

Urinary tract cancers: An overview for general practice

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ABSTRACT

Urinary tract cancers are common and comprise a gamut of lesions ranging from small benign tumors to aggressive neoplasms with high mortality. The predominant urinary tract malignancy is bladder cancer. The clinical challenge is early detection and adequate follow-up because recurrence is high and delayed diagnosis is associated with poor prognosis. Primary care physicians form a key part of the management apparatus for these patients and may be responsible for ensuring adequate ongoing surveillance. This article aims to outline the evaluation of patients in whom urinary tract cancer is suspected and briefly review the general principles of treatment.

Keywords: Cancer, hematuria, screening, transitional cell, urothelial

Introduction

The urinary tract is lined by epithelium extending from the renal collecting tubules proximally to the urethral meatus distally. These epithelial cells are known as the urothelium or transitional cells. They are highly specialized cells with elasticity and variable shape. Any segment of the urothelium can be affected by malignant transformation. Greater than 90% of urinary tract cancers are transitional cell carcinomas (TCC) known today as urothelial carcinomas (UC).^[1] Rarer cancers include squamous cell carcinoma, small cell carcinoma, and adenocarcinoma. Benign neoplasms are also sometimes seen.

This article is intended to provide an overview of the biology and clinical features of urinary tract cancer and to offer a basic approach to diagnosis and treatment. While the varieties of malignancy are manifold [Table 1] most are very uncommon, and content of this review is limited to UC.

Bladder Cancer

Etiology and epidemiology

Bladder cancer is one of the most common cancers, and its incidence continues to rise. It accounts for 3% of new cancers

and is the second most common urological cancer.^[2-4] The precise mechanisms of etiopathogenesis are unestablished, but there is most likely an interplay between environmental and genetic factors. In contrast with most tumors, the risk of bladder cancer is unrelated to family history.^[5,6] The mean age of diagnosis is 65 years of age with the disease more frequent in men than women.^[2,7]

There are several well-known risk factors for the development of bladder cancer. Cigarette smoking is the strongest risk factor and is implicated in 60% of cases.^[7] Certain occupational exposures are also associated with bladder cancer, typically of workers in chemical and textile industries.^[8] Prior radiation exposure also increases risk.

Clinical manifestations

Painless macroscopic hematuria is the presenting symptom in 85%–90% of patients.^[7,9] It is a frequent reason for consulting a primary care physician. In a small number of cases that complaint is accompanied by urinary storage symptoms, particularly with high-grade tumors. Dysuria is the second most common initial complaint quoted to family physicians, which leads to a diagnosis of bladder cancer.^[10] Symptoms are often intermittent which can lead to delays in diagnosis. Features occasionally seen in advanced disease include bone pain from metastasis,

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Access this article online

Quick Response Code:



Website:
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DOI:
10.4103/2249-4863.197258

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How to cite this article: Yaxley JP. Urinary tract cancers: An overview for general practice. *J Family Med Prim Care* 2016;5:533-8.

retroperitoneal muscle-invasive tumors causing flank pain, and ureteric obstruction due to bladder or regional invasion.

A complete physical examination is mandatory and should be performed in all patients with suspected bladder cancer. There are usually no physical signs in early disease. In more advanced disease, cachexia, lymphadenopathy, and bony tenderness are common findings. Very rarely, large volume tumors may produce a palpable abdominal or rectal mass.

Investigations

Macroscopic hematuria is a red flag for malignancy and always requires full urologic workup. It should be considered malignant until proven otherwise. The likelihood of UC in patients with frank hematuria is approximately 12%.^[11,12] The entire urinary tract requires evaluation in this instance to establish the cause of bleeding. A suggested complete workup includes blood and urine tests, imaging studies, and cystoscopy [Table 2].

After exclusion of a malignant cause for bleeding, other nephrologic and genitourinary lesions can be considered [Figure 1].

Microscopic hematuria

The best approach to microscopic hematuria is uncertain. Urinalysis is a basic and widely used tool [Table 3]. Urine dipstick is very sensitive for bleeding but is extremely nonspecific, and the rate of false positives is high. Confirmation and quantification are therefore required with microscopy. Microscopic hematuria is defined as at least three red cells per high powered field visible under microscopy.^[13] Most laboratories report in the International System of Units with hematuria classified as a urinary erythrocyte count $\geq 10 \times 10^6/L$.

Incidental detection of microhematuria is a common phenomenon. In early stages, most patients with bladder cancer have microscopic hematuria. However, the prevalence of microhematuria in healthy individuals is approximately 10%–15% and the decision about which patients to investigate may thus be difficult.^[15,19] The first step is a repeat urine sample at least several days after the initial positive specimen because many incidental cases are transient. Asymptomatic patients with a single incidental microhematuria sample seldom warrant further workup for cancer.^[15]

The diagnostic approach should be individualized. Only a small number of cases, at approximately 2%, of persistent microscopic hematuria are attributable to malignancy.^[11] If a benign cause is likely, then further investigations for malignancy can probably be safely omitted [Figure 2]. If renal function is impaired or the urinalysis suggests intrinsic renal disease, such as red cell casts or urine eosinophils, then referral to a nephrologist is appropriate. If not thought to be cancer, evaluation and management are guided by the provisional diagnosis.

Table 1: Histological subtypes of urinary tract cancers

Site	Observed cancer types
Renal pelvis and ureter	UCC Squamous cell carcinoma Adenocarcinoma
Bladder and urethra	UCC Squamous cell carcinoma Adenocarcinoma Small cell carcinoma Sarcoma Paraganglioma Melanoma Lymphoma

Table 2: Suggested investigations for macroscopic haematuria

Blood tests	Full blood count EUCs (electrolytes, urea, creatinine)
Urine studies	Microscopy Culture and sensitivity Cytology
Imaging	CT urography
Cystoscopy	Tissue biopsy

Patients with features suggestive for cancer or in whom an alternative diagnosis is not obvious should be further evaluated to exclude urinary tract malignancy. The American Urological Association (AUA) has developed guidelines for investigating microscopic hematuria.^[15] Patients are stratified by risk with a baseline screen consisting of urine cytology and computed tomography (CT) urography in individuals with lower risk. High-risk features listed by the AUA include age >40 , a history of smoking, industrial chemical exposures, or lower urinary tract symptoms. Many authors propose that age alone should not be characterized as a high-risk factor and that discretion is exercised when no other high-risk factors are evident. Universal full urologic evaluation in patients older than forty without other high-risk features would likely lead to over-investigation and expose patients to unnecessary risk and cost.^[12,20] Limiting testing to urine cytology and CT urography may be adequate in patients at low risk although some urologists elect to perform cystoscopy [Figure 3].

Patients with a negative cancer workup do require follow-up. Other urological or renal pathologies should be considered and managed as deemed appropriate. Re-evaluation for cancer is necessary in patients who develop interval changes such as urinary symptoms or macroscopic hematuria. Persisting microscopic hematuria does not in itself require repeated evaluation for cancer in any age but should prompt nephrology referral to exclude medical kidney disease.^[8]

Management

Treatment decisions for bladder TCC depend on tumor grade and stage. These strongly correlate with tumor recurrence,

progression, and survival. Most tumors are not muscle invasive at the time of diagnosis. There is a relatively large list of options for treatment, full discussion of which is beyond the scope of this article. Specialist treatment may involve chemotherapy, radiotherapy, surgery, or a combination of these. Chemotherapy is commonly administered intravesically through a urinary catheter but may also be systemic. Radical cystectomy is associated with substantial morbidity and has led to various bladder-sparing surgical techniques.

Most pertinent to the primary care setting is the need for adequate follow-up. Tumor recurrence typically occurs within 12 months of definitive treatment and patients are usually closely followed by the treating urologist for the first few years after treatment. Long-term surveillance is an important responsibility of the general practitioner, which is usually conducted in cooperation with the treating specialist. More than 50% of high-grade tumors recur, and most patients require lifelong annual testing.^[1,21-23] Early identification of tumor recurrence benefits the patient. The protocol for follow-up usually involves a combination of regular urine cytology, repeat CT, and regular check cystoscopies.

Figure 1: Differential diagnosis of macroscopic hematuria

- Malignancy
- Benign prostatic hyperplasia
- Calculi
- Pyelonephritis
- Glomerulonephritis
- Trauma
- Cystitis

It is important that physicians in primary care have a working knowledge of the management principles for bladder cancer. Patients frequently present to their general practitioner with questions about the disease and its proposed treatment or with complications of treatment.

Ureteric and Renal Pelvic Cancer

Etiology and epidemiology

Upper urinary tract urothelium shares many morphologic properties with bladder mucosa. The vast majority of upper tract cancers are UCs. The pathogenesis of these neoplasms is similar to bladder cancer. Ureteric cancer and cancer of the renal pelvis are far less common than bladder cancer, comprising only 4% of urothelial malignancies.^[9]

Upper tract UC is frequently multifocal. Tumors often present with concurrent bladder cancer or with bilateral lesions. In one series, 44% of patients with upper tract cancer developed a bladder tumor over a mean interval of 13.9 months.^[24] Approximately 5% of patients develop upper tract tumors of the contralateral side.^[25] There are two theories explaining these observations. One hypothesis, the “field cancerization effect,”

Figure 2: Differential diagnosis of microscopic hematuria

- Causes of macroscopic hematuria
- Vigorous exercise of sexual activity
- Medical renal disease
- Menstruation
- Urinary tract infection

Table 3: Investigations useful in the diagnosis of urinary tracts cancers

Test	Rationale	Utility
Urinalysis	Dipstick and microscopy detect the presence of nitrites, white and red cells, red cell casts, electrolytes and protein	Dipstick detects >91% of cases of microscopic haematuria, with specificity of >65% ^[13] Dipstick associated with frequent false-positives so must be confirmed with microscopy
Cytology	Neoplastic cells are exfoliated and released in urine. After a urine sample is collected, cytology examines urinary sediment for epithelial cells	Insufficiently sensitive when used alone Sensitivity exceeds 90% for high grade tumours but 30% for low grade tumours ^[1] Overall sensitivity for all TCCs is <80% ^[8] Very high specificity of 98-100% ^[14] Low sensitivity for upper tract cancers
Computed Tomography (CT)	CT urography is a CT scanning technique that evaluates the upper urinary tract and assesses depth of invasion or extent of metastasis	Today's imaging modality of choice Must include both abdomen and pelvis, be performed with and without contrast, and include delayed images Sensitivity >92% and specificity >97% ^[8] If CT unavailable or contraindicated, x-ray excretory urography, ultrasound or contrast magnetic resonance imaging (MRI) are inferior but reasonable alternatives ^[15] To reduce radiation, may be replaced by conventional non-contrast CT in low-risk patients younger than. ^[40] Unenhanced CT detects 95% or more of lesions demonstrable on CT urography ^[16,17]
Cystoscopy	Allows direct endoscopic visualisation of the bladder. Ureteropyeloscopy permits view of the upper urinary tract. If a lesion is visualised a biopsy is taken	Gold standard for diagnosis and staging of TCC. ^[8] Required for achieving firm tissue diagnosis in virtually every case For bladder cancer, sensitivity is 98%, specificity is 94%, positive predictive value is 80%, and negative predictive value is 99% ^[18] Sensitivity for ureteric or renal pelvic TCC of >90% ^[9]

CT: Computed tomography; MRI: Magnetic resonance imaging; TCCs: Transitional cell carcinomas

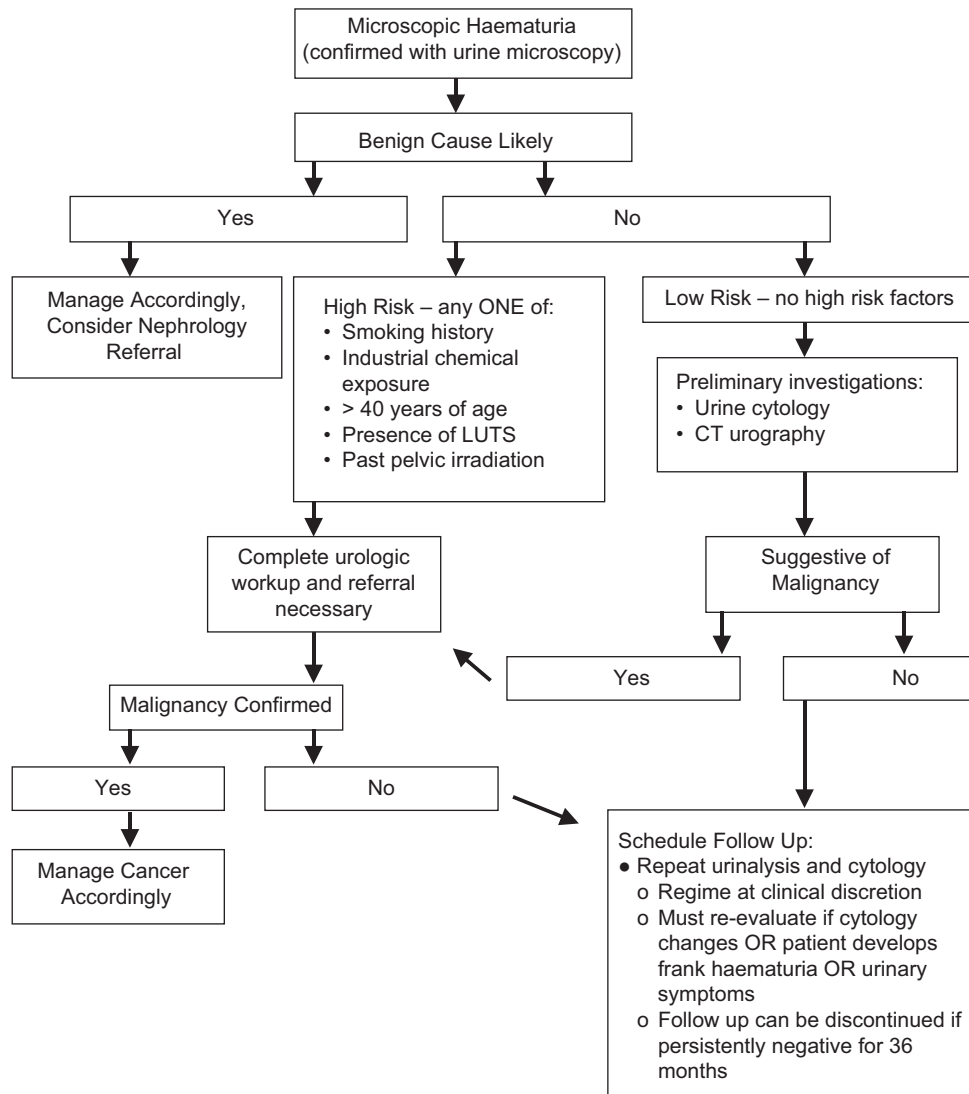


Figure 3: A suggested algorithm for the diagnostic approach to microscopic hematuria. Generally consistent with American Urological Association guidelines however some authorities do not consider age alone to be a high-risk factor

is that the entire urothelium is bathed in the same carcinogenic material, giving rise to the development of distant lesions. The other is the “monoclonality” hypothesis of intraluminal seeding and intraepithelial cell migration.

While many patients with upper tract cancers develop bladder tumors, patients with bladder cancer seldom develop an upper tract lesion. This is probably because of longer exposure to urinary carcinogens in the bladder during bladder filling.

Clinical manifestations

Macroscopic hematuria is noted in 90% of patients.^[9] This is classically painless and may be accompanied by lower urinary tract symptoms. Flank pain is a relatively common problem due to ureteral obstruction from blood clots.

Investigations

The approach to diagnosis of ureteric or renal pelvic UC is analogous to that for bladder cancer. Frank hematuria necessitates

a full urologic workup while patients with microscopic hematuria should be risk stratified. Urine cytology is less reliable for detecting upper tract cancers, and a pathologist with particular expertise in this area is mandatory to interpret such specimens. Low-grade upper tract TCC is not usually associated with positive urine cytology.

Management

Surgery is the only potentially curative measure for upper urinary tract cancer. Nephroureterectomy is the procedure of choice, which is usually performed in addition to excision of a cuff of bladder. There is a move toward more conservative ablative operations in select patients, which may be indicated in patients with a solitary kidney, bilateral malignancy, or those patients with localized low-grade disease. Adjuvant chemotherapy and radiation therapy have been trialed for upper tract cancers, but their efficacy is unknown.

Ongoing follow-up in the primary care environment is of vital importance. Like bladder cancer, the natural history of renal

pelvic and ureteric cancers is punctuated by tumor recurrence. Lifelong surveillance is necessary and is often conducted in unison between specialist and general practitioner.

Screening

Urinary biomarkers

Several new methods for detecting urine biomarkers are emerging. They identify various proteins in urine exposed to neoplasia and overcome shortcomings of the modalities currently available. Assays under development include bladder tumor antigen, nuclear matrix protein 22, and fibrin degradation product. These are available in some areas of the world but have not been widely adopted because of their limited utility. Experimental results are promising, but most kits still achieve sensitivities of <90%.^[9,26-28] In addition, specificity has proven low, and the cost is prohibitively expensive. Clinical trials are ongoing, and the optimal role of urinary biomarkers as a screening tool or in the management of bladder cancer is yet to be determined.

Recommendations

Screening refers to the detection of disease in patients without symptoms. An ideal screening test is inexpensive, sensitive, and specific. Bladder cancer is a potential candidate for screening because of its prevalence and significance. However, no major organizations recommend bladder cancer screening in asymptomatic adults.^[29-31] There is no evidence that population screening improves patient outcomes or alters the natural history of the disease.^[32-34] Furthermore, identification of high-risk groups that may benefit from screening has been unsuccessful. Screening is limited by feasibility, cost-effectiveness, and the potential harms of invasive tests. The role of screening for bladder cancer will continue to be reevaluated as advancements in testing modalities are refined.

Summary

Urinary tract cancers are common and impose a significant cost burden on society. Frank hematuria warrants a full urological workup in all patients and should be considered malignant until proven otherwise, particularly in individuals older than 40 years of age. The approach to microscopic hematuria is controversial. Patients with risk factors for malignancy or in whom a cause is not clear should undergo further testing. The natural history of UC is typified by tumor recurrence, and the primary care setting is a pivotal space to encourage patient adherence to surveillance protocols following cancer treatment. Despite its prevalence, screening for bladder cancer is not supported by evidence and cannot be recommended.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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