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Bladder cancer

Current management

Background
Over 2000 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.

Objective
This article provides an update on the presentation of bladder cancer, its risk factors, investigations and treatment, and discusses the role of chemotherapy as a neoadjuvant and adjuvant treatment.

Discussion
Bladder cancer most commonly presents with microscopic or macroscopic haematuria. Evaluation is required of all patients with macroscopic haematuria, patients with persistent microscopic haematuria, and at risk patients with a single episode of microscopic haematuria. Evaluation consists of imaging, urine cytology and cystoscopy. Nonmuscle invasive bladder cancer patients can undergo tumour resection with adjuvant intravesical treatments, while muscle invasive bladder cancer patients are optimally treated with cystectomy and urinary diversion.

Keywords: urinary bladder neoplasms

Two thousand and twelve cases of bladder cancer were diagnosed in Australia in 2005.[1] Bladder cancer is categorised as either nonmuscle invasive bladder cancer or muscle invasive bladder cancer.[2] Inaccurate diagnosis can compromise survival as the two categories require very different management strategies. This article aims to provide a succinct update on the presentation, investigation and treatment of this common disease.

Epidemiology and presentation

Bladder cancer occurs most commonly from the fifth to seventh decades of life and is more common in men.[3] 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.[4] 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[5])
- aromatic amines, benzene derivatives and aniline dyes
- drugs such as cyclophosphamide, phenacetin and arsenic[5]
- having undergone external beam radiotherapy for gynaecologic or prostatic cancer[6,7]
- 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.[2]

Classification

Histological classification (*Table 1*)[8,9] 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

Table 1. 2004 WHO grading for urothelial carcinoma[8,9]

Urothelial papilloma	• Papillary lesion with no abnormal histological features • Classified as benign • Very rare but may occur in conjunction with UC • Do not recur once resected
Papillary urothelial neoplasm of low malignant potential	• Papillary lesion with no cytologic features of malignancy • Negligible risk for progression • May recur
Low grade papillary urothelial carcinoma	• Moderately differentiated papillary lesions • Cytologic features of malignancy are present
High grade papillary urothelial carcinoma	• Poorly differentiated tumours • Marked cytologic abnormalities

Table 2. 2002 TNM classification for bladder cancer[10]

T – primary tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumour invades subepithelial connective tissue (lamina propria)
T2	Tumour invades muscle (muscularis propria) • T2a tumour invades superficial muscle (inner half) • T2b tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue • T3a miscroscopic • T3b macroscopic (extravesical mass)
T4	Invasion of adjacent structures • T4a tumour invades prostate, uterus, vagina • T4b tumour invades pelvic or abdominal wall
N – lymph nodes	
Nx	Regional nodes cannot be assessed
N0	No regional lymph node disease
N1	Metastasis in single node 2 cm or less
N2	Metastasis in single or multiple nodes between 2–5 cm
N3	Metastasis in lymph node greater than 5 cm
M – metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

noninvasive.[8] However, CIS is a poorly differentiated and aggressive tumour which is associated with, and may progress to, muscle invasive bladder cancer.[11] Staging is based on the 2002 TNM Classification of Malignant Tumors (ie. tumour, nodes, metastasis) (*Table 2*).[10]

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.[12] Progression rates to muscle invasion may be as high as 48% for T1 tumours.[2]

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.[8] *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[13] 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.[13,14] Guidelines[13,14] suggest that the

Table 3. Risk groups for nonmuscle invasive bladder cancer[15]

Low risk	Solitary, primary low grade Ta
Intermediate risk	Multiple or recurrent low grade tumours
High risk	Any T1, high grade disease and/or CIS

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 irritative voiding symptoms) without symptoms of a primary renal disorder that could account for the haematuria.[16] 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,[16] 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.[17] There is a lower likelihood of positive cytology in the presence of low grade UC.[2]

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[2] 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. *Figure 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.

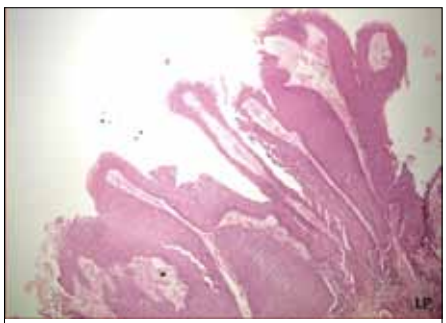

Figure 1. Low grade urothelial carcinoma. Notice the delicate papillary (frond-like) structure with a central core; uniform nuclei with mild differences in shape, contour and chromatin distribution; and infrequent mitoses. In this specimen there is no lamina propria (LP) invasion making it pTa (papillary)

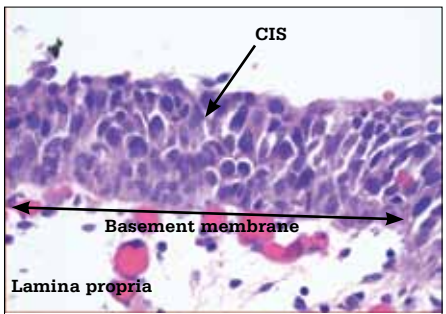

Figure 2. Carcinoma in situ (CIS). Notice the highly malignant cells with disordered architecture and pleiomorphic nuclei. Mitoses are present. The basement membrane is intact

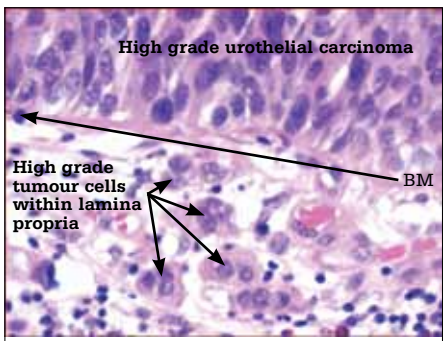

Figure 3. High grade T1 bladder cancer. Notice the disordered architecture with pleiomorphic nuclei and high nuclear to cytoplasmic ratio. Islands of tumour cells within the lamina propria make this T1 bladder cancer
BM = basement membrane

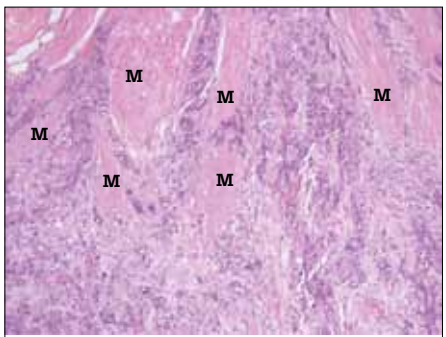

Figure 4. High grade muscle invasive (T2) bladder cancer. Tumour cells can be seen invading into the detrusor muscle (M)

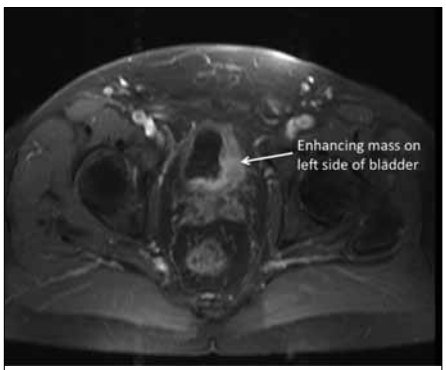

Figure 5. MRI of the male pelvis demonstrating an enhancing mass on the left side of the bladder. This patient was found to have high grade muscle invasive urothelial carcinoma

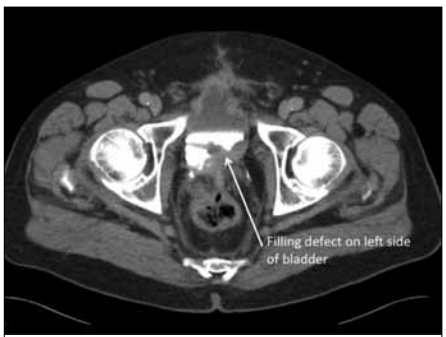

Figure 6. CT of the pelvis in the urogram phase demonstrating a filling defect in the bladder. This is a large mass consistent with muscle invasive bladder cancer

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/biospy/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. As 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[2]

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

1. Australian Bureau of Statistics. Yearbook Australia 2009–10. Canberra: ABS, 2010.
2. Babjuk M, Oosterlinck W, Sylvester R, et al. Guidelines on TaT1 (non-muscle invasive) bladder cancer, 2009. Available at www.uroweb.org/?id=218&gid=1.
3. Ferlay J, Autier P, Boniol M, et al. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007;18:581–92.
4. Khadra MH, Pickard RS, Charlton M, et al. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. J Urol 2000;163:524–7.
5. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum 2004;83:1–1438.
6. Chrouser K, Leibovich B, Bergstralh E, et al. Bladder cancer risk following primary and adjuvant external beam radiation for prostate cancer. J Urol 2005;174:107–10; discussion 110–11.
7. Boorjian S, Cowan JE, Konety BR, et al. Bladder cancer incidence and risk factors in men with prostate cancer: results from Cancer of the Prostate Strategic Urologic Research Endeavor. J Urol 2007;177:883–7; discussion 887–8.
8. Eble JN, Sauter G, Epstein JI, et al. Pathology and genetics of tumours of the urinary system and male genital organs. In: World Health Organization. Classification of tumours. Lyon: IARC Press, 2004;90–157.
9. Epstein JI, Amin MB, Reuter VR, et al. The World Health Organization/International Society of Urological Pathology. Consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. Am J Surg Pathol 1998;22:1435–48.
10. Sobin DH, Ch W, editors. Bladder cancers. New York: Wiley-Liss, 2002.
11. Sylvester RJ, van der Meijden A, Witjes JA, et al. High-grade Ta urothelial carcinoma and carcinoma in situ of the bladder. Urology 2005;66(6 Suppl 1):90–107.
12. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:466–5; discussion 75–7.
13. Grossfeld GD, Litwin MS, Wolf JS, et al. Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy-part I: definition, detection, prevalence, and etiology. Urology 2001;57:599–603.
14. Wollin T, Laroche B, Psooy K. Canadian guidelines for the management of asymptomatic microscopic hematuria in adults. Can Urol Assoc J 2009;3:77–80.
15. Lamm D, Colombel M, Persad R, et al. Clinical practice recommendations for the management of non muscle invasive bladder cancer. European Urology Supplements 2008;7:651–66.
16. Grossfeld GD, Wolf JS Jr, Litwan MS, et al. Asymptomatic microscopic hematuria in adults: summary of the AUA best practice policy recommendations. Am Fam Physician 2001;63:1145–54.
17. Lokeshwar VB, Habuchi T, Grossman HB, et al. Bladder tumor markers beyond cytology: International Consensus Panel on Bladder Tumor Markers. Urology 2005;66(6 Suppl 1):35–63.
18. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol 2004;171:2186–90.
19. Bohle A, Bock PR. Intravesical bacille calmette-guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. Urology 2004;63:682–6; discussion 686–7.
20. Sylvester RJ, van der MA, Lamm DL. Intravesical bacillus calmette-guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol 2002;168:1964–70.
21. Leissner J, Hohenfellner R, Thuroff JW, et al. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. BJU Int 2000;85:817–23.
22. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 2005;48:202–5; discussion 205–6.

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