In 2011, 7452 men and 2900 women were diagnosed with bladder cancer, making it the fourth most common cancer in men (behind prostate, lung and colorectal cancer) and the 13th most common cancer in women (Figure 1). The incidence of bladder cancer has fallen in western societies since the 1970s and this is thought to reflect a reduction in smoking prevalence and exposure to industrial carcinogens. However, the mortality has remained unchanged and consequently survival is now worse, making it the only cancer in which survival has actually worsened over the past 20 years. By comparison, over the same time period, survival rates for all other urological cancers have improved significantly.

Women have consistently worse outcomes than men: doctors interpret the clinical importance of haematuria differently in women than men, women are more likely than men to require three or more primary care consultations before referral, and women have worse survival from bladder cancer than men. Such a lack of improvement in outcomes is particularly disappointing, given that 75–80% of patients with bladder cancer have non-muscle-invasive bladder cancer at presentation (NMIBC, previously called ‘superficial’ bladder cancer), which is not immediately life threatening. In the absence of any foreseeable advances in treatment, efforts must be made to improve the early diagnosis and expeditious treatment of this disease.

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### Presenting Symptoms

The commonest presenting symptom of bladder cancer is haematuria. Visible
haematuria (also called frank or macroscopic haematuria) is associated with an 18.9% risk of urinary tract malignancy, while non-visible haematuria (also called microscopic or dipstick haematuria) is associated with a 4.8% risk of malignancy.6

Patients with visible haematuria, or those over 40 with non-visible haematuria, require referral to a urologist without delay. In England and Wales, patients with haematuria are covered by the 2005 NICE referral guidelines for suspected cancer and must be referred under the 2-week rule (Box 1). However, patients with bladder cancer can present with other symptoms such as recurrent urinary tract infections (UTIs) and lower urinary tract symptoms (LUTS). Any patient with recurrent or persistent UTI associated with haematuria, or those who also present with macroscopic haematuria, investigations should be undertaken to diagnose and treat the infection before consideration of referral. If infection is not confirmed, the patient should be referred urgently in an increase in bladder cancer diagnoses (analyses of these data are awaited).

INVESTIGATIONS

There is little benefit in investigating patients with haematuria in primary care beyond the exclusion of infection, and assessment of basic renal parameters such as estimated glomerular filtration rate (eGFR), urine albumin:creatinine ratio and measurement of blood pressure. Once referred, patients will require a flexible cystoscopy and upper tract imaging, which are usually performed in a ‘one-stop’ haematuria clinic.7

Urine cytology should not be used in primary care because of its low sensitivity; hence, a negative urine cytology result does not exclude malignancy.8 There is unit-by-unit variation in the chosen modality of upper tract imaging, but usually ultrasound, CT or CT urography are utilised. Abnormalities are found in about 20% of patients, including bladder cancer (10.3%), kidney stones (8.4%), renal cell carcinoma (1.5%) and upper tract urothelial cancer (0.3%).6

DIAGNOSIS AND TREATMENT

The diagnosis of bladder cancer is usually made at the time of flexible cystoscopy in the one-stop haematuria clinic, although about 4% of cases will be found incidentally, usually during imaging to investigate non-urological symptoms. The patient will require a further admission (within 31 days in the UK) for transurethral resection of bladder tumour (TURBT) under general or spinal anaesthesia to confirm the diagnosis (see Figure 1) and to provide pathological grading and staging. Patients should receive a single instillation of intravesical chemotherapy immediately after TURBT to reduce seeding of bladder cancer cells released during surgery, thus reducing the recurrence rate.9

STAGE, GRADE AND RISK CATEGORISATION

Pathological staging uses the standard TNM nomenclature (Box 2). There are two grading systems: the 1973 and the 2004 WHO classifications; the former is commonly used in the UK. All new bladder tumours should be discussed at the urology local multidisciplinary team (MDT) meeting. Approximately 75–80% of new tumours will be NMIBC, defined as stage Ta or T1.10,11 In the past these were called ‘superficial’ bladder cancers, but the use of

Box 1. Indications for urgent (2-week) referral in patients with suspected bladder cancer

- Male or female adult patients of any age who present with painless macroscopic haematuria should be referred urgently
- In male or female patients with symptoms suggestive of a urinary infection who also present with macroscopic haematuria, investigations should be undertaken to diagnose and treat the infection before consideration of referral. If infection is not confirmed, the patient should be referred urgently
- In all adult patients aged 40 years and older who present with recurrent or persistent urinary tract infection associated with haematuria, an urgent referral should be made
- In patients under 40 years of age with persistent asymptomatic non-visible haematuria, blood pressure, urine albumin:creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR) should be measured. Referral to a renal physician should be made only if meeting the criteria in the NICE chronic kidney disease guidelines. If renal parameters are normal, patients should be monitored in primary care with annual eGFR, ACR and blood pressure for as long as the haematuria persists, only referring to nephrology if renal function deteriorates, or to urology if there is visible haematuria. In patients aged 40 years and older who are found to have persistent asymptomatic microscopic haematuria, an urgent referral should be made to a haematuria clinic

- In patients aged 40 years and older who are found to have persistent asymptomatic microscopic haematuria, an urgent referral should be made to a haematuria clinic
this term is now discouraged as it includes patients with high-risk (HR) NMIBC who are at significant risk of progression and death from their disease.\(^5\)

Patients with NMIBC should be placed into one of three risk categories (low, intermediate and high risk) for recurrence and progression based on their stage, grade, number and size of tumours, and whether carcinoma in situ (CIS) is present (Table 1).\(^6\) This allows the most appropriate management to be selected based on the patient’s risk category.

Patients with HR NMIBC and the approximately 20% of new bladder tumours that are muscle invasive (MIBC) at diagnosis should also be discussed at a regional specialist MDT (SMDT) meeting to ensure that they receive optimal treatment.

### Treatment of Non-Muscle-Invasive Bladder Cancer

#### Low Risk

Patients with low-risk NMIBC (LR NMIBC) include those with solitary grade 1–2, stage pT1a bladder cancer. They have a very low risk of progression (Table 1) and the aim of treatment is to prevent recurrence while reducing morbidity and the cost of treatment. The mainstay of treatment is regular cystoscopic surveillance with TURBT or fulguration for recurrences. Additional intravesical therapy following ‘single-shot’ post-TURBT mitomycin C is unnecessary.

Because of the very low risk of progression, attention is now focused on reducing the cost and burden of follow-up in this group. Active surveillance of small LR NMIBC recurrences has been described and is safe.\(^7\) Ultrasound has been shown to be effective at detecting clinically significant recurrences and may eventually replace cystoscopic follow-up in this group altogether. However, large-scale prospective studies are required before such strategies can be recommended for this group.

#### Intermediate Risk

Patients with intermediate-risk NMIBC include patients with multifocal or recurrent grade 1–2, stage pT1a bladder cancer. These patients have a significant risk of recurrence and a moderate risk of progression (Table 1) and should be offered additional intravesical therapy. In the UK this usually takes the form of intravesical mitomycin. Treatment usually consists of six weekly instillations. Most patients will experience moderate cystitis and dysuria but will usually complete the course of treatment. Recently the European Association of Urology guidelines have suggested a minimum of 1 year’s treatment with bacillus Calmette-Guerin (BCG) as an alternative,\(^8\) although this has not been adopted in the UK because of the significantly greater incidence of side-effects associated with BCG.\(^9\)

#### High Risk

Patients with HR NMIBC include those with grade 2–3, stage pT1 bladder cancer with or without associated CIS. These patients have a significant risk of progression to MIBC (Table 1) and if this occurs they have a worse outcome than those with primary organ-confined MIBC. All patients with HR NMIBC should undergo an early repeat resection (re-TURBT) of the tumour site at 4–6 weeks, as it has been shown that these patients have a high rate of residual disease and up to one-third are understaged at the initial TURBT and are found to have MIBC at re-resection. All patients with HR NMIBC should be discussed at a regional bladder cancer SMdT. The optimal management of these patients is controversial and there is variation in practice. In the USA, patients are often

### 2009 TNM Classification of Bladder Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis:</td>
<td>Carcinoma in situ: ‘flat tumour’</td>
</tr>
<tr>
<td>Ta:</td>
<td>Non-invasive papillary carcinoma</td>
</tr>
<tr>
<td>T1:</td>
<td>Tumour invades subepithelial connective tissue (lamina propria)</td>
</tr>
<tr>
<td>T2:</td>
<td>Tumour invades detrusor muscle (muscularis propria)</td>
</tr>
<tr>
<td>– T2a:</td>
<td>Tumour invades superficial muscle (inner half)</td>
</tr>
<tr>
<td>– T2b:</td>
<td>Tumour invades deep muscle (outer half)</td>
</tr>
<tr>
<td>T3:</td>
<td>Tumour invades perivesical tissue:</td>
</tr>
<tr>
<td>– T3a:</td>
<td>Microscopically</td>
</tr>
<tr>
<td>– T3b:</td>
<td>Macroscopically (extravesical mass)</td>
</tr>
<tr>
<td>T4:</td>
<td>Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall</td>
</tr>
<tr>
<td>– T4a:</td>
<td>Tumour invades prostate, uterus or vagina</td>
</tr>
<tr>
<td>– T4b:</td>
<td>Tumour invades pelvic wall or abdominal wall</td>
</tr>
</tbody>
</table>

### Box 2. 2009 TNM classification of bladder cancer

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Low (%)</th>
<th>Intermediate (%)</th>
<th>High (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Total</td>
<td>50</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Recurrence (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>15–24</td>
<td>24–38</td>
<td>24–62</td>
</tr>
<tr>
<td>5 year</td>
<td>31–46</td>
<td>46–62</td>
<td>46–78</td>
</tr>
<tr>
<td>Progression (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>&lt;1</td>
<td>&lt;1–5</td>
<td>1–17</td>
</tr>
<tr>
<td>5 year</td>
<td>1–6</td>
<td>1–17</td>
<td>6–45</td>
</tr>
</tbody>
</table>

### Table 1. Risk categories for recurrence and progression of non-muscle-invasive bladder cancer.
**USEFUL WEBSITES**

- Action on Bladder Cancer: www.actiononbladdercancer.org
- Fight Bladder Cancer: www.fightbladdercancer.co.uk
- The Urology Foundation: www.theurologyfoundation.org

Bladder cancer, which can lead to problems with compliance. However, BCG has significant side-effects, weekly instillations every 6 months for 3 years. Maintenance therapy with three weekly instillations at 3 and 6 months and three are given a 6-week induction course and, offered radical cystectomy if deemed suitable. In the UK and Europe, patients are usually offered intravesical therapy with BCG. This is a live attenuated form of the Mycobacterium bovis that has been shown to be particularly effective against HR NMIBC and CIS. Patients who fail to respond or are intolerant of BCG and who have refused effects of intravesical chemotherapy and have shown promising results. However, at the present time, these treatments are indicated only in patients who have failed or are intolerant of BCG and who have refused or are unfit for radical cystectomy.

Instillations of standard intravesical chemotherapy are less effective than BCG in HR NMIBC, but device-assisted therapy such as hyperthermia and electromotive drug administration appear to augment the effects of intravesical chemotherapy and have shown promising results. However, at the present time, these treatments are indicated only in patients who have failed or are intolerant of BCG and who have refused or are unfit for radical cystectomy.

**Follow-up**

A large part of the workload of a urology department consists of regular long-term cystoscopic follow-up of bladder cancer patients, usually using a flexible cystoscope. The optimal frequency of cystoscopic follow-up is unknown. For patients with HR NMIBC, surveillance is usually lifelong and voided urine cytology should be obtained at each visit to detect CIS. The upper tracts should be imaged every 1–2 years to detect upper tract urothelial carcinoma. Alternatively, patients with LR NMIBC who do not recur can be safely discharged after 5 years.

**TREATMENT OF MUSCLE–INVASIVE BLADDER CANCER**

Most cases of MIBC are already invasive at first presentation and account for about 20% of new bladder cancer diagnoses. However, a small but significant proportion of MIBC arises as a result of progression of NMIBC, usually in the high-risk group. All cases of MIBC should be discussed and managed by the regional bladder SDT at a regional cancer centre. All patients should be staged with CT or magnetic resonance imaging of the abdomen, a chest CT and a bone scan if indicated.

Patients should be counselled by the bladder SDT team about their options, which include radical cystectomy with ileal conduit or neo-bladder reconstruction or radical radiotherapy. Both these options may be preceded by neoadjuvant chemotherapy, which has been shown to confer a 5% absolute improvement in survival at 5 years (50% versus 45%). More advanced cases may be offered palliative radiotherapy, while metastatic disease is usually managed with chemotherapy using a combination of gemcitabine and cisplatin or carboplatin, which has fewer side-effects and less nephrotoxicity than the standard regimen of methotrexate, vinblastine, doxorubicin and cisplatin.

**FUTURE DEVELOPMENTS**

New technological developments such as optically enhanced cystoscopy using photodynamic diagnosis or narrow band imaging, intravesical thermochemotherapy, and robot-assisted radical cystectomy are promising and are currently being evaluated in a number of clinical trials.

The recent publication of NICE guidelines on bladder cancer (February 2015) should improve many of the current variations in practice that exist in the UK.

Perhaps most important of all, however, is the need to raise public awareness of this common cancer because at present early diagnosis represents the best strategy for improving survival from bladder cancer. With this in mind, in the UK two bladder cancer charities, Action on Bladder Cancer and Fight Bladder Cancer have joined forces with The Urology Foundation (TUF) to launch a major campaign to raise awareness of this disease among the public and government.

**Declaration of interests**

Richard Bryan has contributed to advisory boards for Olympus Medical Systems with regard to narrow band imaging cystoscopy.

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