Two thousand and twelve cases of bladder cancer were diagnosed in Australia in 2005. Bladder cancer is a relatively common disease with high morbidity if left untreated. Bladder cancer is categorised as either ‘nonmuscle invasive bladder cancer’ or ‘muscle invasive bladder cancer’. Treatment varies significantly for each type.

Epidemiology and presentation
Bladder cancer occurs most commonly from the fifth to seventh decades of life and is more common in men. In most cases, at diagnosis the cancer will not have invaded the muscle. Bladder cancer commonly presents with intermittent or persistent microscopic or macroscopic haematuria; rates may be as high as 25% in patients with macroscopic haematuria and 9.4% in patients with microscopic haematuria. Other symptoms can include frequency, urgency and dysuria. Advanced bladder cancer can cause ureteric obstruction which manifests as hydronephrosis or deteriorating renal function.

Risk factors
Risk factors for bladder cancer include:
- Tobacco smoking (risk is related to duration and quantity consumed; cessation gradually reduces the risk)
- Aromatic amines, benzene derivatives and aniline dyes
- Drugs such as cyclophosphamide, phenacetin and arsenic
- Having undergone external beam radiotherapy for gynaecologic or prostatic cancer
- Chronic urothelial irritation secondary to urinary tract infections; kidney stones or parasitic infections may lead to bladder squamous cell carcinoma (SCC). Caffeine, artificial sweeteners and dietary factors have not been implicated.

Classification
Histological classification (Table 1) is based on the architecture and degree of differentiation. Papillomas are essentially benign and do not recur. ‘Papillary urothelial neoplasms of low malignant potential’ have a very low risk for malignant transformation but may recur and therefore require ongoing surveillance.

Low and high grade papillary urothelial carcinoma (UC) and carcinoma in situ (CIS) are ‘true’ malignancies. Carcinoma in situ, which is confined by the basement membrane, is not included in the 2004 World Health Organization classification and technically is considered
noninvasive. However, CIS is a poorly differentiated and aggressive tumour which is associated with, and may progress to, muscle invasive bladder cancer. Staging is based on the 2002 TNM Classification of Malignant Tumors (ie. tumour, nodes, metastasis) (Table 2).

Ta, T1 and CIS are traditionally categorised as nonmuscle invasive bladder cancer or ‘superficial’ bladder cancer. This however, represents a heterogeneous group of tumours with very different prognoses. Accordingly, nonmuscle invasive bladder cancer is stratified into low, intermediate and high risk groups (Table 3). Five year recurrence rates are approximately 31% for low risk, 62% for intermediate, and 78% for those with high risk bladder cancer. Progression rates to muscle invasion may be as high as 48% for T1 tumours.

Primary bladder cancer is most commonly ‘pure’ or ‘typical’ urothelial carcinoma – formerly known as transitional cell carcinoma (TCC). Other primary bladder cancers include pure SCC, adenocarcinoma, neuroendocrine or mesenchymal tumours. Figure 1–4 show histological slides which demonstrate the different features of muscle invasive and nonmuscle invasive urothelial carcinoma (or TCC).

### Diagnosis and examination

All patients with macroscopic haematuria should undergo evaluation that consists of urine cytology, cystoscopy and upper tract imaging to assess for the presence of UC. Benign causes of haematuria include urinary tract infection, foreign bodies (bladder, ureteric or renal calculi, ureteric stents) or bleeding secondary to benign prostatic enlargement.

The degree of investigation required for a single episode of microscopic haematuria is controversial. Microscopic haematuria is defined as 2–3 red blood cells per high powered field. Guidelines suggest that the

<table>
<thead>
<tr>
<th>Table 3. Risk groups for nonmuscle invasive bladder cancer</th>
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<tbody>
<tr>
<td><strong>Low risk</strong></td>
</tr>
<tr>
<td><strong>Intermediate risk</strong></td>
</tr>
<tr>
<td><strong>High risk</strong></td>
</tr>
</tbody>
</table>

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Table 1. 2004 WHO grading for urothelial carcinoma

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urothelial papilloma</td>
<td>Papillary lesion with no abnormal histological features, classified as benign, very rare but may occur in conjunction with UC, do not recur once resected</td>
</tr>
<tr>
<td>Papillary urothelial neoplasm of low malignant potential</td>
<td>Papillary lesion with no cytologic features of malignancy, negligible risk for progression, may recur</td>
</tr>
<tr>
<td>Low grade papillary urothelial carcinoma</td>
<td>Moderately differentiated papillary lesions, cytologic features of malignancy present</td>
</tr>
<tr>
<td>High grade papillary urothelial carcinoma</td>
<td>Poorly differentiated tumours, marked cytologic abnormalities</td>
</tr>
</tbody>
</table>

Table 2. 2002 TNM classification for bladder cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumour invades subepithelial connective tissue (lamina propria)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades muscle (muscularis propria), T2a tumour invades superficial muscle (inner half), T2b tumour invades deep muscle (outer half)</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades perivesical tissue, T3a microscopic, T3b macroscopic (extravesical mass)</td>
</tr>
<tr>
<td>T4</td>
<td>Invasion of adjacent structures, T4a tumour invades prostate, uterus, vagina, T4b tumour invades pelvic or abdominal wall</td>
</tr>
<tr>
<td>Nx</td>
<td>Regional nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node disease</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in single node 2 cm or less</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in single or multiple nodes between 2–5 cm</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in lymph node greater than 5 cm</td>
</tr>
<tr>
<td>Mx</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
presence of microscopic haematuria should be confirmed by repeating the urine microscopy so that at least two of three tests are positive.

Once confirmed, full evaluation is required in all high risk patients (ie. age over 40 years, smoking or chemical exposure history, or irritable voiding symptoms) without symptoms of a primary renal disorder that could account for the haematuria. Low risk patients with persistent haematuria and no symptoms of primary renal disease require imaging and either cytology or cystoscopy. Low risk patients with negative initial investigations can be monitored, however, medicolegal implications may result in a lower threshold for imaging and cystoscopy.

**Urine cytology**

Patients should have their voided urine cytology examined on 3 separate days using fresh urine.

Urine containing frank blood and the first void of the day should be avoided. The specificity of urine cytology may be as high as 90% in the hands of an experienced cytopathologist and if positive is highly suggestive of high grade UC or CIS. There is a lower likelihood of positive cytology in the presence of low grade UC.

Positive or atypical cytology may indicate the presence of UC anywhere in the urinary tract and these patients require full evaluation. High risk patients with negative cytology also require full evaluation as a negative result does not preclude bladder cancer.

**Imaging studies**

Imaging is used to examine the renal parenchyma and upper tract urothelium. Three phase computerised tomography (CT) urography is first line as the delayed contrast phase outlines the renal collecting system, ureters and bladder. Lymphadenopathy and tumour size can also be determined.

Magnetic resonance imaging (MRI) is second line, costly and is usually reserved for patients with contrast allergy, when detailed examination of the pelvic soft tissues is required, or in pregnancy. Renal impairment limits the use of contrast in both modalities. Figures 5 and 6 demonstrate the appearance of bladder cancers on cross-sectional imaging.

Ultrasonography is sometimes used in low risk patients but provides little detail about the urothelium.

Asymptomatic patients with large muscle invasive tumours or patients with bone pain or bony lesions on CT scan should undergo a nuclear whole body bone scan to assess the skeleton for bony metastases.
Positron emission tomography is a second line investigation which may be used to characterise lesions found on CT or bone scan.

**Treatment**

**Cystoscopy**

Patients with radiological evidence of a bladder lesion or positive cytology should undergo cystoscopy/biopsy/resection under general anaesthesia. Flexible cystoscopy to confirm the presence of the lesion is unnecessary. When cytology is positive and no lesions are seen in the bladder, the upper tracts should be evaluated at the time of cystoscopy with retrograde pyelograms, selective urine cytology of each kidney as well as flexible ureteroscopy if indicated.

When imaging is normal and cytology is negative, flexible cystoscopy, with the patient awake, is reasonable. Patients with abnormal flexible cystoscopy findings can then proceed to biopsy or transurethral resection (TUR) under general anaesthetic.

The goal of TUR is to resect all visible tumours and to obtain staging information. Resection into the detrusor muscle is essential to assess for muscle invasion.

Erythematous areas may represent CIS or dysplasia and should also be biopsied. If the treatments for T1 and T2 bladder cancer differ, careful staging is required to detect T2 UC. The use of a single immediate instillation of postoperative intravesical chemotherapy following TUR reduces the recurrence rate by 12% with minimal side effects. 2,18

**Adjuvant treatment for nonmuscle invasive bladder cancer**

After macroscopic tumour removal, patients with high grade nonmuscle invasive bladder cancer and CIS should undergo intravesical immunotherapy with Bacillus calmette-guerin (BCG), which prevents or at least delays recurrences.19,20 Weekly instillations are given for 6 weeks once the bladder has healed. Cystoscopy is repeated 6 weeks after the final instillation. Maximum benefit from intravesical therapy can only be obtained with maintenance BCG,2,19,20 although the optimal instillation schedule is unclear. 2,19

Adjuvant BCG treatment is not recommended for low grade nonmuscle invasive bladder cancer as these tumours respond poorly. 2 Aside from immediate postoperative instillations of chemotherapy, patients with recurrent low grade tumours can be treated with a course of intravesical mitomycin C.

**Cystectomy for muscle invasive bladder and BCG failures**

Patients with T2 tumours or BCG refractory nonmuscle invasive bladder cancer are optimally treated with cystectomy and urinary diversion. Lymphadenectomy is also performed and provides a small survival advantage. 21 The most commonly performed urinary diversions are the creation of a orthotopic neobladder or ileal conduit. Diversion type is based on patient preference and other patient factors, such as manual dexterity, renal and hepatic function, body habitus, age and previous surgery or radiotherapy. (A full discussion on urinary diversion is beyond the scope of this paper.)

Neoadjuvant chemotherapy can be given to patients with large tumours. According to a meta-analysis, this results in a 5% survival advantage at 5 years. 22 Tumours may reduce in size and unresectable lesions may become resectable. However, in these patients cystectomy is delayed and in nonresponders this may worsen survival.

Adjuvant chemotherapy should be offered to patients with positive lymph nodes following cystectomy or when there is pT3/4 disease. Tumour stage and nodal involvement are the only real predictors of survival. The 5 year survival for patients with positive lymph nodes may be as low as 33%. 2

Palliative cystectomy and urinary diversion can be performed when there is no hope of surgical cure. Suitable candidates are patients with intractable pain or haematuria requiring repeated transfusions. Bilateral ureteric obstruction can also occur and palliative urinary diversion (ileal conduit) can be performed leaving the bladder in situ. Palliative radiotherapy may alleviate symptoms. Cystectomy is not indicated as a curative procedure when there is metastatic disease.

**Radiotherapy**

While cystectomy is the ‘gold standard’ for muscle invasive bladder cancer treatment, some patients, especially the elderly or infirm, may opt for bladder preservation with multimodal treatment combining chemotherapy and radiotherapy. Where possible, these patients should undergo repeat TUR to exclude residual macroscopic tumour.

**Follow up**

Patients with nonmuscle invasive bladder cancer require follow up with repeat imaging and cystoscopy. Frequency depends on the predicted recurrence and progression rates for the particular tumour (Table 4).

Postcystectomy patients require 6 monthly contrast enhanced abdominal and pelvic CT scans and chest X-ray (or CT). Renal function should also be monitored as strictures can occur in the anastomosis between ureter and ileal conduit or neobladder. In general, surveillance is recommended for 5 years following cystectomy. Patients with orthotopic

| Table 4. Guidelines for surveillance of nonmuscle invasive bladder cancer<sup>2</sup> |
|---------------------------------|---------------------------------|
| **Low risk**                    | • Cystoscopy at 3 months        |
|                                 | • If negative follow up cystoscopy at 9 months |
|                                 | • If negative continue annual cystoscopy for 5 years |
| **High risk**                   | • Cystoscopy and cytology at 3 months |
|                                 | • If negative cystoscopy and cytology every 3 months for 2 years |
|                                 | • If negative increase interval to 4 months for third year |
|                                 | • If negative increase interval to 6 months for fourth and fifth years |
|                                 | • Annual cystoscopy thereafter |
|                                 | • Annual upper tract evaluation |
| **Intermediate risk**           | • A combination of the surveillance strategies for low and high risk bladder cancer tailored to individual needs |
neobladders should have annual cytology and cystoscopy to ensure there is no urethral recurrence.

**Conclusion**

Bladder cancer is a common disease and early detection and investigation is important. Nonmuscle invasive bladder cancer can be stratified into low, intermediate and high risk categories and patients require endoscopic resection followed by adjuvant intravesical treatment and careful surveillance.

Muscle invasive bladder cancer requires extirpative surgery in patients with good performance status. There is a role for neoadjuvant chemotherapy in some of these patients. Patients with poor performance status may benefit from multimodal therapy with TUR and a combination of chemotherapy and radiotherapy rather than cystectomy. Following cystectomy patients found to have extravesical disease (pT3 or above) and/or lymph node metastasis may benefit from adjuvant chemotherapy.

**Key points**

- The most common presentation of bladder cancer is painless haematuria.
- All patients with macroscopic haematuria or persistent microscopic haematuria should be referred to a urologist for evaluation.
- Smoking is the most important risk factor for developing bladder cancer.
- Negative urine cytology does not preclude the presence of bladder cancer.
- Patients with nonmuscle invasive bladder cancer can be treated endoscopically, while those with muscle invasive bladder cancer are best treated with cystectomy if they are surgical candidates.
- Following treatment for bladder cancer careful surveillance is required.

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**References**


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