Bladder Cancer

In developed countries 90% of bladder cancers are transitional cell carcinomas.\(^1\) Squamous cell carcinomas make up most of the remainder.

Cancer arising from the transitional cells of the mucosal urothelium may present as a non-invasive, papillary tumour protruding from the mucosal surface, or as a solid, non-papillary tumour that invades the bladder wall and has a high propensity for metastasis. The non-papillary tumours originate from in situ dysplasia.

Epidemiology\(^2\)

- Bladder cancer is the seventh most common cancer in the UK. It is the most frequently occurring tumour of the urinary system and accounts for around 1 in every 30 new cases of cancer each year in the UK. Bladder cancer is the 4th most common cancer in men and the 11th most common in women.
- The overall incidence in the UK is 11.4 per 100,000 population.
- Bladder cancer is the cause over more than 5,000 deaths in the UK each year.\(^3\)
- The majority of cases occur in patients aged over 60 years. Men outnumber women by 3:1 but women tend to have a poorer prognosis.

Risk factors

- The main risk factor for bladder cancer is increasing age.
- About half of bladder cancers are caused by smoking. Tobacco smoke contains aromatic amines and polycyclic aromatic hydrocarbons, which are renally excreted.
- The risk of developing bladder cancer is 2-6 times greater in smokers than in non-smokers.\(^4\)
- Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons is the second most important risk factor for bladder cancer, accounting for about 10% of all cases. This type of occupational exposure occurs mainly in industrial plants processing paint, dye, metal and petroleum products. NB: in developed industrial settings, these risks have been reduced by work safety guidelines so that chemical workers no longer have a higher incidence of bladder cancer compared to the general population.
- Other risk factors include industrial exposure to aromatic amines in dyes, paints, solvents, leather dust, inks, combustion products, rubber and textiles.
- Radiation to the pelvis and cyclophosphamide are risks.
- Squamous cell tumours usually follow chronic inflammation from stones or indwelling catheters.
- In developing countries, particularly the Middle East, squamous cell carcinoma related to schistosomiasis accounts for around 80% of cases of bladder cancer.

Presentation

- The presenting feature is painless haematuria that is gross in 80-90%. There is usually no abnormality on standard physical examination. Painless haematuria must be treated as malignancy of the urinary tract until proved otherwise.
- Advanced disease may cause voiding symptoms, although these can even be produced by carcinoma in situ (CIS).
- Although most diagnosed cases of muscle-invasive bladder cancer present as primary invasive bladder cancer, up to 15% of patients have a history of non-muscle-invasive bladder cancer.\(^5\)
- Women are more likely to present with muscle invasive disease.\(^6\)
- At diagnosis, only about 5% of patients have metastatic disease, usually to lymph nodes, lung, liver, bone and central nervous system. Around 30% have involvement of the muscle layer.\(^7\) Around 70% have superficial disease, of which 10% is CIS.

NB: Microscopic (non-visible) haematuria is still associated with around half the risk of bladder cancer seen with visible haematuria. It is therefore very important that patients with microscopic haematuria, especially those aged over 60 years, be referred for assessment for bladder cancer.\(^8\)

Referral guidelines\(^9\)

Current recommendations are for the following patients to be referred urgently for a urological assessment:

- Adults over 45 years and have unexplained visible haematuria without urinary tract infection.
- Adults over 45 years with visible haematuria that persists or recurs after successful treatment of urinary tract infection.
- Adults aged 60 and over and have unexplained non visible haematuria and either dysuria or a raised white cell count on a blood test.

A non-urgent referral for bladder cancer is recommended for those people aged 60 and over with recurrent or persistent unexplained urinary tract infection.
Differential diagnosis

- Haemorrhagic cystitis
- Nephrolithiasis
- Renal cancer
- Urethral trauma
- UTI

Investigations

The diagnosis mainly depends on the cystoscopic examination of the bladder, biopsy and urine cytology:

- Urinalysis including culture should be performed to exclude infection.
- FBC should be arranged to exclude anaemia.
- Renal function tests and electrolytes should be arranged.
- Urine cytology may be helpful but negative results do not exclude disease.
- CT or MRI staging should be considered before transurethral resection of bladder tumour (TURBT) if muscle-invasive bladder cancer is suspected.

Cystoscopy permits direct inspection of the bladder and biopsy of suspicious lesions.

The National Institute for Health and Care Excellence (NICE) recommends that white light-guided TURBT should be offered with one of photodynamic diagnosis, narrowband imaging, cytology or a urinary biomarker test (such as UroVysion using fluorescence in-situ hybridisation (FISH), ImmunoCyt or a nuclear matrix protein 22 (NMP22) test) to people with suspected bladder cancer. This should be carried out or supervised by a urologist experienced in TURBT. However, in practice urinary biomarkers are usually only used in research.

Biopsy of the prostatic urethra is recommended for cases of bladder neck tumour, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible.

The diagnosis of CIS

- Urine cytology is important in the diagnosis and follow-up of Tis (see 'Staging', below) because of its high sensitivity and specificity (over 90%).
- As stated above, biopsy of the prostatic urethra is recommended when bladder CIS is present or suspected.
- If equipment is available, fluorescence-guided biopsy should be performed when bladder CIS is suspected (eg, positive cytology, recurrent tumour with previous history of a high-grade lesion).

Investigations for staging the tumour

- T-staging: either MR imaging with fast dynamic contrast enhancement or CT with contrast enhancement is recommended for patients considered suitable for radical treatment.
- For patients with confirmed muscle-invasive bladder cancer, CT of the chest, abdomen and pelvis is the optimal form of staging, including CT urography for complete examination of the upper urinary tracts.
Staging

The tumour, node and metastasis (TNM) classification is as follows:[11]

- **T** - primary tumour:
  - Ta: non-invasive papillary carcinoma.
  - Tis: CIS; ‘flat tumour’.
  - T1: tumour invades subepithelial connective tissue.
  - T2: tumour invades muscularis:
    - T2a: superficial muscle (inner half).
    - T2b: deep muscle (outer half).
  - T3: tumour invades perivesical tissue (beyond muscularis):
    - T3a: microscopically.
    - T3b: macroscopically (extravesical mass).
  - T4: tumour invades any of the following - prostate, uterus, vagina, pelvic wall, abdominal wall:
    - T4a: prostate, uterus, or vagina.
    - T4b: pelvic wall or abdominal wall.

- **N** - lymph nodes:
  - NX: regional lymph nodes cannot be assessed.
  - N0: no regional lymph node metastases.
  - N1: metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral).
  - N2: metastases in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral).
  - N3: metastasis in common iliac lymph node(s).

- **M** - distant metastasis:
  - MX: metastasis not assessed.
  - M0: no distant metastasis.
  - M1: distant metastasis.

Management

**Non-invasive tumours**[10]

- The management of non-muscle-invasive bladder cancer usually depends upon the risk category of the patient. The risk is either low, intermediate or high and depends upon the size of the cancer, the number of the cancers and the grade of the cancer.
- The standard initial therapy for solitary Ta and T1 papillary bladder tumours is complete macroscopic transurethral resection (TUR) including a part of the underlying muscle. A second TUR should be considered if there is a suspicion that the initial resection was incomplete.
- People with suspected bladder cancer should be offered a single dose of intravesical mitomycin C given at the same time as the first TURBT.
- People with newly diagnosed intermediate-risk non-muscle-invasive bladder cancer should be offered a course of at least six doses of intravesical mitomycin C.
- Intravesical induction and maintenance immunotherapy with BCG is the preferred and most effective agent for patients with CIS and high-grade disease and reduces both recurrence and progression.[12]
- The choice of treatment should be based on a full discussion which should include:
  - The type, stage and grade of the cancer, the presence of variant pathology, prostatic urethral or bladder neck status and the number of tumours.
  - Risk of progression to muscle invasion, metastases and death.
  - Risk of understaging.
  - Benefits of both treatments, including survival rates and the likelihood of further treatment.
  - Risks of both treatments.
  - Factors that affect outcomes (for example, comorbidities and life expectancy).
  - Impact on quality of life, body image and sexual and urinary function.

**Invasive tumours**[7]

- Neoadjuvant chemotherapy using a cisplatin combination regimen should be offered before radical cystectomy or radical radiotherapy to people with newly diagnosed muscle-invasive urothelial bladder cancer for whom cisplatin-based chemotherapy is suitable.[16]
- Radical cystectomy is the preferred curative treatment for localised bladder neoplasms. Radical cystectomy includes removal of regional lymph nodes. The terminal ileum and colon are the intestinal segments of choice for urinary diversion:
  - Laparoscopic cystectomy is a safe, feasible and minimally invasive alternative to open radical cystectomy and is associated with fewer complications.[13]
  - Despite advances in perioperative care, radical cystectomy is associated with significant morbidity.[14]
An orthotopic bladder substitute should be offered to male and female patients lacking any contra-indications and who have no tumour in the urethra and at the level of urethral dissection.

Adjuvant cisplatin combination chemotherapy after radical cystectomy can be considered for people with muscle-invasive or lymph node-positive urothelial bladder cancer for whom neoadjuvant chemotherapy was not suitable (because muscle invasion was not shown on biopsies before cystectomy).

The use of cisplatin-based neoadjuvant chemotherapy for bladder cancer has been shown to give a 9% absolute increase in five-year disease-free survival compared with radical cystectomy alone.\(^5\)

A radiosensitiser (such as mitomycin in combination with fluorouracil (5FU) or carbogen in combination with nicotinamide) should be used when giving radical radiotherapy for muscle-invasive urothelial bladder cancer.\(^10\)

External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach.\(^7\)

Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival by 5-7% at five years, irrespective of the type of definitive treatment. However, neoadjuvant chemotherapy is not recommended in patients with poor performance status and impaired renal function.

For patients with inoperable locally advanced tumours (T4b), primary radical cystectomy is not a curative option but a palliative cystectomy may be indicated for symptom relief.

Metastatic disease\(^7\)

The role of first-line chemotherapy should be discussed with people who have locally advanced or metastatic bladder cancer. The prognosis of their cancer and the advantages and disadvantages of the treatment options, including best supportive care, should be discussed.

First-line treatment for 'fit' patients: use cisplatin-containing combination chemotherapy. Carboplatin and non-platinum combination chemotherapy is not recommended.

First-line treatment in patients ineligible ('unfit') for cisplatin: use carboplatin combination chemotherapy or single agents, preferably with gemcitabine/carboplatin.

In patients progressing after platinum-based combination chemotherapy for metastatic disease, second-line should be offered.

Managing symptoms of locally advanced or metastatic cancer\(^10\)

Bladder symptoms:
- Palliative radiotherapy may benefit those with symptoms of haematuria, dysuria, urinary frequency or nocturia caused by advanced bladder cancer.

Loin pain and symptoms of acute kidney injury:
- Percutaneous nephrostomy or retrograde stenting (if technically feasible) may be an option for people with locally advanced or metastatic bladder cancer and ureteric obstruction who need treatment to relieve pain, treat acute kidney injury or improve renal function before further treatment.
Intractable bleeding:
- Hypofractionated radiotherapy or embolisation may be considered for people with intractable bleeding caused by incurable bladder cancer.

Pelvic pain:
- Hypofractionated radiotherapy, nerve block or palliative chemotherapy may be options for those with pelvic pain caused by incurable bladder cancer.

Surveillance for recurrent bladder cancer\textsuperscript{[10, 11]}

- Patients with non-invasive bladder tumours (TaT1) need to be followed up after completion of treatment, because of the risk of recurrence and progression.
- Those people who have had low-risk non-muscle-invasive bladder cancer and who have no recurrence of the bladder cancer within 12 months can be discharged to primary care. Those people with intermediate-risk non-muscle-invasive bladder cancer should be offered cystoscopic follow-up at 3, 9 and 18 months, and once a year thereafter. Those people with high-risk non-muscle-invasive bladder cancer should be offered cystoscopic follow-up every 3 months for the first 2 years, then every 6 months for the following 2 years, then once a year thereafter.
- The result of the first cystoscopy after TUR at three months is a very important prognostic indicator for recurrence and progression.
- After radical cystectomy a follow-up protocol should consist of:
  - Monitoring of the upper tracts for hydronephrosis, stones and cancer using imaging and glomerular filtration rate (GFR) estimation at least annually.
  - Monitoring for local and distant recurrence using CT of the abdomen, pelvis and chest 6, 12 and 24 months after radical cystectomy.
  - Monitoring for metabolic acidosis and B12 and folate deficiency at least annually.
  - Urethral washing for cytology and/or urethroscopy annually for 5 years to detect urethral recurrence for men with a defunctioned urethra.

- After radical radiotherapy a follow-up protocol should involve:
  - Rigid cystoscopy 3 months after radiotherapy has been completed, followed by either rigid or flexible cystoscopy every 3 months for the first 2 years, then every 6 months for the next 2 years, then every year thereafter, according to clinical judgement and the person’s preference.
  - Upper tract imaging every year for 5 years.
  - Monitoring for local and distant recurrence using CT of the abdomen, pelvis and chest 6, 12 and 24 months after radical radiotherapy has finished.

Complications

- UTI.
- Urinary retention.
- Hydronephrosis.
- Recurrence of tumour. The risk of upper urinary tract tumour recurrence increases in patients with multiple and high-risk bladder tumours.
- Increased risk of urethral transitional cell carcinoma.
- Complications of surgery include bowel obstruction, obstruction of the ureter, pyelonephritis and infection of the wound.
- Radical cystectomy damages the S2,3,4 outlet and causes complete erectile dysfunction, although a nerve-sparing approach can reduce this to about half.
- Orthotopic bladders have a risk of urinary incontinence.

Prognosis

- The recurrence rate for superficial transitional cell cancer of the bladder is high (70% within five years). As many as 80% of patients have at least one recurrence.
- Patients with tumour recurrences within two years have an aggressive tumour and an increased risk of disease progression (especially with recurrences within 3-6 months).
- The most significant prognostic factors for bladder cancer are grade, depth of invasion, and the presence of CIS.
- Patients with superficial tumours have an excellent prognosis with five-year survival rates between 80-90%.
- Patients with muscle-invasive bladder cancer have five-year survival rates of between 30-60%\textsuperscript{[7]}
- Prognosis for metastatic cancer is poor, with only 10-15% of patients living for five years after diagnosis.

Further reading & references

- Bladder cancer; NICE Quality Standard, December 2015
- Non-muscle-invasive Bladder Cancer; European Association of Urology Guidelimes (2016)
- Muscle-invasive and Metastatic Bladder Cancer; European Association of Urology Guidelines (2016)

2. Cancer Statistics; Cancer Research UK
3. Sayburn A; Likelihood of bladder cancer associated with non-visible haematuria is quantified for first time. BMJ. 2014 Sep 1;349:g5415. doi: 10.1136/bmjg5415.

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Author: Dr Louise Newson
Peer Reviewer: Dr Helen Huins

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