Prompt diagnosis key in bladder cancer

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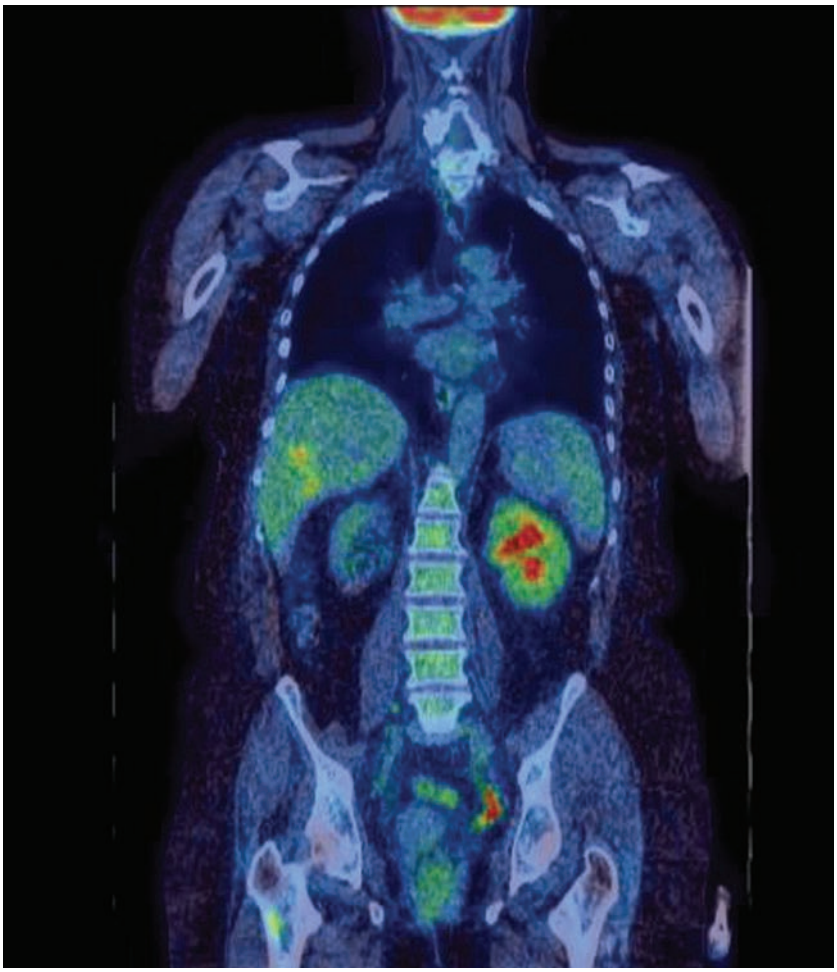


FIGURE 1
Metastatic transitional cell carcinoma of the bladder: FDG PET CT scan demonstrating metastases in the liver and extensive bone metastasis including right proximal femur and multiple vertebrae. Note the presence of left-sided hydronephrosis

How should bladder cancer be diagnosed?

What are the treatment options?

How should patients be followed up?

BLADDER CANCER IS THE MOST FREQUENTLY DIAGNOSED CANCER INVOLVING THE URINARY tract and is the seventh most common cancer in the UK. It accounted for 10,324 new diagnoses of cancer in 2010 and 5,081 deaths in 2011.[1]

Delayed diagnosis is associated with high-grade muscle invasive disease which has the potential to progress rapidly, metastasise and is often fatal.

Urothelial cancer — transitional cell carcinoma (TCC) — is the predominant histological subtype in Europe, where it accounts for 90% of all bladder cancers. Non-urothelial cancers i.e. of mesenchymal origin (which include mixed carcinoma, adenocarcinoma, sarcoma, and small cell carcinoma) are frequently found in other parts of the world. In the Middle East and North Africa squamous cell carcinoma accounts for up to 50% of bladder cancers which is attributed in part to the prevalence of schistosomiasis.

PRESENTATION

Haematuria which is typically intermittent, frank, painless and at times present throughout micturition is the classical and most common presentation of bladder cancer. However, irritative symptoms such as dysuria, urgency, urge incontinence and frequency as well as obstructive symptoms i.e. feeling of incomplete voiding, intermittent stream and straining can also be experienced.

Pain (abdominal, bone, flank, or pelvic) can be attributed to locally advanced or metastatic tumour. The distribution of pain is related to the size and location of the primary tumour or its metastases. Pain may accompany other benign diagnoses e.g. urinary tract infection, prostatitis or passage of renal calculi, this often contributes to delays in diagnosis and subsequently a poorer prognosis.

A diagnosis of bladder cancer is 15% more likely in patients presenting with gross haematuria than in those with microscopic haematuria.[2-4]

Fatigue; weight loss; anorexia; renal failure; respiratory symptoms (e.g. cough, dyspnoea, haemoptysis) and a suprapubic palpable mass are usually signs of advanced or metastatic malignancy. »

Table 1

Haematuria: Indications for specialist referral adapted from NICE CG27: Referral guidelines for suspected cancer

Urgent referral
● Painless frank haematuria
● Patients with symptoms suggestive of urinary tract infection (UTI) presenting with frank haematuria in whom infection is excluded
● Patients aged 40 and over presenting with recurrent/persistent UTI associated with haematuria
● Patients aged 50 and over with unexplained microscopic haematuria
● Abdominal mass identified on clinical or radiological exam arising from the urinary tract
Non-urgent referral
● Patients aged under 50 with microscopic haematuria with normal creatinine and no proteinuria

Table 2

Classification of bladder cancer

Non-muscle invasive bladder cancer (NMIBC)
Cancer is confined to the bladder mucosa (urothelium, lamina propria) and has not infiltrated the muscular wall. (Ta, CiS, T1)
Muscle-invasive bladder cancer (MIBC)
Cancer has invaded the muscular wall of the bladder and/or spread to nearby organs and/or lymph nodes. (T2-T4)
Advanced/metastatic disease
Cancer has spread to distant organs (lung, liver, bone, brain) and lymph nodes

The NICE guidance on specialist referral for patients with haematuria is summarised in table 1, above.

AETIOLOGY

Risk factors for the development of bladder cancer are strongly linked to lifestyle and environmental influences.

'Smoking is the main risk factor for bladder cancer'

Smoking is the main risk factor for bladder cancer.[5-7] Cigarette smokers have up to four times the risk of developing bladder cancer compared with non-smokers. The risk is proportional to the number of pack years of smoking. In fact exposure to tobacco carcinogens in utero or during breastfeeding may lead to bladder cancer in later life. Smoking cessation reduces risk, but risk in ex-smokers remains higher than non-smokers for more than 20 years.[8]

Other risk factors include:

- Exposure to aniline dyes
- Long-term cyclophosphamide use[15-16]
- History of pelvic radiation (as treatment for cervical, testicular or prostate cancer)[11-14]
- Exposure to chemical carcinogens associated with certain industries (e.g. rubber or leather production, aluminium smelting) and exposure to diesel exhaust[9-10]
- Spinal cord injuries requiring long-term indwelling catheters[17]
- Type 2 diabetes treated with pioglitazone[18]
- Condylomata acuminata

Studies indicate that consumption of large volumes of chlorinated water and coffee may play a role in bladder cancer development.

In many developing countries, particularly in the Middle East and Africa, chronic infection with *Schistosoma haematobium* accounts for up to 50% of cases of bladder cancer. The majority of these are squamous cell carcinomas which have a worse prognosis than urothelial cancers.

DIAGNOSIS

The GP is the patient's first point of contact and plays a key role in referring the patient for diagnosis, staging and definitive treatment.

The diagnosis of bladder cancer can be challenging and there is no substitute for a detailed history and physical examination. Though frank haematuria has a high diagnostic yield for malignancies involving the urinary tract, initial routine tests should be directed towards identifying a variety of potential non-malignant causes. Important considerations include:

- Features suggestive of a urinary tract infection
- Circumstances surrounding the haematuria i.e. fever, physical activity
- Hereditary diseases or a tendency for urinary calculus formation
- Travel abroad (schistosomiasis, malaria etc)
- Medication i.e. use of NSAIDs or cytotoxic agents (cyclophosphamide)

'The diagnosis of bladder cancer is based on urine cytology, cystoscopy and pathological assessment of bladder biopsy'

A thorough physical examination should be undertaken to identify evidence of bleeding diathesis, metastatic malignancy (cachexia, lymphadenopathy or organomegaly including prostatomegaly). Suggested laboratory investigations include FBC, coagulation, creatinine and PSA.

The diagnosis of bladder cancer is based on urine cytology, cystoscopy and pathological assessment of the bladder biopsy. It is recommended that all tumour tissue should be resected. In addition to obtaining a tissue biopsy, cystoscopy aims to assess the number of tumours and presence of muscle invasion.

An algorithm for the diagnosis and treatment of bladder cancer is shown in figure 2, opposite.

TREATMENT

The treatment of bladder cancer is complex and all cases should be discussed in a multidisciplinary team meeting attended by specialist urologists, oncologists, pathologists, radiologists and clinical nurse specialists.

Treatment is guided by the biopsy findings in particular the histological subtype, tumour grade, muscle invasion and lymph node involvement. On the basis of these findings bladder cancer can be classified for treatment purposes into non-muscle invasive bladder cancer (NMIBC), organ confined muscle invasive bladder cancer (MIBC) and advanced or

metastatic disease, see table 2, left. Each entity has its own clinical behaviour, prognosis, and treatment.

Disease staging is the next step if histology confirms muscle invasion. This can be carried out either by computer tomography (CT) or magnetic resonance imaging (MRI). CT should include the chest, abdomen and pelvis. The role of MRI is in local pelvic staging. The aim of imaging is to assess the extent of local disease (i.e. extravesical invasion, pelvic lymph node involvement) and distant disease spread. The presence of hydronephrosis predicts a poorer clinical outcome.[19]

A bone scan may be used to evaluate bone metastasis when clinically indicated. Positron emission tomography (PET) is highly specific for the presence of metastatic TCC but lacks sensitivity. It is best utilised as an imaging modality that assists in diagnostic staging dilemmas (see figure 1, p23).[20] Information obtained from pathological and radiological examination is corroborated in order to stratify disease burden on the basis of staging.

The standard staging system is the TNM (tumour, node, and metastasis) system.[21] The TNM staging system is applied to urothelial carcinoma and non-urothelial carcinomas. A consensus classification system established by the WHO and International Society of Urological Pathology (ISUP) for urothelial (transitional cell) neoplasms allows further stratification on the basis of grade.

Non-muscle invasive bladder cancer

NMIBC is treated with complete transurethral resection of bladder tumour (TURBT). Those tumours with a high risk of recurrence and »

FIGURE 2
Algorithm for the diagnosis and treatment of bladder cancer

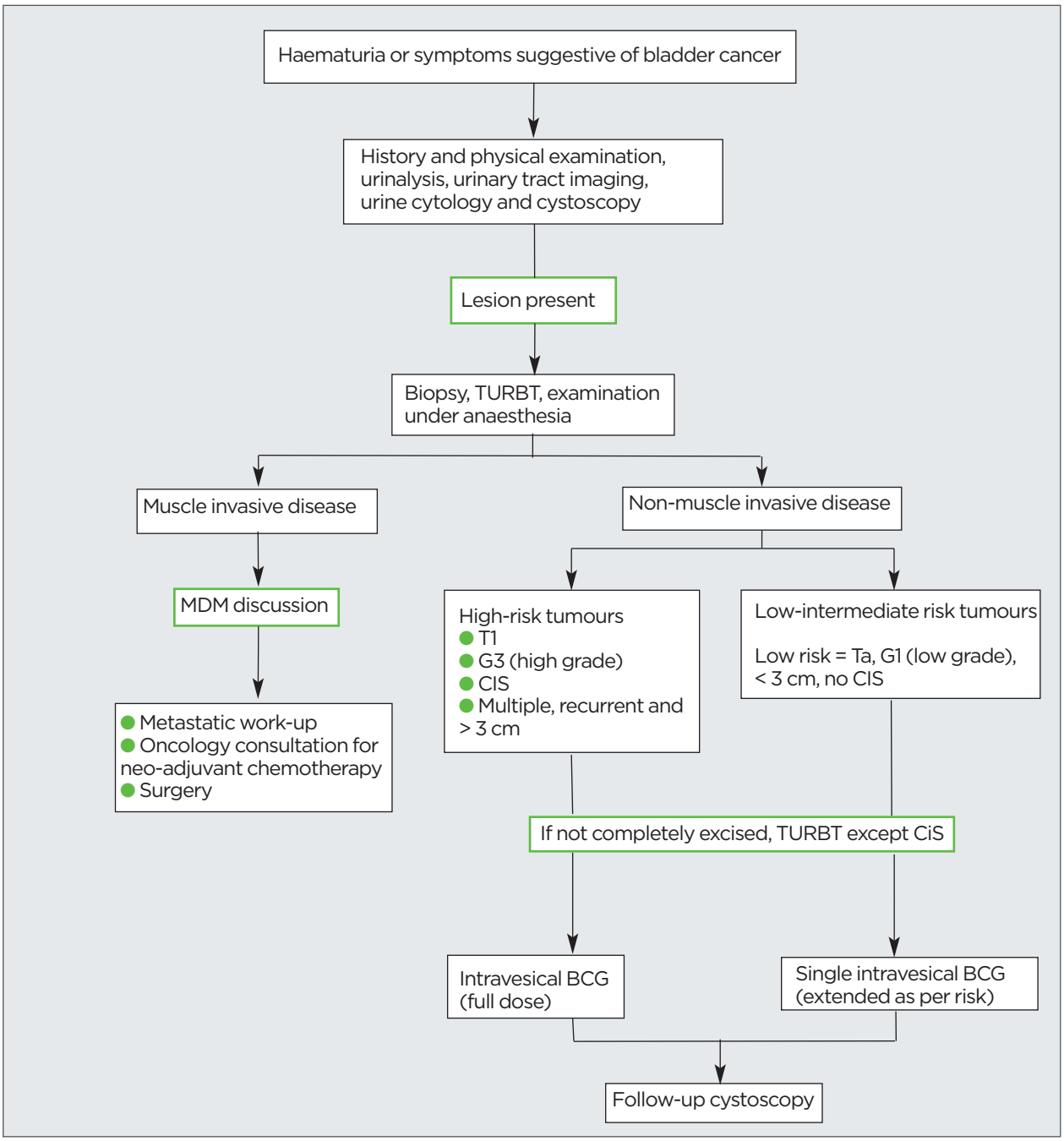


Table 3

Recommendations for surveillance after receiving treatment for bladder cancer

Treatment	Surveillance method	Frequency of follow-up
TURBT for NMIBC		
Low-risk tumours	Cystoscopy Urine cytology	At 3 months, 12 months then yearly for 5 years
High-risk tumours	Cystoscopy Urine cytology	Every 3 months for 2 years then every 6 months for 5 years and yearly thereafter[23]
Bladder preservation strategy	Cystoscopy Urine cytology	Every 3 months for 2 years then every 6 months thereafter[29]
Cystectomy	Radiological surveillance (thorax/abdomen/upper urinary tract)	Every 3 months for 2 years then every 6 months for 5 years[29]

progression after TURBT require the use of adjuvant treatments.[23-25] This entails instillation of chemotherapeutic agents, usually mitomycin C (MMC), or immunotherapeutic agents such as BCG, either alone or in various combinations.

High-risk tumours could have a second TUR. Cystectomy should be considered in patients with Tis or high grade T1 disease, if BCG has failed.

Muscle invasive bladder cancer

Radical cystectomy with lymphadenectomy (extended) or chemoradiotherapy are the definitive local treatment options. Extended lymphadenectomy may still be curative in patients with limited pelvic lymph node involvement.

Progression-free survival and overall survival have been correlated with the number of lymph nodes removed during surgery.

Urinary diversion options include urostomy (ileal conduit), Mitrofanoff, and Mainz-II. Some highly motivated patients may be suitable for a neo-bladder. Neoadjuvant cisplatin-based chemotherapy has been shown to confer a modest survival benefit, and a recent meta-analysis now suggests a similar benefit for adjuvant chemotherapy in high-risk cases.

Organ preservation using radical radiotherapy is a reasonable alternative to surgery for patients with solitary small volume TCC, with no evidence of CIS elsewhere in the bladder, no hydronephrosis, and good bladder function. They should undergo maximal resection before starting treatment.

It is also considered in patients not fit for surgery, and those who wish to avoid a cystectomy. The addition of radiosensitisers has been shown to improve outcomes.

The BC2001 study demonstrated improved local control with the addition of concomitant chemotherapy to radical radiotherapy.[26] The BCON trial demonstrated improved survival with the addition of nicotinamide and carbogen during treatment, the effect being most apparent in tumours demonstrating necrosis.[27]

Following radical radiotherapy patients need to be willing to undergo regular cystoscopic surveillance, and about 15% will subsequently require a cystectomy because of disease recurrence or development of new bladder tumours.

Advanced and metastatic disease

Cisplatin-containing combination chemotherapy with gemcitabine (GC) or accelerated MVAC (methotrexate, vinblastine, adriamycin and cisplatin) is standard in patients fit enough to tolerate cisplatin. Gemcitabine and cisplatin has been shown to have lower toxicity and is the gold standard first-line treatment in fit patients. New studies indicate the addition of paclitaxel to GC might prove beneficial.[28]

Around 50% of patients are unfit for cisplatin-containing chemotherapy because of poor performance status, impaired renal function or comorbidities. Palliation with carboplatin-based regimens or single agent taxane or gemcitabine are reasonable treatment options. Palliative radiotherapy may be used to reduce symptoms such as pain and bleeding.

FOLLOW-UP

Follow-up of patients who have received treatment for bladder cancer is imperative either for response evaluation or to detect salvageable recurrence, see table 3, above.

Response evaluation during chemotherapy is usually scheduled midway through the treatment protocol and radiographic testing is necessary.[29]

PROGNOSIS

Tumour stage is the most important prognostic factor for progression and overall survival for invasive bladder cancer. In patients with NMIBC, the number of tumours and tumour size also influence prognosis.

Age-standardised relative survival rates for bladder cancer in England during 2005-2009 show that 58.2% of men and 50.2% of women are expected to survive their disease for at least five years. The past decade has seen advances in the diagnosis and treatment of bladder cancer. Mortality rates in Europe appear to have declined in the past decade, by approximately 16% in men and 12% in women. [22] UK statistics for different stages of cancer are unavailable. Table 4, left, shows relative survival rates according to tumour stage. (These statistics are from Cancer Research UK and were obtained from different sources including expert opinion.)

Table 4

Relative survival rates for bladder cancer based on stage

Tumour stage	Relative survival rate	
T1	80–90%	5 years
T2	50%	3 years
T3	25%	3 years
T4 (amenable to resection)	30%	5 years
Distant metastases	10-15%	5 years

www.cancerresearchuk.org/cancer-help/type/bladder-cancer/treatment/bladder-cancer-statistics-and-outlook

key points

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Bladder cancer is the most frequently diagnosed cancer involving the urinary tract and is the seventh most common cancer in the UK. Delayed diagnosis is associated with high-grade muscle invasive disease which has the potential to progress rapidly, metastasise and is often fatal. Urothelial cancer (transitional cell carcinoma) is the predominant histological subtype in Europe, where it accounts for 90% of all bladder cancers.

Haematuria, which is typically intermittent, frank, painless and at times present throughout micturition, is the classical and most common presentation of bladder cancer. However, irritative symptoms such as dysuria, urgency, urge incontinence and frequency as well as obstructive symptoms can also be experienced. Fatigue; weight loss; anorexia; renal failure; respiratory symptoms and a suprapubic palpable mass are usually signs of advanced or metastatic malignancy.

Cigarette smokers have up to four times the risk of bladder cancer compared with non-smokers. Other risk factors include: exposure to aniline dyes; use of cyclophosphamide; history of pelvic radiation; exposure to chemical carcinogens associated with certain industries; spinal cord injuries requiring long-term indwelling catheters; type 2 diabetes treated with pioglitazone and condylomata acuminata.

Frank haematuria has a high diagnostic yield for malignancies involving the urinary tract and initial routine tests should be directed towards identifying a variety of potential non-malignant causes. A thorough physical examination should be undertaken to identify evidence of bleeding diathesis and metastatic malignancy. Suggested laboratory investigations include FBC, coagulation, creatinine and PSA. The diagnosis of bladder cancer is based on urine cytology, cystoscopy and pathological assessment of the bladder biopsy.

Bladder cancer can be classified for treatment purposes into non-muscle invasive bladder cancer (NMIBC), organ confined muscle invasive bladder cancer (MIBC) and advanced or metastatic disease. Disease staging can be with either CT or MRI. A bone scan may be used to evaluate bone metastasis when clinically indicated.

NMIBC is treated with complete transurethral resection of bladder tumour (TURBT). Those tumours with a high risk of recurrence and progression after TURBT require the use of adjuvant treatments. Radical cystectomy with lymphadenectomy (extended) or chemoradiotherapy are the definitive local treatment options in MIBC. Extended lymphadenectomy may still be curative in patients with limited pelvic lymph node involvement.

Follow-up of patients who have received treatment for bladder cancer is imperative for response evaluation or to detect salvageable recurrence. Tumour stage is the most important prognostic factor for progression and overall survival for invasive bladder cancer.

FUTURE DIRECTIONS

Bladder cancer is an active research area with ongoing studies into urinary biomarkers that may have a role in diagnosis or detection of recurrence of bladder cancer. Research into intravesical therapies, photodynamic therapy, surgery, radiotherapy and systemic therapy are likely to improve outcomes for patients with bladder cancer.

SUMMARY

Smoking is the main preventable risk factor for bladder cancer. The presence of unexplained haematuria requires rapid evaluation for a possible malignancy.

Cystoscopy is the initial procedure for both the diagnosis and management of urothelial malignancy. A flexible cystoscope is used for diagnostic purposes and rigid cystoscope for tissue biopsy and resection. Surveillance is important either for response evaluation or to detect salvageable recurrence.

A strong patient support network is essential to help patients with bladder cancer. The GP and community palliative care services are important members of the extended multidisciplinary team.

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Useful information

For patients
Cancer Research UK
www.cancerresearchuk.org

Macmillan Cancer Support
www.macmillan.org.uk

For healthcare professionals
European Association of Urology
www.uroweb.org/guidelines

European Society for Medical Oncology
www.esmo.org/Guidelines-Practice

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