Bladder cancer

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Abstract

Bladder cancer is the most frequently occurring tumour of the urinary tract and the eighth most common cause of cancer death in the UK. It is characterized by a high recurrence rate, pathological progression and poor survival in advanced metastatic disease. Owing to the long follow-up period and associated costs of disease monitoring, it is one of the most expensive cancers to manage. Local therapy and surveillance are the mainstays of management of early disease, which comprises 75% of cases. Radical surgery and radiotherapy are the main curative options in advanced non-metastatic disease. Chemotherapy can be used in a neoadjuvant, adjuvant or palliative setting. There remains a great need for effective tumour markers to aid diagnosis, staging, monitoring and predicting prognosis.

Keywords Bladder cancer; chemotherapy; intravesical therapy; radical cystectomy; radical radiotherapy; urinary markers

Epidemiology

Bladder cancer is 2.5 times more prevalent in men than women, with a peak incidence in the sixth and seventh decades of life. In the UK, it accounts for more than 10,000 new diagnoses and 5000 deaths annually. Its incidence peaked in the 1990s and has gradually declined by approximately 40% since, possibly due to reductions in smoking and occupational carcinogens, and to alterations in disease coding.[1] It remains however, a significant economic burden to the National Health Service.

Aetiology

Risk factors include cigarette smoking, occupational exposure to chemicals such as aniline dyes and aromatic amines,[2,3] consumption of analgesics containing phenacetin, chronic infection or irritation of the bladder (e.g. by indwelling catheters or calculi) and chemotherapeutic agents such as cyclophosphamide. Smokers have a fourfold increased risk compared with those who have never smoked. The risk persists for nearly 20 years before it reduces to baseline, although after only 4 years' smoking cessation the increased risk is reduced by about 40%.[4]

Pathology

Over 90% of malignant tumours of the bladder are 'urothelial' transitional cell carcinoma (TCC). Less common forms of bladder cancer include squamous cell carcinoma, adenocarcinoma and neuroendocrine tumours. Squamous cell carcinoma accounts for only for 5% of bladder cancers in industrialized countries but represents more than 50% of tumours presenting in Africa and the Middle East, where bilharzia (*Schistosoma haematobium*) is endemic. Adenocarcinoma in the bladder may represent a metastatic lesion from another pelvic organ (prostate, ovary, rectum).

Grading and staging

Tumour grade and stage are strong predicting factors for disease behaviour and prognosis. Tumours are graded from 1 to 3, higher grade lesions carrying a greater risk of tumour recurrence and progression. The universal staging system used is the TNM (tumour, nodes, metastases) classification (Figure 1).

Diagnosis

Haematuria is the most common symptom of bladder cancer and is present in almost 75% of patients. Urgent urological referral is mandated in all patients with painless visible haematuria and those over 50 years of age with microscopic haematuria. Other less common symptoms (less than 30% of patients) include urinary urgency or frequency and bladder pain. Weight loss, abdominal pain and renal impairment secondary to ureteric obstruction are usually signs of advanced disease.

All patients in whom bladder cancer is suspected are appropriately investigated with a diagnostic cystoscopy and upper urinary tract imaging by ultrasonography, intravenous urogram or computed tomography (CT) (to identify lesions within the ureter, renal pelvis and renal parenchyma). Urine cytology can be a useful test in diagnosing high-grade disease.

Initial management and staging

Primary treatment of bladder cancer is endoscopic transurethral resection of the bladder tumour (TURBT). Care must be taken to avoid perforating the bladder wall, which may be very thin, particularly around the dome in elderly women. Muscle should be included in the resection specimen to stage the disease accurately. Bimanual palpation should also be performed, although modern imaging has reduced its importance. If the tumour is palpable after resection, the tumour is staged as cT3, or cT4 if the bladder is fixed.

Seventy-five percent of patients present with 'superficial' non-muscle-invasive bladder cancer (NMIBC), which includes lesions confined to the mucosa (Ta and carcinoma *in situ*), and those that invade through the basement membrane into the lamina propria (T1). Carcinoma *in situ* (CIS) has a high rate of recurrence and progression. It usually occurs in association with high-grade papillary and invasive tumours but can also present on its own.

More than 50% of patients with NMIBC TCC experience recurrence and 10–15% progress to muscle-invasive bladder cancer (MIBC). Increasing tumour grade, stage, size and multifocality are associated with an increased risk of progression.[5]

Management of NMIBC

Further management is based upon risk factors and the stage/grade of the disease, with patients are divided into low,

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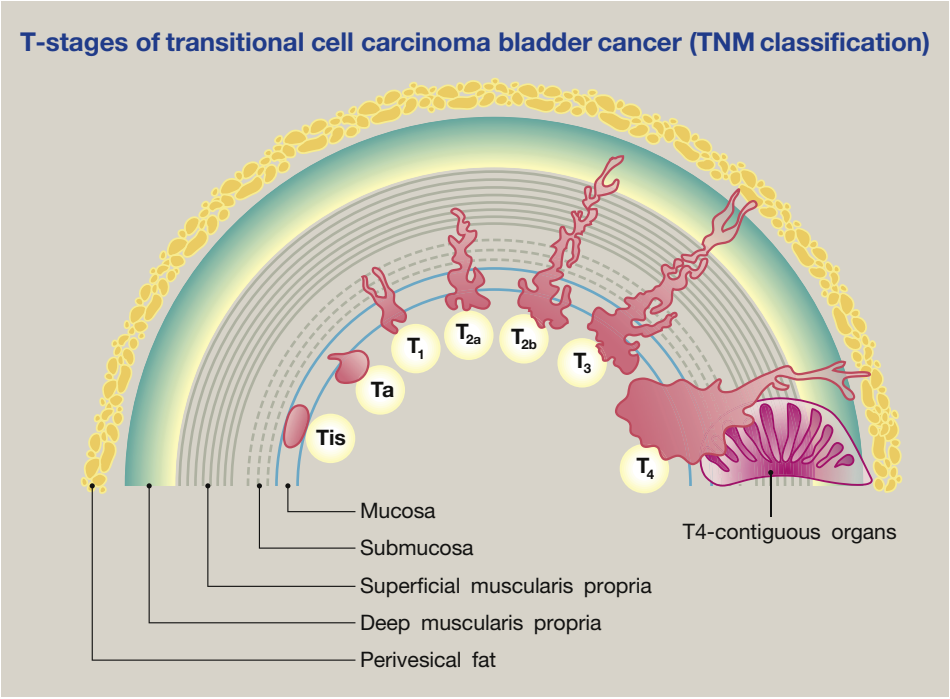

Figure 1

intermediate and high-risk groups.[6] Low-risk patients generally need only surveillance while intermediate-risk patients are recommended to have intravesical chemotherapy or immunotherapy. In patients with high-risk disease a second cystoscopy and resection is highly recommended to avoid understaging, which can occur in up to 30%. While low- and intermediate-risk patients very rarely die of bladder cancer, high-risk patients often progress to MIBC. Hence while intravesical therapy is an option they should also be offered early radical surgery (cystectomy); the only chance of cure for patients with MIBC is cystectomy or radiotherapy as discussed below, although the 5-year survival remains only 50%. An approach to the management of bladder cancer is summarized in Figure 2.

Intravesical chemotherapy and immunotherapy

It has been shown that a single installation of intravesical chemotherapy (mitomycin, epirubicin) within 6 hours of TURBT reduces the recurrence rate of NMIBC by 50%. A meta-analysis of over 2500 patients with Ta/T1 TCC suggested equal efficacy for all agents used and that recurrence rates were reduced after a median follow-up of nearly 8 years, but progression and survival were unaltered.[7] In those with intermediate-risk tumours, a subsequent course of 6-weekly mitomycin instillations is recommended.[6]

Intravesical bacillus Calmette–Guérin (BCG) remains the most effective treatment in NMIBC. Although the precise mechanism is not fully understood, it has been suggested that the key element of its antitumour activity resides in its ability to initiate extensive local inflammatory reaction in the bladder wall. The complex immunological cascade starts with the initial adherence of live attenuated mycobacteria to the urothelial lining, and proceeds to an immune response with natural killer cells and T lymphocytes as critical mediators. Due to this strong local inflammatory reaction patients very often experience adverse effects, especially irritative voiding symptoms, so it is generally reserved for high-risk patients and those with intermediate-risk who do not respond to intravesical chemotherapy.[8]

Disease surveillance

Patients should be subject to a period of endoscopic surveillance with check flexible cystoscopy under local anaesthetic 3 months after initial TURBT. Frequency of further follow-up depends on the risk group. Although recurrence is a life-long risk, patients can be discharged after a period free of recurrence (1 year if low-risk, 5 years if intermediate-risk).[6] High-risk patients should not be discharged; in addition to cystoscopy, urine cytology and CT scanning are recommended in the follow-up.

There is a need for urinary markers that can detect bladder cancer earlier and decrease the need for cystoscopic surveillance. Urine cytology has a high sensitivity (70–80%) and specificity (90–95%) for detecting high-grade disease but is poor at diagnosing well-differentiated cancers. Other bladder tumour markers have been developed and evaluated, including nuclear matrix protein 22 (NMP22), bladder tumour antigen, hyaluronic acid–hyaluronidase, ImmunoCyt™ and genomic-based markers (UroVysion® test and microsatellite analysis). Despite being approved, none has gained widespread clinical application as they cannot match the accuracy of cystoscopy.[9]

Management of T2+ muscle-invasive bladder cancer

About 15–20% of Ta/T1 bladder cancers progress to MIBC and 25% of new cases are muscle-invasive at initial presentation. MIBC have a high rate of metastatic disease and a poor long-term