Bladder cancer

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Abstract

Urothelial carcinoma of the bladder is the most common malignancy affecting the urinary tract. This review examines the current standards in the diagnosis and management of this disease. Cystoscopy and urine cytology remain important tools in the diagnosis and follow-up of bladder cancer. Alternatives include photodynamic diagnosis and narrow band imaging. These have been investigated with the aim of improving both the sensitivity of detection of tumours and improving the quality of transurethral resection which has the ultimate aim of reducing recurrence rates when compared with standard resection in white light. We discuss intravesical chemotherapy, immunotherapy and adjuncts to improve drug delivery across the urothelium. For patients with muscle-invasive bladder cancer, laparoscopic radical cystectomy and robot-assisted radical cystectomy have been shown to reduce perioperative morbidity, and are oncologically equivalent to open radical cystectomy. It remains to be seen whether equivocal perioperative morbidity justify its on-going use. Bladder-preservation strategies entail resection and chemoradiation, and in selected patients give equivalent results to surgery.

Keywords Bladder cancer; cystoscopy; intravesical therapy; narrow-banded imaging; photodynamic diagnosis; radical cystectomy; radical radiotherapy; urine markers

Introduction

Epidemiology and statistics

Bladder cancer is a malignancy affecting the urothelium of the bladder. Although this epithelial surface lines the bladder, it extends beyond this covering nearly all of the urinary tract. Bladder cancer is the most common malignancy of the urinary tract and accounts for approximately 3.2% of all cancer worldwide where it remains the seventh most commonly diagnosed malignancy in the male population.[1] It is a significant cause of cancer morbidity and mortality, accounting for an estimated 380,000 new cases and 150,000 deaths worldwide in 2008. In the UK, it is the ninth most common malignancy, with incidence being three times greater in men than in women. There were approximately 10,300 new cases of bladder cancer in the UK in 2013.[2]

The incidence of bladder cancer increases with advancing age, and the majority of cases (80%) occur in individuals' aged over 65 years. Of note, in the UK, the incidence of bladder cancer has reduced by approximately 12% in the past decade. Despite this, the mortality rate from bladder cancer has not changed for over 20-years. Overall, it remains the seventh leading cause of cancer death in the UK, and accounts for around 5200 deaths in the UK each year. Of newly diagnosed bladder cancer cases, the 5- and 10-year survival rates are 53% and 50%, respectively, in England and Wales (2010–2011).[2]

Aetiology

Causative risk factors for the development of bladder cancer can be broadly divided into inherited (genetic predisposition) and acquired (due to environmental exposure). The reality remains that one factor may not be solely responsible for the differing incidence and progression of this disease in different population groups, but rather the complex interaction between factors.

Tobacco smoking is the most important environmental risk factor for bladder cancer. It accounts for approximately 50% of bladder tumours, and smokers have a twofold to sixfold increased risk compared to non-smokers. Tobacco smoke contains known urothelial carcinogens such as β-naphthylamine and polycyclic aromatic hydrocarbons. These compounds are excreted through the kidneys and therefore exert a direct carcinogenic effect on the entire urinary system. Their likely dwell time in the bladder combined with urinary stasis increases exposure of these chemicals to bladder urothelium resulting in an increased incidence of disease in the lower urinary tract compared to the upper tract. There is a latency period of approximately 20–30 years following the initiation of smoking to the development of bladder cancer. Smoking cessation results in an immediate risk reduction of bladder cancer of approximately 40% within 1–4 years;[3] reaching an age-adjusted baseline equivocal of non-smokers by approximately 20 years.

The second most common cause of bladder cancer is occupational exposure to urothelial carcinogens. Specifically these include aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons, which are commonly found in industrial areas processing dyes, rubber, paint, metal and petroleum products. With greater occupational awareness and tighter regulations, exposure to these carcinogens is falling.

There remain other environmental influences, some known, others yet to be identified which have a limited role in the development of bladder cancer. Examples include exposure to arsenic in drinking water where large population based studies in Chile have been shown to increase the risk of bladder cancer.

Therapeutic strategies in medicine themselves can predispose individuals to bladder cancer, either as a consequence of medical treatment or through direct causation. External beam radiotherapy for pelvic malignancies can increase the risk of bladder cancer. Additionally, the cytostatic agent, cyclophosphamide, commonly used in the management of haematological malignancy has been associated with the development of squamous cell carcinomas of the bladder. Chronic inflammation is an established cause of bladder cancer, typically squamous cell carcinoma. This can develop secondary to chronic

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schistosomiasis haematobium infection, chronic cystitis, bladder calculi and indwelling urinary catheters.

Our understanding of the genetics that influence bladder cancer is growing. At present, the best-established risk factors for bladder cancer are genomic variations in the N-acetyl transferase enzymes (NAT1, NAT2) that are involved in the detoxification of extrinsic carcinogens. A slow NAT2 genotype (less effective) was found to increase the risk of bladder cancer if exposed to environmental factors such as tobacco. Furthermore, it has been shown that inherited mutations in the retinoblastoma tumour suppressor gene are associated with the development of bladder cancer. Increasing evidence has identified many other gene associations in bladder cancer, these have been linked to development, recurrence and progression risk, and whilst their definitive role remains unclear, it is hoped further research could tailor detection, prognostication and treatment strategies.

Pathophysiology

The principle histological sub-type of bladder carcinomas in the Western World is the urothelial or transitional cell carcinoma, accounting for 90% of cases. The remaining groups are comprised of squamous cell carcinoma (SCC) (5%), adenocarcinoma (2%) and other rare tumours (including sarcoma, small cell, and metastatic deposits). In countries where schistosomiasis is prevalent, SCC is more common; however, this trend is changing in favour of urothelial carcinoma with increasing environmental influences through globalization.

Bladder cancers tend to originate from the urothelial layer and stage migration is observed through direct invasion into the submucosa, lamina propria, muscularis layers and serosa. Bladder cancers have the ability to spread directly to adjacent pelvic structures, including prostate, urethra, vagina, uterus and bowel. Lymphatic spread is seen through obturator, presacral, iliac and para-aortic lymph nodes. Haematogenous spread typically results in metastatic deposit to liver, lung, bone and adrenal glands.[4]

Classification

Staging of bladder cancer: the TNM (tumour, node, metastasis) classification, based on tumour depth, nodal or metastatic spread, is widely used to stage bladder cancer and guide management (Box 1).

Approximately 75% of patients will have disease confined to the mucosa (pTa, Tis) or lamina propria (pT1), which can be classified as non-muscle invasive bladder cancer (NMIBC) (Figure 1). The remaining 25% of newly diagnosed bladder tumours invade the muscularis propria bladder wall (pT2) and are termed muscle invasive bladder cancer (MIBC).

Grading: the WHO grading of bladder cancer been updated in 2004 to recognize 'superficial' bladder cancers as a unique heterogenous group of tumours with a range of histological descriptions and clinical manifestations.[5] The new classification consists of four groups: urothelial papilloma (a benign lesion), papillary urothelial neoplasm of low malignant potential (PUNLMP) and low- and high-grade papillary cancer. This system, based on architectural and cytological findings, has greater prognostic value that the previous classification system where tumours were graded according to a scale of de-differentiation (grade I–III).

The TNM staging system for bladder cancer

Primary tumour (T)

Tx: Primary tumour cannot be assessed
T0: No evidence of primary tumour
Ta: Noninvasive papillary carcinoma
Tis: Carcinoma in situ
T1: Tumour invades lamina propria
T2: Tumour invades muscularis propria bladder wall
  T2a: Tumour invades superficial muscle
  T2b: Tumour invades deep muscle
T3: Tumour invades perivesical tissue
  T3a: Microscopically
  T3b: Macroscopically
T4: Invasion of: prostate, uterus, vagina, pelvic and abdominal wall
  T4a: Tumour invades prostate, uterus, or vagina
  T4b: Tumour invades pelvis or abdominal wall

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Single regional lymph node metastases,
N2: Multiple regional lymph nodes metastases
N3: Common iliac lymph node metastases

Distant metastasis (M)

Mx: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

Box 1

Diagnosis

Haematuria remains the cardinal sign of urothelial malignancy, with some 70% of patients with bladder cancer presenting with painless haematuria. Others present with non-specific lower urinary tract symptoms (LUTs) including recurrent infections, frequency, urgency and nocturia. Whilst it is less common for pTa and pT1 tumours to present with bladder pain, CIS might be suspected in patients presenting with non-specific LUTs resistant to treatment.

Non-specific LUTs can be found in a wide variety of urological disease and therefore a number of differential diagnosis may be suspected; including urinary tract infections, urinary calculi, renal and prostatic malignancy. Early suspicion and investigation may avoid a delay in diagnosis in some.

Urine cytology

Urine cytology allows for a non-invasive method for detecting malignant urothelial cells. It has good sensitivity and specificity for the detection of high-grade tumours and CIS (median sensitivity 64%), but a low sensitivity for low-grade tumours (median sensitivity 12%).[6] Thus, negative cytology does not exclude the presence of tumour. A number of urinary markers have been

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