Bladder cancer: a current update

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In the UK, 10 000 new cases of bladder cancer are reported per annum. Earlier diagnosis and better care have improved survival rates, but the incidence is still rising. This article updates the current understanding of bladder cancer diagnosis and management.

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Bladder cancer is the second commonest cancer of the genitourinary tract, and the fifth most common malignancy in Europe (Jensen et al, 1990). The annual incidence in the UK is 34.0 (male) and 13.3 (female) per 100 000 population (Office of National Statistics, 1998). Caucasians are at highest risk, with average age at diagnosis of 65 years. At the time of diagnosis most bladder cancer is organ confined, but up to 25% of cases will have muscle invasion or nodal disease (Waters, 1996).

Bladder cancer commonly presents with painless gross haematuria, but can be associated with other symptoms or signs (*Table 1*). Rarely, systemic disturbances occur during presentation of advanced disease, but generally bladder cancer has no signs at the time of diagnosis.

TABLE 1.
Presenting features of bladder cancer

Features	Frequency
Painless gross haematuria	90%
Microscopic haematuria	10%
Urinary symptoms: frequency, urgency, dysuria	25%
Systemic symptoms (bone pain or acute renal failure)	Rare

TABLE 2.
Risk factors for bladder cancer

Factor	Example
Cigarette smoking	Multiple carcinogens
Occupational exposure	2-naphthylamine, benzidine, 4-aminobiphenyl
Dietary factors	Caffeine, artificial sweeteners (controversial)
Drugs	Cyclophosphamide, phenacetin
Chronic infections	Schistosomiasis, indwelling catheters
Chromosomal changes	Alteration in tumour suppressor genes p53, Rb
Radiotherapy	For cervical cancer and thyroid cancer

Rb = retinoblastoma gene

TABLE 3.
Pathological classification of bladder tumours

	Type	Frequency
Benign	Papilloma	<2%
Malignant	Transitional cell carcinoma	90%
	Squamous cell carcinoma	5–10% (Western world)
		60–70% (Middle East/Africa)
	Adenocarcinoma	<2%
	Undifferentiated	<2%
	Mixed carcinoma	4–6%
	Epithelial/non-epithelial	Rare

RISK FACTORS

The commonest risk factor is cigarette smoking, which is thought to cause bladder cancer in 50% of men and 30% of women (Wynder and Goldsmith, 1997). Individuals working in certain industries (e.g. those involving dyes, chemicals, printing, rubber, petroleum, and leather) are also at high risk of bladder cancer (Matanoski and Elliot, 1981). Risk factors are summarized in *Table 2*.

PATHOLOGY

Transitional cell carcinoma accounts for 90% and squamous cell carcinoma comprises 5–10% of all bladder cancer in the Western world (*Table 3*). Squamous cell carcinoma is associated with schistosomiasis, which is endemic in Africa and the Middle East, accounting for 60–70% of bladder cancer (El-Bolkainy et al, 1981).

STAGING AND GRADING

Bladder cancer can be broadly divided into superficial (<pT2) and muscle-invasive tumours (≥pT2). The tumour (primary), nodes, metastasis (TNM) staging system classification (Union Internationale Contre le Cancer (UICC), 1997) allows estimation of the prognosis and selection of appropriate treatment. Pathological grade predicts recurrence, invasion and progression. Overall prognosis is estimated using both factors (*Table 4*).

MANAGEMENT

Figure 1 summarizes the investigations and treatments for superficial and invasive bladder cancer.

Urine

Urine cytology shows malignant cells, especially in high-grade tumours. Other urine tests include bladder tumour antigen (Sarsody et al, 1997) and nuclear matrix protein 22 (NMP22) (Soloway et al, 1996) which detect exfoliated markers. These tests should not be performed in the initial evaluation of haematuria but should be reserved for use in patients after diagnosis of bladder cancer.

Imaging

Ultrasound and intravenous urogram can detect bladder cancer and upper tract abnormalities. Computed tomography scan or magnetic resonance imaging and nuclear bone scan are performed to stage bladder cancer.

Cystoscopy

The best way of diagnosing a bladder cancer is via cystoscopy (rigid or flexible).

TREATMENT

Figure 1 highlights the treatment options for muscle-invasive bladder cancer. Treatment of superficial bladder cancer is summarized below, including local intravesical therapy.

Superficial cancer

Patients diagnosed with low grade, single tumour can be treated by transurethral resection followed by surveillance. The chances of recurrence and progression are high with multiple, recurrent tumours or carcinoma in situ, so intravesical therapy is recommended after tumour resection.

Intravesical therapy

Between 50 and 70% of superficial bladder cancer recurs after initial endoscopic resection. In order to prevent this, intravesical therapy is given post-resection. Many studies have shown that intravesical therapy reduces recurrence of the tumour, but none have shown evidence of definite reduction in tumour progression (Amling, 2001).

Several agents are used (mitomycin C, thiotepa, adriamycin, and doxorubicin) with limited side effects. The immunotherapeutic agent bacille Calmette-Guérin (BCG) has also a role to play. Morales et al (1976) popularized the use of this agent. The side effects can be striking, with systemic tuberculosis occurring in certain cases (Steg et al, 1989), however, in modern use these are limited. BCG has been shown to be more effective against carcinoma in situ (Rogerson, 1994).

TABLE 4.
Five-year survival rate following cystectomy

Pathological stage	5-year survival
Superficial disease	78–91%
Invasive disease	20–80%

From Stein (2000)

Muscle-invasive tumours

Transurethral resection cannot completely remove muscle-invasive bladder tumour: it only helps in diagnosing and staging the muscle-invasive disease. Similarly intravesical chemotherapy or immunotherapy has no role in invasive disease. For the last 50 years definitive treatment has consisted of either radical cystectomy or external beam radiotherapy. Among British urologists there was a reluctance to perform radical surgery (Hendry, 1986) and radiotherapy was preferred. Improvements in anaesthetic techniques, postoperative care and better knowledge of pelvic anatomy has caused a resurgence in radical surgery.

After surgery the urine is diverted via ileal conduit, orthotopic bladder reconstruction or continent urinary diversion. This aspect of the surgery requires follow up as patients can have systemic (metabolic) and local problems.

ROLE OF CHEMOTHERAPY

Chemotherapy can be given before cystectomy (neo-adjuvant) (Kolaczyk et al, 2002) or after

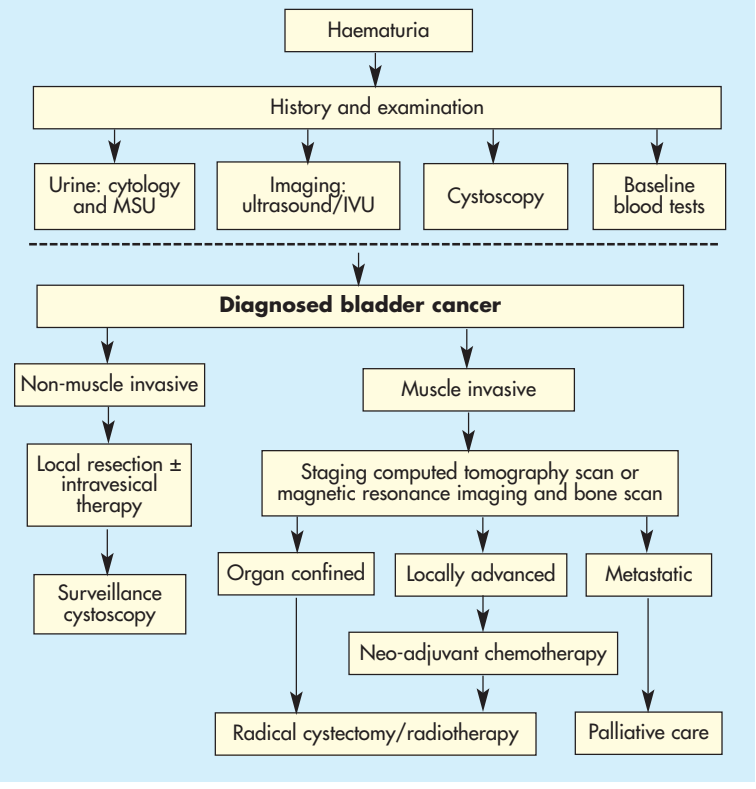

Figure 1. Simplified management pathway for bladder cancer. IVU=intravenous urogram; MSU=midstream urine specimen.

radical treatment (adjuvant). At the time of diagnosis 15% of bladder cancer patients have lymph node positive disease or distant metastasis. After cystectomy and bilateral pelvic lymphadenectomy 20–35% of patients are found to have lymph nodes affected by the cancer. Without treatment the survival is limited. Randomized prospective trials are under way to establish the role of neoadjuvant chemotherapy, but the follow-up period is still too limited to draw any firm conclusions. The commonly used chemotherapy agents are cisplatin, methotrexate, doxorubicin, vinblastine, cyclophosphamide and 5-fluorouracil. Following cystectomy, patients at high risk of systemic relapse because of lymph node metastasis or regionally advanced disease are candidates for adjuvant chemotherapy (Skinner et al, 1991).

FOLLOW-UP

After resection of superficial bladder cancer the patient is followed up cystoscopically to detect early recurrence. This is done initially every 3 months for 2 years, 6-monthly for the next 3 years and then annually for life, assuming no recurrence occurs.

Patients with treated invasive bladder cancer require monitoring of areas where transitional cell epithelium remains (kidneys, ureters) by imaging and endoscopy. Cystoscopy is required in orthotopic reconstruction as there is a potential risk of adenocarcinoma within the bowel epithelium, or recurrent transitional cell carcinoma in post-radiotherapy bladders.

RECENT ADVANCES

Currently, histological methods may not reliably predict the behaviour of bladder cancer. Profiling the disease at the cellular and molecular level may help improve this situation and thus allow tailored treatment. Current markers being developed include blood group-related antigens (ABH and Lewis antigen), microvessel density, retinoblastoma and p53 genes (Stein et al, 1998).

Intravesical therapy for high-risk patients or patients who fail first-line therapy are being developed. These agents include alpha interferon (Belldegrun et al, 1998), bropiramine (Sarosdy et al, 1998) and AD-32 (Greenberg et al, 1997).

KEY POINTS

- In the UK 10 000 new cases of bladder cancer are reported per annum.
- The commonest presenting feature of bladder cancer is painless gross haematuria.
- Smoking is thought to be responsible for bladder cancer in 50% of men and 30% of women.
- Basic investigations of urine cytology, intravenous urogram/upper tract ultrasound scan and cystoscopy should be performed in every patient suspected of having bladder cancer.

CONCLUSIONS

Early detection of bladder cancer is essential to improve survival. Improving the public's perception and health-care professionals' awareness of this is as important as reducing environmental exposure to carcinogenic factors. Future molecular profiling to predict bladder cancer behaviour will hopefully improve the treatment efficacy. HM

Conflict of interest: none.

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