical

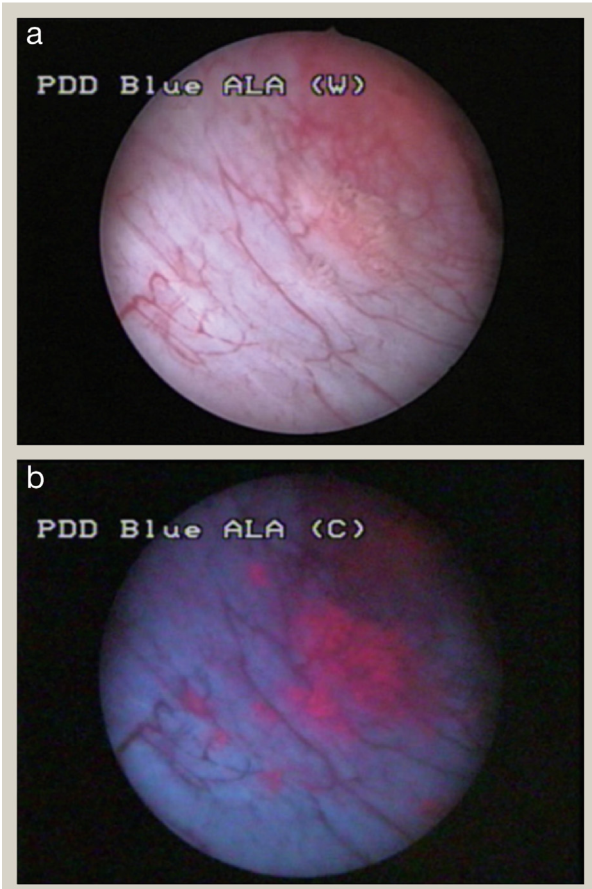

Figure 3 Example of (**a**) papillary urothelial lesions as seen on white light cystoscopy and (**b**) comparison to lesions when prephotosensitized to 5-ALA and on application of blue light.

chemotherapy (using Mitomycin-C or in certain circumstances BCG) is advised in this group of patients.

- High-risk tumours (pT1, high grade G3, CIS OR Multiple, recurrent and large (>3 cm) low grade) have a 5-year recurrence rate of 78% and progression rate to muscle-invasive disease of 45%. Thus, this group of patients should all be referred for specialist multidisciplinary team (MDT) discussion. Patients with high-risk NMIBC should receive maintenance BCG. Cystoscopy and cytology should be performed at 3 months and, if negative, cystoscopy and cytology every 3 months for 3 years, 6 monthly for 5 years and then yearly thereafter. CT or IVU should be performed yearly.
  - Highest risk subgroup (G3 associated with concurrent CIS in bladder or prostatic urethra; multiple or large or recurrent G3 high grade; lymphovascular invasion or variant histology) should be considered for upfront radical cystectomy.

Intravesical treatment: Intravesical therapy involves the instillation of cytotoxic agents, usually mitomycin-C (MMC), or immunotherapy with BCG. These agents can be administered as either a single instillation or as a scheduled dose regimen over a period of time.

MMC is an antibiotic chemotherapeutic agent that inhibits DNA synthesis resulting in cell death. A single instillation of intravesical MMC given within 24 hours after the initial resection has been shown to reduce the absolute risk of recurrence by 39%, and is recommended routine practice for all superficial bladder cancers (low and intermediate risk) following TURBT.

Strategies to optimize the delivery of MMC and improve therapeutic efficacy have been studied. One method that has showed promise is chemohyperthermia therapy (C-HT). It is thought that the combination of intravesical MMC and microwave induced bladder wall hyperthermia improves the depth of drug penetration by increasing the permeability of the urothelium and therefore the efficacy of MMC. In a systematic review, C-HT, when compared to MMC alone, was shown to reduce the recurrence rate in patients with intermediate- and high-risk NMIBC by 59%. More work is needed; however, it has been suggested that this technique may become acceptable in high-risk patients with recurrent tumours who are not suitable for RC.

Electromotive administration (EMDA) of MMC is a novel method used to enhance the delivery MMC through the bladder urothelium. The application of an electric field within the bladder is thought to increase the permeability of the bladder mucosa allowing effective MMC delivery. In an RCT, Di-Stasi et al. compared EMDA of MMC immediately before TURBT with passive MMC instillation immediately after TURBT. Both recurrence rates and the disease-free interval were favourable in the EMDA cohort, making this a promising alternative to traditional methods of MMC delivery.

BCG therapy has been shown to reduce recurrence and progression and is the preferred treatment for patients with high-risk NMIBC. BCG is an immunotherapeutic agent, stimulating an antigen-mediated type IV immune response against malignant cells. Meta-analyses have demonstrated that intravesical BCG after TURBT results in a significant reduction in the risk of recurrence *and* progression of NMIBC. The optimum maintenance regimen of BCG remains undefined; however, typically treatment is recommended for 1–3 years, depending on tolerability to allow a sustained host immune response. Side effects of BCG include cystitis, haematuria, prostatitis, as well as systemic effects such as fever, arthralgia and malaise. As such, the risks of BCG therapy outweigh the benefits if offered in low-risk NMIBC.

For optimal efficacy and to reduce the toxicity associated with frequent BCG exposure, combination therapy incorporating MMC has been suggested. Di Stasi et al. reported that sequential BCG therapy, followed by the instillation of EMDA-MMC resulted in lower recurrence and progression rates and improved overall survival in patient with high-risk NMIBC.[9] The available evidence to date provides rationale for combining MMC with BCG, however further data is required to substantiate this.

Patients who fail to respond to BCG should be considered for RC. In patients unsuitable for RC, there are several bladder preservation strategies available. These include C-HT, intravesical gemcitabine and combination therapies.

Muscle-invasive bladder cancer

Almost 30% of patients present with muscle-invasive bladder cancer at diagnosis. Patients with NMIBC may also progress to MIBC. The prognosis of patients varies with stage and pelvic lymph node involvement. MIBC confined to the bladder muscle

(T2) without evidence of the lymph node metastases and absence of lymphovascular invasion has almost 90% disease free survival at 5 years. On the contrary this is reduced to 40–50% in patients with locally advanced disease (pT3-T4) and even lower at 15–35% in those with lymph node metastases.

Despite significant advancements in surgical techniques, very little progress has been made in improving outcomes following MIBC. Over 22 % of patients succumb to systemic disease despite excellent local control with surgery (7% recurrence). It is thought this represents a significant number of patients with micrometastatic disease at diagnosis.

Special investigations in MIBC: All patients with established MIBC, a CT chest, abdomen and pelvis, with or without the addition of an MRI pelvis are required to stage the disease. Technetium labeled radioisotope bone scans are not routinely performed, however, can be useful in patients with suspected bone metastasis. Fluorodeoxyglucose positive emission tomography (FDG-PET) is particularly useful for troubleshooting equivocal lymph nodes or suspicious metastatic lesions. Imaging should be ideally performed 6 weeks prior to considering radical treatment, as rate of disease progression can be rapid.

Perioperative chemotherapy: ***Neo-adjuvant chemotherapy*** – Patients with MIBC who have a good performance status and baseline renal function (estimated glomerular filtration rate >60 ml/min) are suitable receive neo-adjuvant chemotherapy. The aim for is to downstage a proportion of malignancies which would otherwise be inoperable, and to facilitate micro-metastatic tumour control.

Current regimens used have shown modest 5% survival benefit over 5 years. The 10-year follow-up of MRC/EORTC trial of neoadjuvant cisplatin, methotrexate and vinblastine (CMV) has demonstrated an improved 10-year survival from 30% to 36%. The South West Oncology Group 8710 study involving methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) showed an improved survival of 77 months versus 46 months with surgery alone.

Despite the level 1 evidence in support of effectiveness of neo-adjuvant chemotherapy a multi-institutional study revealed significant under-utilization of neo-adjuvant chemotherapy with only 15% of patients receiving neo-adjuvant chemotherapy prior to surgery.

Patients not suitable for neo-adjuvant chemotherapy are those with impaired renal function, present with bilateral obstruction of the upper urinary tract, suffer intractable haematuria or severe lower urinary tract symptoms and are of a poor performance status. In some cases, patient preconceptions of chemotherapy and their side effects some decline chemotherapy.

Adjuvant chemotherapy – The underutilization of neo-adjuvant chemotherapy and the knowledge that half of patients undergoing curative cystectomy develop metastasis within 2 years has prompted active recommendation of adjuvant chemotherapy in patients who have not received neo-adjuvant chemotherapy to improve outcome.

Cisplatin-based trials has demonstrated a 23% reduction in mortality with adjuvant chemotherapy. Adjuvant chemotherapy appears to be most beneficial in those with extravesical disease extension (pT3a-T4a) or in lymph node positive patients. One clinical trial of MVAC has suggested similar long-term outcome between neoadjuvant and adjuvant chemotherapy.

Based on the current evidence The International Consultation on Bladder Cancer in 2012 recommended patients with pT3/4 and/or lymph node-positive urothelial carcinoma of the bladder who had not received neoadjuvant chemotherapy could be considered for cisplatin-based adjuvant chemotherapy if performance status and renal function support this.

Radical cystectomy (RC) with appropriate urinary diversion remains the mainstay of surgical treatment. Select group of patients or those unfit or unwilling for surgery are treated with external beam radiotherapy. RC has traditionally been performed through an open approach, but in recent years minimally invasive cystectomy (laparoscopic or robotic) have been increasingly adopted worldwide in an attempt to reduce the morbidity of the procedure.

The evidence comparing minimally invasive versus open radical cystectomy has been controversial. The evidence demonstrates minimally invasive surgery is associated with less blood loss, reduced need for blood transfusion and decreased analgesic requirements. Oncological outcomes appear to be promising with similar or better lymph node yields using robot assisted radical cystectomy (RARC) compared to open RC. In addition, the rate of positive surgical margins appear to be similar. Nevertheless, evidence regarding complication rates, length of stay and long-term outcomes is mixed with current evidence indicating that they are similar between open and robotic techniques. Furthermore, the operative time is significantly longer in comparison to open surgery. As length of stay and complication rates currently appear to be similar and operative time is longer, the overall cost of robotic surgery is greater than the open technique due to initial equipment costs.[10] It remains to be seen with more experience whether operative time, length of stay and perioperative morbidity can be reduced and therefore improve cost effectiveness.

Pelvic lymphadenectomy is the integral component of radical cystectomy. It is both prognostic and therapeutic. There is evidence to show the number of lymph nodes removed directly impacts on oncological outcomes from urothelial carcinoma. There is however, no consensus as to the level of lymph node dissection required to have a significant impact on cancer-specific survival. There remain considerable variations in outcomes even with well-defined templates for lymphadenectomy. This is due to a lack of standardization of pathologic assessment of the tissue removed, variation in the number of regional lymph nodes in individual patients and the quality of dissection amongst surgeons.

Urinary diversions techniques: Urinary diversions may be incontinent or continent. Options for incontinent urinary diversion options include cutaneous ureterostomy or the more commonly performed ileal conduit urinary diversion. Although technically less demanding, these entail application of an external stomal appliance and hence aesthetically less acceptable to some patients.

The options of continent diversions include the orthotopic bladder substitution, continent catheterizable pouches (Mitrofanoff), or the Mainz-II which relies on natural evacuation of mixture of urine and faeces provided the patient has a competent anal sphincter.

Cutaneous ureterostomy – involves direct drainage of urine from the ureters to an appliance over the abdominal wall. The most suitable patients for this kind of urinary diversion are high-risk patients with symptomatic bladder cancer combined with palliative cystectomy, diversion in patients with urinary fistula or in salvage surgery.

This type of diversion is ideal for the elderly and the frail patient requiring a cystectomy but should not be considered in patients who are obese, have had pelvic radiotherapy, have short ureteric stumps or have either denuded poorly vascularized ureters. The principle risk is that of ureteric stricturing which require periodic dilatation or stenting.

Ileal conduit/colonic conduit – This is the most commonly performed diversion. It is a passive conduit for urine to drain into an appliance. Most commonly a segment of ileum is used to construct the conduit; however, a colonic segment may be used as alternative in cases of previous pelvic radiation. Complications are common with either diversion technique. Early complications include ischaemia/infarction, ileus/bowel obstruction and bowel or urinary leak. The commonest delayed complications include upper tract deterioration, urinary tract infection and stomal retraction.

Catheterizable pouch – Mitrofanoff in 1980 first described continent supra-vesical catheterizable channel, using appendix on vascular pedicle. In patients who have either lost appendix at operation or do not have suitable lumen or length alternatives have been used including small bowel, ureter, Fallopian tube, colon, vas deference and stomach. This catheterizable channel can be integrated into a ileal or colonic pouch to allow drainage of a bladder subsititution.

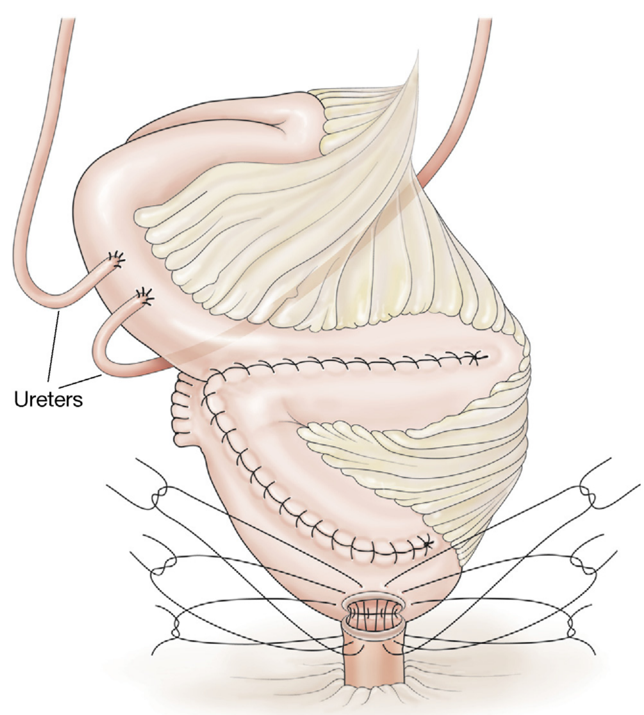

Figure 4 The Studer neobladder.

Early and late complications associated with orthotopic bladder substitution and/or a catheterizable channel

Mortality	0–4%
Small bowel obstruction	4–20%
Ischaemic necrosis of channel	0–12%
Peri-stomal abscess	0–2.1%
Stones	40–100%
Difficulty in catheterization	27–60%
Revision rate	16–50%
Stenosis	10–40%
Prolapse	2%
Pouch-like dilation	28%
Urinary tract infections	40–100%

Table 1

Orthotopic bladder substitution – Although there is no ideal urinary diversion this option is closest to the native bladder as patients opting for this type may void spontaneously, be continent and also maintain the body image. A variety of techniques have been described but currently the most widely used is the Studer technique (Figure 4).[11] The bladder substitution will, however, produce mucus, which requires drainage, require regular emptying (every 3 hours) and night-time incontinence is common (50–80%) and day-time incontinence up to 30%. Up to 50% require long-term self-catheterization. Further associated complications are shown in Table 1.

Enhanced recovery after surgery (ERAS) is a multimodal multidisciplinary approach to reduce postoperative complications and expedite recovery from surgery, in this case cystectomy. It is an evidence-based pathway to achieve early recovery following major abdominal surgery. Originally designed to reduce postoperative complications and shorten length of stay following colorectal surgery,[12] it has also shown to be beneficial in other surgical specialties.

The four principles of enhanced recovery are preoperative planning and preparation, reducing stress of surgery, post-operative care and early mobilization. Preoperative planning, education and counselling, optimal pain management, antibiotics administration perioperatively, fluid management and avoiding overhydration, prevention of ileus and early mobilization have been shown to impact on outcomes following cystectomy.

Bladder preservation strategies: Not all patients are fit for radical surgery or prefer such a life-changing operation. Trimodal therapy involving TURBT, concomitant radiation and chemotherapy demonstrated a median overall ten year survival of 30.9% in the group of multimodal therapy versus 35.1% undergoing radical cystectomy. Current recommendations advocate trimodal therapy for bladder preservation in selected patients (T2N0M0 with no CIS) or in patients unfit for radical surgery.[13] Radiotherapy may be given as a split-dose regimen or single continuous regimen with significant geographical variation. Radiotherapy may be offered on its own as palliation, especially in patients suffering from haematuria. Chemotherapy regimens vary, with no evidence indicating superiority of either

Summary of novel PD-1/PD-L1 currently being investigated for use in bladder cancer. ORR= Objective response rate

Drug name	Action	Use	Results	Side effects
Atezolizumab	PD-L1 inhibitor	**First line:** Locally advanced or metastatic Bladder cancer ineligible for platinum based chemotherapy OR **Second line**: Those who have progressed after chemotherapy	**IMvigor 210 trial-** 16% ORR. 28% in patients with ≥5% expression of PD-L1	Fatigue: 31% Nausea: 14%
Pembrolizumab	PD-1 inhibitor	**First line:** Locally advanced or metastatic Bladder cancer ineligible for platinum based chemotherapy OR **Second line**: Those who have progressed after chemotherapy	**KEYNOTE 045 trial**- Greater median survival in the pembrolizumab group, as compared with chemotherapy group (10.3 months vs 7.4 months).	Fewer adverse effects in the pembrolizumab group compared to chemotherapy (60% vs 90%)
Avelumab	PD-L1 inhibitor AND antibody dependent cell mediated cytotoxicity	**Second line**: Those who have progressed after chemotherapy	**JAVELIN trial-** 17% ORR, 50% in patients with PD-L1 expression.	41% serious adverse reactions.
Durvalumab	PD-L1 inhibitor	**Second line**: Those who have progressed after chemotherapy	31% overall ORR, 46% in those with PD-L1 expression	Fatigue: 13% Diarrhoea: 10%

Table 2

neoadjuvant or adjuvant regimes with the most commonly used agents being cisplatin or MMC and 5 fluorouracil.

Recurrences and follow-up of MIBC: Patients after cystectomy remain at risk of cancer recurrence and also prone to complications from urinary diversion. Follow-up is therefore stringent. Knowledge regarding the pattern of recurrence is paramount to monitoring. Recurrence rates of approximately 48.6% have been reported after radical cystectomy over 20 years follow up[14] with most cases within the first 2 years. Tumour recurrence can occur locally in the pelvis, upper urinary tract, urethra or metastases to lung, liver and bone. Cross-sectional imaging is therefore required with intervals dependant on postoperative stage of disease and nodal involvement.

Metastatic disease

Approximately 10–15% of patients with bladder cancer have metastatic disease at diagnosis. Systemic chemotherapy can achieve some degree of response and, where clinically appropriate, treatment can prolong survival up to 12–14 months. Cisplatin-containing combination chemotherapy regimens are the standard first-line treatment. However, significant side effects are associated with such treatments and therefore careful consideration of the costs and benefits are made on an individual basis.

Metastatic bone disease is common in patients with advanced bladder cancer (30–40%), with consequential impacts on pain and quality of life. Zoledronic acid and densumab work to inhibit bone resorption and can therefore alleviate the pain associated with skeletal metastases. European guidelines recommends palliative cystectomy should only been offered when it is the only option. The alternatives are repeated transurethral resection, palliative radiotherapy or chemotherapy or best supportive care with or without nephrostomy insertion to relieve urinary obstruction. Involvement of the specialist palliative care team is necessary in such patients.

Novel immunotherapeutic agents

The premise of immunotherapy in cancer treatment is to allow or stimulate the body's own immune defenses to target tumour cells. Tumour cells have a number of mechanisms to avoid detection by the host immune system, this includes downregulation of tumour antigens and expression of immunosuppressive cell surface proteins. The programmed death ligand-1/programmed cell death protein-1 (PD-L1/PD-1) axis has been a focus of investigation in many tumour types. It has been shown that binding of PD-L1 on tumour cells to PD-1 on T cells leads to an immunosuppressive effect, allowing tumour cells to avoid detection by the host immune system. In addition, increased levels of PD-L1 expression has been correlated to increased postoperative recurrences, BCG resistance and reduced survival in bladder cancer.

A number of agents targeting this axis have been granted FDA approval and are either awaiting or have been given approval in Europe. The various drugs and the results of recent trials are summarized in Table 2. The first agent to be granted FDA approval was atezolizumab, a PD-L1 inhibitor, for the treatment of metastatic or locally advanced bladder cancer which progressed with or after platinum based chemotherapy or in those unsuitable for platinum based chemotherapy. Trials of some immunotherapy agents have shown results comparable or exceeding those of current chemotherapy agents with a more favourable side effect profile. A potential future use of these agent is tailoring the agent according to tumour cell phenotype, as trials have shown differing response to immunotherapy agents according to PD-L1 expression.

Conclusions

Urothelial carcinoma of the bladder comprises two recognized disease entities with distinct molecular features and clinical outcomes. Low-grade non-muscle-invasive tumours recur frequently but rarely progress to muscle invasion, whereas muscle-invasive tumours are usually diagnosed *de novo* and frequently metastasize. Technological advancements have allowed more accurate visualization of bladder tumours using PDD, NBI and SPIES. The use of new energy modalities has allowed the development of en-bloc resection which may overcome the drawbacks of traditional TURBT. Intravesical therapies for NMIBC have been investigated, including chemo-hyperthermia, BCG in combination with EMDA-MMC and intravesical gemcitabine. Minimally invasive radical cystectomy has been increasing in popularity over the past 10 years with growing evidence for robotic cystectomy. For patients who wish for bladder preservation, TURBT with combination chemotherapy and radiotherapy regimens has shown equivalent outcomes to radical surgery for selected patients. The management of metastatic bladder cancer is undergoing a revolution through the use of novel systemic immunotherapy agents. ◆

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