Carcinoma of the bladder

Cancer of the bladder is a commonly diagnosed malignancy that is frequently seen in the elderly population and accounts for significant morbidity and mortality. The annual statistics for the UK report that 10,000 cases are diagnosed and that there are almost 5000 deaths each year, of which 90% are in people over the age of 65 years. Almost 90% of the patients have transitional cell carcinoma of the bladder.

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Bladder cancers represent a spectrum of disease processes varying from early superficial bladder cancers that can be treated by local resection, often in combination with intravesical therapies, to aggressive muscle invasive bladder cancers that are treated by neoadjuvant chemotherapy. This can be followed by cystectomy or radiotherapy to those cancers that have metastasised to distant sites and are managed with palliative therapies including chemotherapy and local radiation. The management of bladder cancers presents many challenges to the multidisciplinary team, especially as this group of patients often have other medical comorbidities.

Incidence, survival and death rates

It is estimated that 356,000 new cases of bladder cancer are diagnosed worldwide each year. Bladder cancer is the seventh most common malignant tumour diagnosed in the UK, with over 10,000 people diagnosed each year.[1] It is more common in the elderly, and 80% of those diagnosed are over the age of 65 years. There are more than twice as many cases diagnosed in men (male: female ratio is 5:2), making it the fourth commonest cancer in men and the 11th commonest in women in the UK.

The overall five year survival rates for bladder cancer are approximately 60%. The most important factor in determining survival is the stage at diagnosis. Those bladder tumours that are classified as superficial (not invading beyond the lamina propria) have five year survival rates between 80% and 90%. This contrasts with those patients who have muscle invasive tumours, who have five year survival rates of around 50%. It is therefore very important to diagnose these malignancies at an early stage when the tumour is still superficial. Survival rates are also higher for patients who are diagnosed at an earlier age.

A consistently improved survival advantage has been demonstrated for men in comparison to women, with five year survival rates of around 66% and 57% respectively in the UK. It has been suggested that these differences may be due to earlier diagnosis in men, but the differences are still apparent for relative survival rates. Other suggestions have included the differences in the male to female bladder anatomy, but the reasons for these survival differences are not completely understood.[2]

Bladder tumours are the eighth most common cause of cancer death in the UK (4,900 deaths each year), and 90% of those deaths are in people over the age of 65 years.

Aetiology

The most common risk factor associated with bladder cancer is cigarette smoking,[3] which has been estimated to be a causal factor in up to two thirds of men and one third of women diagnosed with this disease. The risk of developing bladder cancer increases with the duration of smoking history and the number of cigarettes smoked each day, and is around two to six times higher than for non-smokers. The risk is reduced with cessation of smoking but it takes around 20 years for the incidence to reach the same levels as a non-smoking population. The exact mechanism by which cigarette smoking induces

Box 1: Risk factors for bladder cancer

Cigarette smoking
Aromatic amines such as benzidine and ß-naphthylamine (eg, used in industry for manufacture of dyes and pigments, rubber industry and pesticides)
Polycyclic aromatic hydrocarbons – combustion processes
Hair dyes (possible)
Medicines (eg, phenacetin and cyclophosphamide)
Radiation to the pelvis
Medical conditions (eg, paraplegia)
Hormones
Family history
Food and drink

bladder cancer remains unclear. It has been reported that some smokers have higher levels of aromatic amines in their urine, which are classified as urothelial carcinogens.

It has been estimated that up to 5–10% of male bladder cancers in Europe are caused by occupational exposure.[4] There is a strong association between exposure to aromatic amines, such as benzidine and ß-naphthylamine, and bladder cancer. These compounds were frequently used in the manufacture of dyes and pigments for paper, plastics, textiles and hair dyes. They were also used in drugs and pesticides, and used as antioxidants in the rubber and cable industries. Since 1953, bladder cancer has been classified as a prescribed industrial disease. Exposures to polycyclic aromatic hydrocarbons have additionally been associated as a causative factor for bladder cancer in around 4% of European men. These are by-products of combustion processes and are present in a range of large industries. There has been some debate about the use of hair dyes as a risk factor for bladder cancer. Initial occupational studies of hairdressers suggested an increased risk for those chronically exposed to the chemicals in these dyes, but a recent report[5] with more modern hair dyes has contradicted this. In medical practice, certain drugs such as phenacetin and chemotherapy agents (eg, cyclophosphamide) are known to be carcinogenic to the bladder. Radiation exposure including therapeutic radiotherapy to the pelvis for pelvic malignancies is also known to increase the risk of bladder cancer. It is important to monitor patients treated in these ways very carefully for potential symptoms of bladder cancer.

Other medical conditions can also predispose to bladder malignancies. It is known that paraplegics have a greater risk of squamous carcinoma of the bladder and this has been attributed to recurrent urinary tract infections and increased incidence in urinary tract stone formation. There have been associations reported with genital warts and HPV infections and early menopause.

A positive family history with first-degree relatives can increase the risk of an individual developing bladder cancer by 2–6 fold, especially if the relative was diagnosed before the age of 45 years.

The relationship between diet and bladder cancer is poorly understood. There have been various reports of fruit reducing the risk of bladder tumours with other compounds such as soya, maraschino cherries and heavy coffee consumption potentially increasing the risk. There are also geographical differences, with a very high incidence rate in certain areas of Africa and the Middle East where urinary schistosomiasis is endemic.

Clinical presentation

The most common presentation of bladder cancer in over 80% of cases is visible (macroscopic) haematuria. This is usually painless and often intermittent. Haematuria is not specific and other non-malignant conditions such as infection or inflammation of the urinary tract may present in a similar way. However since early detection is vitally important to increase the cure rate of bladder tumours, it is essential that any patient with haematuria is urgently referred to a urology clinic under the two week rule for urgent investigation. Other symptoms include lower urinary tract symptoms with urinary frequency, dysuria and urgency. Patients with advanced disease can present with pelvic or bony pain, lower-extremity oedema from iliac vessel compression, or flank pain from ureteral obstruction.

Investigations

Patients with haematuria must be referred as suspected cancers to the urologist for further investigations. Most hospitals have a one-stop urology clinic. Urine analysis should be performed for cytology and culture. Flexible cystoscopy is performed to visualise the urethra and bladder and to biopsy any abnormal areas for diagnosis of bladder tumours. Imaging of the upper urinary tracts with an ultrasound scan of the kidneys and bladder and/or an IVU (intravenous urogram) or a CT scan of the abdomen and pelvis is an alternative. These

investigations will help to differentiate bladder cancer from other conditions presenting with haematuria including kidney or bladder stones, infections and carcinomas of the kidney or upper urinary tract. In women, a gynaecological investigation may be necessary to determine the site of the bleeding. A recent prospective analysis of over 4000 patients attending a protocol-driven haematuria clinic in the UK found that 10% of patients investigated had bladder cancer.[6]

If a tumour is confirmed, a further rigid cystoscopy is performed with transurethral resection of the bladder tumours (TURBT) under a general or spinal anesthetic. A biopsy of any suspicious lesions must be performed and an attempt must be made to include the bladder muscle in the biopsy specimen and from the border of the resected area, as this will give information on the grade of the tumour and the depth of invasion. Patients should receive a single dose of intravesical chemotherapy immediately after the TURBT as this has been shown to reduce the risk of implantation of bladder cells released during the procedure. A recent development to enhance the detection of bladder tumours has been the use of photodynamic or fluorescence cystoscopy. A photosensitising compound (hexaminolevulinate) is inserted into the bladder prior to the cystoscopy and this causes tumours and suspicious areas within the bladder to fluoresce bright pink when a "blue light" is shone into the bladder during the procedure. This technique has been shown to increase the detection of flat lesions and especially carcinoma-in-situ (CIS), which had been traditional difficult to detect with conventional cystoscopy.[7]

For patients being considered for radical treatment, further staging investigation includes a CT scan of the chest abdomen and pelvis and a bone scan to determine the presence or absence of local or distant metastases.

Staging and pathology

The most commonly used staging system is the TNM (tumour, nodes, metastasis) system (box 2). This incorporates local staging with depth of cancer penetration within the bladder wall and also local or distant metastases.

The most common type of bladder cancer is transitional cell carcinoma, which arises from the urinary tract epithelium and accounts for more than 90% of all bladder cancers. Bladder cancers are separated clinically into superficial tumours and muscle invasive tumours depending on their depth of invasion. The tumour is also graded using the World Health Organization classification, with Grade 3 being the most aggressive: grade 1 — well differentiated tumour; grade 2 — moderately differentiated tumour; grade 3 — poorly differentiated tumour.

CIS is where very early, high grade, cancer cells are detected only in the innermost layer of the bladder lining and has particular prognostic implications as will be discussed below.

Other tumour types can be diagnosed in the bladder. Squamous cell carcinoma accounts for only 3–7% of bladder cancers in Western countries, but in certain countries where parasites are very common (especially schistosomiasis), it is found much more frequently. The parasites can cause chronic irritation of the bladder and development of cancer. Adenocarcinoma of the bladder accounts for around 1–2% of bladder cancers and can also be seen as metastases from other primary sites. Other rare malignancies tumours of the bladder include small cell carcinoma, sarcoma, lymphoma and malignant melanoma

Management of bladder tumours

Management of all bladder tumours must be discussed at a multidisciplinary meeting. Tumour factors such as grade, size, number, stage and CIS, response to previous treatment and patient factors such as age, comorbidities, life expectancy, performance status, side effects of treatment and impact on quality of life and bladder symptoms are taken into consideration.

There are three main types of bladder cancer: superficial, muscle-invasive and advanced or metastatic disease, and the management of each will be considered separately.

Superficial bladder tumours

Superficial bladder cancers (or non-muscle invasive — NMIBC) account for about 70–80% of bladder tumours. The majority of superficial tumours can be effectively treated with resection with or without additional intravesical therapy. However there can be a tendency for recurrence and progression to invasive disease dependent upon the presence or absence of pathological prognostic factors.

Superficial bladder cancers can be classified into three risk groups, low-risk, intermediate-risk and high-

risk groups according to pathological stage (pT), size and number of tumours and histological grade.

Low-risk patients have a very low risk of progression (1-5% at five years) and the aim of therapy is to prevent recurrence, which can occur in 15-24% of patients at one year and 31-46% at five years. Treatment consists of TURBT followed by a single instillation of intravesical chemotherapy with mitomycin C within six hours.[8] These patients continue with regular cystoscopic surveillance.

Patients with intermediate-risk disease (pTa G1, G2 more than 3 cm in diameter and multiple or recurrent tumour pT1G 2 less than 3 cm in diameter and solitary tumour) have a significant risk of recurrence (24–38% at one year and 46–62% at five years) and a moderate risk of progression (up to 17% at five years). These patients are treated with TURBT followed by a single instillation of intravesical chemotherapy with mitomycin C within six hours and are considered for further bladder instillations. This is given as six weekly doses of intravesical chemotherapy usually with either mitomycin C or epirubicin. The side effects of intravesical chemotherapy include irritative bladder symptoms with dysuria and frequency, and haematuria. Allergic skin reactions have been reported with mitomycin

High-risk patients have a significant risk of progression to muscle invasive bladder cancer with reported rates of 6–45% at five years. Those patients who progress have a worse outcome than those treated for primary muscle invasive bladder cancer. They are treated with TURBT followed by a single instillation of intravesical chemotherapy with mitomycin C within six hours and intravesical BCG (Bacillus Calmette-Guerin), which involves six weekly installations. BCG has been shown to be effective for high-risk superficial bladder and CIS.[9] Following the induction course, patients are reassessed with a cystoscopy. If there is a complete response to therapy, they proceed to a maintenance course of intravesical BCG. This involves three weekly instillations at three and six months, and then three weekly instillations every six months for a total of three years. There are regular cystoscopic reviews to ensure ongoing remission. The side effects of intravesical BCG include local toxicity, such as bacterial cystitis, BCG induced cystitis, and macroscopic haematuria, which occurs in 75% of patients and also systemic side effects including fever, general malaise and skin rash.

Patients who fail to respond to intravesical therapy or who progress to muscle invasive disease should be considered for salvage cystectomy.

Box 2: TNM staging for bladder cancer

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumour"
T1	Tumour invades sub epithelial connective tissue
T2	Tumour invades muscle
pT2a	Tumour invades superficial muscle (inner half)
pT2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4a	Tumour invades prostate, uterus, vagina
T4b	Tumour invades pelvic wall, abdominal wall regional nodes (those within true pelvis; all others are distant lymph nodes)
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node, 2 cm or less in greatest dimension
N2	Metastasis in single lymph nodes, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node, more than 5 cm in greatest dimension

Distant metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Muscle invasive bladder cancer

Patients with evidence of muscle invasion on bladder biopsy, but no evidence of metastatic disease on staging investigations are amenable to local radical treatment. This group accounts for around 20% of all new diagnoses, and a further 2% will be those patients who have progressed for superficial disease. There is no consistent evidence from superiority of the two main radical treatments: radical radiotherapy or radical cystectomy. Management decision should take into account patient factors such as age, renal function, comorbidities, performance status and patient choice.

For those patients who are fit for curative treatment, the current standard of care is a combination of

neoadjuvant chemotherapy with MVAC (methotrexate, vinblastine, adriamycin and cisplatin) or gemcitabine and carboplatin followed by radical cystectomy or radical radiotherapy. Usually patients receive three to four cycles of neoadjuvant treatment.

Neoadjuvant chemotherapy before radical surgery or radiotherapy has shown a 5% survival benefit at five years.[10] All patients will need to have an EDTA assessment prior to chemotherapy to assess their renal function. Those patients with poor renal function or comorbidities and hence not suitable for neoadjuvant chemotherapy may still be appropriate for radical treatment and can be offered radical cystectomy or radical radiotherapy.

Cystectomy

Radical cystectomy involves the removal of the bladder and draining lymph nodes. In women the urethra lower end of ureters, anterior wall of vagina, uterus, fallopian tubes and ovaries are also removed. In younger women, the ovaries may be preserved. In men, cystectomy involves removal of the bladder, prostate, lower end of ureters and sometimes the urethra. The operation has to be extensive due to the likelihood of local invasion from the original site. The ureters can be attached to the ileum with the formation of an ileal conduit, or in some cases an orthotopic neobladder can be constructed. The reported long-term effects of radical cystectomy with pelvic lymph node dissection with invasive bladder cancer from large series demonstrate 2·5% peri-operative deaths and 28% early complications. Recurrence-free and overall survival at five years have been reported as 68% and 60%, respectively, and 66% and 43%, respectively, at 10 years.[11]

Radical radiotherapy

External beam radiotherapy can be delivered to the whole bladder to a dose of 64 Gray in 32 fractions over a period of six and a half weeks. The advantage of radiotherapy over cystectomy is bladder preservation. Side effects during treatment are usually reversible and include fatigue, skin erythema, urinary frequency, dysuria, diarrhoea and proctitis. There can also be "late" toxicities[12] that are permanent and can cause chronic reduced bladder capacity due to fibrosis, which can lead to the need for cystectomy due to a small and nonfunctional bladder. Other long-term side effects can include haematuria, urinary incontinence, faecal urgency and rectal bleeding. In men, there is a risk of permanent erectile dysfunction. Overall survival rates of 40–50% for T2 tumours, 20–30% for T3 tumours and 5–10% for T4 tumours have been reported with radical radiotherapy. More recently, clinical studies of chemo-radiotherapy have demonstrated improvements in survival rates and bladder preservation rates.[13]

The results of the UK BC 2001 study should help to clarify whether chemo-radiotherapy is a valuable option in the conservative management of invasive bladder cancer. For patients with local relapse after radical radiotherapy, a salvage cystectomy can be considered depending on performance status and fitness for a surgical approach.

Advanced or metastatic disease

Patients with advanced or metastatic disease are diagnosed with or have progressed to have disease that has spread to distant sites and are not suitable for radical local therapy. Treatment aims are to palliate symptoms and slow disease progression. These patients may present with local symptoms such as haematuria, urinary outflow obstruction, back pain due to ureteric obstruction, pelvic pain, lymphoedema, chest symptoms or bone pain. Based on patient symptoms and fitness, one could consider local radiotherapy, chemotherapy or supportive care.

Local symptoms are often best treated with palliative radiotherapy. Palliative radiotherapy is very effective in relieving haematuria and urinary symptoms due to locally advanced bladder cancer.

A randomised trial has shown 21 Gy in three fractions over one week has similar palliation rates when compared to higher dose palliation of 35 Gy in 10 fractions over two weeks.[14] Thus a short course of palliative radiotherapy may be beneficial and is usually with minimal toxicity.

Ureteric obstruction caused by bladder tumour could be relieved by either stent insertion, TURBT or palliative radiotherapy. Bone pain due to metastases can be treated by analgesics and short courses of palliative radiotherapy. A single treatment with radiotherapy can often be beneficial for painful bone metastases.

Those patients who have rapidly progressive metastatic disease or are symptomatic can be offered palliative chemotherapy. It is important to take into consideration patients' ability to tolerate treatment, and the treatment should be effective and have reasonable chance to improve tumour related symptoms. The toxicity of chemotherapy should not exceed tumour related symptoms.

Response rates to palliative chemotherapy are not very encouraging and median survival is in the order of six to nine months. Various combination chemotherapy

schedules are available – MVAC (methotrexate, vinblastine, adriamycin and cisplatin), CMV (methotrexate, vinblastine, and cisplatin) and gemcitabine and carboplatin. The preferred combination is gemcitabine and carboplatin as it has similar survival rates and less toxicity compared with MVAC chemotherapy.[15] Combination chemotherapy can prolong symptom-free and overall survival in patients with advanced bladder cancer.

Future of bladder cancer

Bladder cancer is a common disease and has excellent cure rates when detected at an early stage. Clinical research efforts are investigating early detection and this needs to be matched with greater awareness. Cigarette smoking is a major causative factor and programmes to aid cessation of smoking to prevent bladder cancer and other life threatening conditions must continue. In the future, targeted screening programmes may assist in detecting the disease at an earlier stage. Clinical trials are investigating a variety of compounds and antibodies (eg, BTA and NMP22) that can be detected in the urine and may be beneficial for future screening. Advances in surgery include the potential use of laparoscopic or robotic assisted cystectomy, which is now under investigation. There are several clinical trials investigating how radiotherapy is best used to treat invasive bladder cancer and also the optimal combinations with concomitant chemotherapy. Many clinical trials are under way to test new combinations of chemotherapy drugs for advanced bladder cancer. The evidence base to determine optimal therapies and their timing is rapidly growing and we await the results of trials of conventional combinations and also the newer targeted drugs and chemotherapy with great interest.

Conflict of interest: none

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