UROLOGICAL MALIGNANCY—II: UROTHELIAL TUMOURS

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Epidemiology of urothelial tumours

Tumours of urinary tract

- Transitional cell carcinoma
- Squamous cell carcinoma
- Adenocarcinoma

Main factors associated with bladder cancer

- Occupational chemical exposure
- Cigarette smoking
- Bacterial and parasitic infections (and bladder calculi)

Tumours of the urinary tract vary in type. Less than 1% of cases of bladder cancer in Britain are due to squamous cell carcinoma (although 75% of cases in Egypt are), and less than 2% of primary bladder cancers are adenocarcinomas. Adenocarcinomas of the rectum, uterus, breast, ovary, and prostate may metastasise to the bladder, and very rarely adenocarcinoma may also arise in a urachal remnant.

Most bladder cancers are transitional cell carcinomas, and the incidence in men is nearly three times that in women. Bladder cancer is currently the fourth most common cancer in men, after prostate cancer, lung cancer, and colorectal cancer).

Occupational exposure to chemicals in development of bladder cancer

Occupations

- Dental technicians
- Dry cleaners
- Leather workers
- Mechanics and lorry drivers
- Painters and decorators
- Paper manufacturers

Chemical

- Aniline dyes
- 2-Naphthylamine
- Xenylamine
- Benzidine

Several factors are associated with the development of bladder cancer. Occupational exposure to chemicals is thought to precipitate up to one third of bladder cancers. The risk of developing bladder cancer in people who smoke is four times that in non-smokers, and a third of all bladder cancers may be related to cigarette smoking. (Nitrosamines and 2-naphthylamine have been found in cigarette smoke and may be the causative agents.) All patients with bladder cancer should be told of this relation to smoking and be strenuously encouraged to stop smoking immediately. Chronic cystitis, from any cause, increases the risk of developing squamous cell carcinoma of the bladder. Cystitis related to schistosomiasis is worldwide the most common cause of this form of cancer. Bladder calculi may cause a chronic cystitis and over a long period may predispose to squamous cell carcinoma.

Symptoms and signs of bladder tumours

A pelvic mass may also be palpable in advanced cancers but is seldom seen alone as a presenting feature

Most patients with bladder cancer present with painless haematuria. Some patients present with pronounced irritative bladder symptoms, and such patients may be found to have either carcinoma in situ or invasive bladder cancer. Patients seldom present with flank pain, but when they do, it may signify obstruction of the ureter due to invasive bladder cancer.

Patients presenting with haematuria—points to consider

- Is the blood at the start of the urinary stream or mixed in with the whole stream?
- Is the haematuria painful or painless?
- Does the patient have any other urological symptoms?
- Has the patient had any past urological conditions?
- Is the haematuria macroscopic or microscopic?

Investigation of haematuria

- Microscopy of urine and urinary cytological tests
- Intravenous urography (or plain x ray examination of the kidneys, ureters, and bladder and renal ultrasound examination)
- Rigid or flexible cystoscopy
- Digital rectal examination (mandatory)

Red blood cells in urine.

Intravenous urogram showing tumour of left side of bladder (arrow)—with indentation of base of bladder due to benign prostatic hyperplasia.

Haematuria

Haematuria is an alarming symptom, and most patients present soon after first becoming aware of it, either to their general practitioner or to an accident and emergency department. A clear history of the relevant features must be obtained.

Blood present only at the beginning of the urine stream may originate from a cause related to part of the lower urinary tract, such as the prostate or urethra. Blood in the whole of the urinary stream, however, suggests that the blood has had time to become thoroughly mixed with urine, implying a cause in the bladder or above (kidneys and ureters).

It is important to determine whether haematuria is painful or painless. Painful haematuria may be associated with urinary infection or inflammation. Macroscopic haematuria with no pain suggests the presence of a urothelial cancer until proved otherwise.

Microscopic haematuria is often discovered incidentally by dipstick urine analysis in otherwise asymptomatic patients and presents a dilemma for the clinician. A freshly voided sample of urine should be sent in every case for microscopic analysis and confirmation of the presence of red blood cells.

Microscopy of the urine will also show whether casts or protein is present, and this is important as even heavy bleeding should not appreciably raise the urine protein concentration. The presence of protein casts in the urine may shed light on the cause of the haematuria. Casts form when Tamm-Horsfall mucoprotein precipitates in the tubules. If cells are present in the lumen of the tubules they may be trapped, forming cellular casts. Casts without trapped cells are known as hyaline casts. While hyaline casts are not clinically important, casts containing red blood cells suggest glomerulonephritis, and the presence of other cells indicates non-specific renal tubule or nephron damage.

All patients with macroscopic haematuria should be referred to a urologist for further investigation. The role of urinary cytological tests in the diagnosis of bladder cancer is controversial. Many urologists do not routinely perform these in patients presenting with haematuria, although it is the usual practice of the authors. Cystoscopically normal bladders occur in 5% of cases of carcinoma in situ. Urinary cytological tests are accurate under these circumstances, and a positive cytological result would alert the urologist to perform random bladder biopsies, looking for areas of dysplasia.

The gold standard investigation for macroscopic haematuria remains intravenous urography. Many urology departments, however, now use plain abdominal x ray examination (of the kidneys, ureters, and bladder) and a renal ultrasound examination, instead of urography. Ultrasonography is becoming increasingly sensitive at detecting bladder tumours but is less sensitive for tumours of the upper tract (1-2% of all urothelial tumours). Ultrasound examination may be suitable for patients aged under about 45 years with microscopic haematuria but is not appropriate for older patients (in whom the risks of urothelial cancer are higher) or in patients who have macroscopic haematuria, in whom intravenous urography should still be the investigation of first choice.

Cystoscopic view of transitional cell carcinoma in bladder.

Any patient presenting with macroscopic haematuria should have either a rigid cystoscopy under general anaesthetic or a flexible cystoscopy under local anaesthetic. If a tumour is discovered then definitive treatment has to be performed under general anaesthetic. Biopsies of abnormal mucosa should also be taken. Random biopsies are needed if the cytological result is positive even if the bladder mucosa looks normal.

Treatment of bladder cancer

TNM classification for bladder carcinoma

- Ta Confined to mucosa
- T1 Invades submucosa (lamina propria) only
- T2 Invades superficial muscle
- T3 Invades deep muscle
- T4 Spreads beyond the bladder, including into the prostate or other organs

Staging of bladder cancer

Bladder cancer is staged according to the tumour, node, metastasis (TNM) classification system. When a biopsy is taken or a tumour resected it is crucial to include a specimen of muscle so that the histopathologist can accurately determine whether tumour has invaded any muscle. In addition to being staged, tumours are graded by their state of differentiation.

Stage of transitional cell carcinoma in bladder at presentation; 90% of invasive tumours are present at initial diagnosis.

Superficial bladder cancer (Ta and T1)

The primary treatment of a patient with a Ta or T1 stage transitional cell carcinoma of the bladder is transurethral resection or diathermy. Within two years of such treatment, however, 60% of patients will have developed recurrences. Over a 10 year period 10-15% of such tumours will progress to muscle invasive disease.

Opinions vary widely about how often a patient with such tumours should undergo cystoscopy, but it is important to realise that the aim of surveillance of these patients is to spot the change from superficial exophytic papillary transitional cell carcinoma to either carcinoma in situ or invasive disease rather than to remove superficial tumours from time to time.

Grading of transitional cell carcinoma

- G1 Well differentiated
- G2 Moderately differentiated
- G3 Poorly differentiated

Patients who present initially with either large tumours or many tumours are more likely to suffer recurrences. It is customary to repeat cystoscopy three months after the initial presentation and treatment. Patients with no recurrences at this time tend to be less troubled by further recurrences. There is no clear consensus on the length of time that surveillance should continue. The risk of developing tumour recurrence decreases as the number of tumour free years increases, although a small but finite risk remains of developing further bladder tumours even after a decade of being tumour free. Most urologists would at this stage discontinue cystoscopy and continue to monitor the patient by yearly urinary cytological tests.

Patients with superficial bladder cancer progressing to invasive disease, according to grade of tumour

Grade	% (Range)
G1	10-15
G2	14-37
G3	33-64

Excised specimen of cancerous bladder.

The role of adjuvant surgery is unclear, but some patients who respond to chemotherapy have been shown to benefit if residual disease is present

Aggressive superficial cancer may be defined as high grade (G3) T1 stage tumours or carcinoma in situ. Such tumours need aggressive management. Good evidence exists that intravesical therapy with BCG prevents the recurrence of tumour in many patients and reduces the risk of developing muscle invasive bladder tumour. This treatment is given as once weekly instillations for six to eight weeks, followed by a further six week course if subsequent cystoscopy shows tumour recurrence.

Although, in general, intravesical chemotherapy seems to be ineffective as a maintenance therapy, instillation of epirubicin at the time of transurethral resection of the presenting bladder tumour has been shown to be effective in cases of low grade, low stage tumours, possibly acting by destroying remaining cancer cells or by preventing tumour cell implantation during transurethral resection of the tumour.

Patients with aggressive superficial disease (especially T1G3 tumours or carcinoma in situ) who do not respond to these treatments may need cystectomy, as the risk of tumour progression in these cases is appreciable.

Invasive bladder cancer (T2, T3, T4)

Once the tumour has invaded muscle the characteristics of the disease are altered, with a substantially higher risk of developing metastases—which is the eventual cause of death of almost all patients with invasive bladder cancer. Most patients presenting with invasive bladder cancer will already have micrometastases, and as such their condition will be ultimately incurable. Defining those patients whose condition is potentially curable is, however, difficult.

Radical cystectomy with formation of an ileal conduit is the gold standard treatment for invasive bladder cancer and remains the treatment by which all others are judged. Other treatments include radiotherapy and chemotherapy (both neoadjuvant and adjuvant).

Radiotherapy has been used for several years, but recent studies suggest that radiation on its own does not control local disease in invasive bladder cancer (although patients considered unfit for radical cystectomy may derive some benefit). Radiotherapy before cystectomy has been advocated on the grounds that it may destroy microscopic tumour cells and thus prolong survival after surgery. Recent studies, however, show an identical recurrence rate regardless of whether cystectomy is preceded by radiotherapy.

Bladder cancer is chemosensitive, and various treatment schedules have been tried in the past. Responses to a single drug have been shown to be short lived and incomplete, but greater successes have been achieved with combination chemotherapies. Of these, the most successful remains the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC), and selected patients have exhibited a long term and complete response, although this treatment is extremely toxic.

Transitional cell carcinoma of the upper urinary tracts

Intravenous urogram showing ureteric tumour (arrow).

Less than 4% of patients with bladder cancer will develop a tumour of the upper urinary tract. Upper tract tumours are usually diagnosed with intravenous urography or retrograde ureterography and are seen as filling defects. Cystoscopy is mandatory in patients with upper tract tumours to rule out a coexisting bladder cancer. The standard treatment for tumours of the renal pelvis is a nephroureterectomy with excision of a cuff of bladder mucosa. Solitary or low grade tumours of the upper or mid-ureter may be treated by segmental resection in selected patients, but high grade or multifocal disease should also be treated by nephroureterectomy. Tumours of the lower ureter may also be treated by segmental resection and reimplantation of the ureter.

Vitamin supplementation

- In a recent study of patients with bladder tumours classified as stage Ta, treatment with high doses of vitamins A, C, E, and B6 reduced the rate of recurrence
- The mode of action is unclear—further studies are needed

Photodynamic therapy

Photodynamic therapy uses the chemical photosensitisation of tumour cells then the stimulation of these cells by laser light. Although the technique remains experimental, some patients with carcinoma in situ and papillary bladder tumours have been treated. After intravenous injection of the photosensitiser, cells (both normal and cancerous) take up the chemical, although the photosensitiser concentrates in neoplastic tissues. The bladder is filled with saline and an optical fibre placed in the centre of the bladder delivers the laser light to the interior.

Initial reports suggest that photodynamic therapy can produce complete response rates of up to 80% in suitable patients, although the length of follow up remains short.

Key references

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Style Matters

Ethnicity, race, and culture: guidelines for research, audit, and publication

The following guidelines on the use of ethnic, racial, and cultural descriptions in published research were produced with the help of Drs Kwame McKenzie and Natasha Crowcroft (see also editorial). We hope that authors will use them in describing patients individually and in groups and that both authors and readers will find them helpful

The terminology of race, ethnicity, and culture is likely to be the source of continuing debate and will change because of fashion and political imperatives. So that researchers can compare their results now and in future, authors should try to use accurate descriptions rather than catch all terms in common use. Authors should describe in their methods section the logic behind their "ethnic" groupings. Terms used should be as descriptive as possible and reflect how the groups were demarcated. For example, "black" as a group description is less accurate than "self assigned as black Caribbean (Office of Population Censuses and Surveys category)" and "Asian" less accurate than "UK born individuals of Indian ancestry" or "French born individuals of Vietnamese ancestry."

Categorisation for research or audit should relate to the type of hypothesis under investigation. For instance, genetic make up is the most powerful determinant of biological difference and the most accurate measure of risk; race has limited biological validity. Ethnicity and culture are socially determined variables of limited use in biological research, though they are useful in health services research. All the variables are confounded by socioeconomic status.

If it is unknown which of ethnicity, race, or culture is the most important influence then an attempt should be made to measure all of them.

A range of information is best collected:

- Genetic differences (using relevant genetically determined polymorphism)
- Self assigned ethnicity (using nationally agreed guidelines enabling comparability with census data)
- Observer assigned ethnicity (using OPCS or other national census categorisation or the researchers' own logically argued categories)
- Country or area of birth (the subject's own, or parents' and grandparents' if applicable)
- Years in country of residence
- Religion.

Culture is difficult to measure and describe, and there is scope for a large list of variables, for example, language and diet, which reflect our diversity and may be of importance in a particular study. Any cultural dividing line is arbitrary, but this list gives the minimum that should be expected of researchers.