Continuing Professional Development

CPD

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## 60 Second Summary

There is a worldwide variation in the rates of bladder cancer, which is in general higher in more industrial countries, possibly because of heavy industries, but could also be a reflection on healthcare systems.

Bladder cancer incidences increase with age3, is more common in men and is strongly associated with smoking which is by far the main risk factor.

Haematuria, or blood in the urine, is the presenting complaint for many bladder cancers. A variety of older terms have been used to classify haematuria, including “frank haematuria”, “gross haematuria”, “dipstick haematuria” and “microscopic haematuria”, however the classification of haematuria has been simplified into visible haematuria (VH) and non-visible haematuria (NVH). All instances of VH should be further investigated. NVH can be further divided into asymptomatic (aNVH) and symptomatic (sNVH).

Non-muscle invasive bladder cancer (NMIBC), sometimes erroneously called “superficial bladder cancer” is the most common bladder cancer diagnosed and relates to bladder cancers that are confined to the mucosa (pTa) or lamina propria (pT1) of the bladder mucosa, without invasion into the bladder wall muscle.

For small tumours that appear to be pTa and are completely resected, the administration of a single dose of intravesical mitomycin within 24 hours of resection can help reduce recurrence rates by 14%.

Bladder cancer should be considered as 2 distinct diseases albeit on a continuum. Most present with haematuria. Nonmuscle invasive disease (NMIBC) can be completely managed endoscopically with the occasional use of intravesical treatments.

**1. REFLECT -** Before reading this module, consider the following: Will this clinical area be relevant to my practice?

**2. IDENTIFY -** If the answer is no, I may still be interested in the area but the article may not contribute towards my continuing professional development (CPD). If the answer is yes, I should identify any knowledge gaps in the clinical area.

**3. PLAN -** If I have identified a knowledge gap - will this article satisfy those needs - or will more reading be required?

**4. EVALUATE -** Did this article meet my learning needs - and how has my practise changed as a result?Have I identified further learning needs?

**5. WHAT NEXT -** At this time you may like to record your learning for future use or assessment. Follow the 4 previous steps, log and record your findings.

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# Overview and Factors in Bladder Cancer Management

### Introduction

Bladder cancer is the tenth most common cancer[1] and affects about 490 people in Ireland each year[2]. It has a higher incidence in men (9.5/100,000 person/years) than in women (2.4/100,000 person/years). There is a worldwide variation in the rates of bladder cancer, which is in general higher in more industrial countries, possibly because of heavy industries, but could also be a reflection on healthcare systems.

### Risk Factors - Smoking

Bladder cancer incidences increase with age[3], is more common in men and in strongly associated with smoking which is by far the main risk factor. The incidence of bladder cancer in smokers is almost twice that in non-smokers[3] when blood is present in the urine. Smoking accounts for almost 50% of bladder cancer cases, with environmental exposure (“second-hand smoke”) also leading to an increased risk of bladder cancer

### Other risk Factors:

1. Chemical Exposure: Exposure to certain aromatic amines and certain hydrocarbons, associated with industrial plants associated with paint, dyes and petroleum-based products, is the second most important risk factor and can account for up to 10% of cases.
2. Parasites: Schistosomiasis is a chronic cystitis condition caused by exposure to the *schistosomiasis haematobium* parasite, which is endemic to certain parts of the world, in particular along the Nile delta, and is associated with squamous cell carcinoma of the bladder (The majority of bladder cancer is adenocarcinoma)
3. Medications:

a. Pioglitazone, a medication for the management of type 2 diabetes mellitus, has been associated with a small increase in the risk of bladder cancer.

b. Cyclophosphamide, a chemotherapy agent used in the management of haematological malignancies, has also been implicated in increased bladder cancer risk, up to 9-fold increase. These tumours do not typically occur until 6-13 years after treatment has completed.

4. Radiation: Prior pelvic radiation, can associated with an 2-4-fold increased risk of bladder cancer.

### Clinical Presentation - Haematuria

Haematuria, or blood in the urine, is the presenting complaint for many bladder cancers. A variety of older terms have been used to classify haematuria, including “frank haematuria”, “gross haematuria”, “dipstick haematuria” and “microscopic haematuria”, however the classification of haematuria has been simplified into visible haematuria (VH) and non-visible haematuria (NVH). All instances of VH should be further investigated. NVH can be further divided into asymptomatic (aNVH) and symptomatic (sNVH).

Non-visible haematuria relates to blood detected via either microscopy or urine dipstick testing. Urine dipstick testing utilises an oxidation reaction of heme with ortholodine which produces the classical blue colour on the dipstick. Dipsticks have become so sensitive that further confirmation with microscopy is unnecessary, but it can be subject to several false negatives, especially from red cell lysis as a sample is transported to the laboratory.

A few red blood cells can be found in the urine of normal

healthy people. Transient non-visible haematuria can be detected following rigorous exercise, sexual intercourse or as contaminant from menstruation. Such is the sensitivity of dipstick assessment for haematuria that "trace" blood as detected on these strips is recommend being considered negative.

All cases of visible haematuria, in the absence of a known cause, requires investigation. Symptomatic non-visible haematuria (sNVH) also requires investigation. Persisting asymptomatic non-visible haematuria (present on 2 of 3 dipsticks or microscopy samples) should be referred for investigation. In 2000, a prospective analysis of nearly 2000 patients identified that 22% patients with visible haematuria have a urological malignancy, while only 5% of patients with non-visible haematuria do[5]. A more recent publication has reconfirmed these proportions and has also shown that no cancers were detected in those under 35-years-old with NVH[3].

**Investigation of Haematuria**

**1. Direct Visualisation**

Direct visualisation of the bladder is necessary in all cases of haematuria where there is a concern for bladder cancer[5]. No imaging modality is sensitive enough to replace the cystoscope. Many of these visualisations are performed using a flexible cystoscopy under local anaesthetic, though some patients may require general anaesthetic. Biopsies can be taken via this method, though the sample size tends to be small. Larger biopsies can be taken with the use of a rigid cystoscope, a procedure that usually does require a general anaesthetic. There are a variety of adjunct technologies that can be used to enhance visualisation of the bladder mucosa which are becoming increasingly more common

**2. Imaging**

The main role of imaging in the assessment of haematuria is to evaluate the upper tract (Kidneys and ureters). Either ultrasound (US) or Computed Tomography (CT) assessment may be used, with pros and cons for each. Guidelines differ in their recommendations regarding imaging. US Kidneys will identify most renal tumours and is a relatively cheap quick procedure that does not have associated radiation exposure. However, US can miss a small percentage of upper tract urothelial cancers (UTUC) which can be detected with CT scanning. Debate is ongoing as to the optimal imaging strategy in the investigation of haematuria.

**Non-Muscle Invasive Bladder Cancer**

Non-muscle invasive bladder cancer (NMIBC), sometimes erroneously called "superficial bladder cancer" is the most common bladder cancer diagnosed and relates to bladder cancers that are confined to the mucosa (pTa) or lamina propria (pT1) of the bladder mucosa, without invasion into the bladder wall muscle. Included in this grouping is carcinoma-in-situ (CIS), a high-grade flat tumour that is confined to the mucosal layer.

pTa and pT1 tumours generally appear as papillary type lesions. The number and size of tumours is an important predictor for the risks of recurrence of progression.

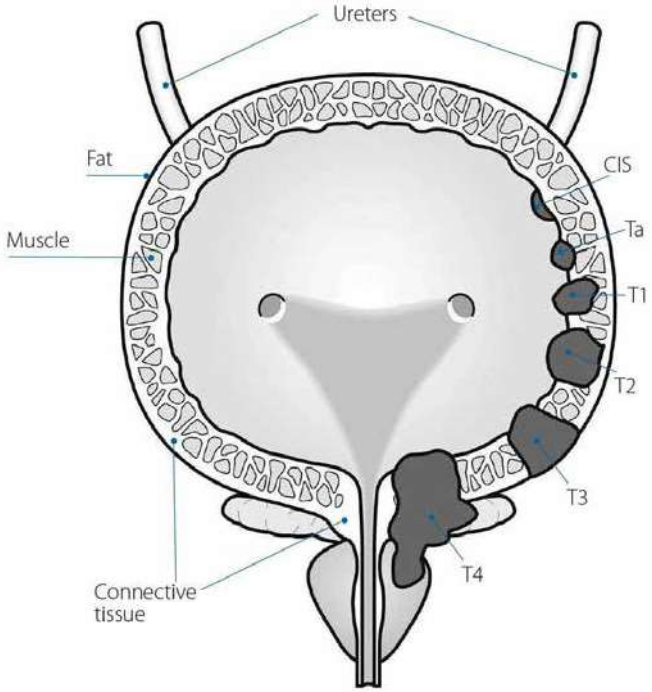
CIS tumours can appear as a "velvety" change to the bladder mucosa. CIS can often present with irritative lower urinary tract symptoms rather than haematuria.

**Management of Non-muscle invasive bladder cancer**

**1. Surgery:** The transurethral resection of bladder tumour (TURBT) is the diagnostic and therapeutic procedure that allows for collection of samples to determine the exact grade and stage of the bladder cancer. Performed under general anaesthetic, a rigid scope is passed into the bladder and an attached electrocautery loop is passed through the tumour and bladder muscle to remove the tumour. These samples are sent for histological analysis. Patients often require an overnight stay and may have a urethral catheter temporarily placed to help monitor for postoperative bleeding.

All NMIBC have a potential risk to either recur or to progress to muscle-invasive bladder cancer (MIBC). The EORTC (European Organisation for Research and Treatment of Cancer) developed a scoring model for predicting disease recurrence and progression, which has been widely adopted6. The scoring system is based on assigning points for each of the following factors

- Number of tumours;
- Tumour diameter;
- Prior recurrence rate;
- Category;
- Concurrent CIS;
- WHO 1973 tumour grade




Stages of bladder cancer

Patients can then also be placed into risk groups which helps determine their surveillance strategy and the use of any adjunct treatments. These would take in to account particular factors, such as the presence of T1 disease, HG disease or CIS.

**2. Surveillance:** after bladder cancer treatment such as TURBT, uses a few different modalities, including regular cystoscope evaluation, CT scans and urinary cytology. The frequency and time intervals are determined by the risk groups of the patient. Adherence to a surveillance protocol can be challenging both from a patient compliance point-of-view as well as a resource allocation.

**3. Intravesical Treatments:** The use of intravesical treatments including chemotherapy agents mitomycin and epirubicin, and BCG, are important in the reduction of the rates of recurrence and progression of NMIBC

For small tumours that appear to be pTa and are completely resected, the administration of a single dose of intravesical mitomycin within 24 hours of resection can help reduce recurrence rates by 14%. These low risk tumours do not usually require any additional treatments

Tumours that are of intermediate risk of progressing may benefit from a yearlong treatment of either intravesical BCG or intravesical chemotherapy. High recurrence risk tumours benefit from up to 3 years of intravesical BCG to reduce the risk of progression.

A small subgroup of very-high risk groups should have a discussion regarding early radical cystectomy as they are at a very high risk of progression to muscle invasive disease. The risk of a patient with NMIBC progressing to muscle invasive disease can be as high as 45% in 5 years.

Image from Irish Cancer Society .https://www.cancer.ie/cancer-information-and-support/cancer-types/bladder-cancer/grading-and-staging-of-bladder-cancer

| Factor | | Recurrence Points | Progression Points |
|---|---|---|---|
| Number of tumours | single | 0 | 0 |
| | 2-7 | 3 | 3 |
| | 8 | 6 | 3 |
| Tumour diameter | <3cm | 0 | 0 |
| | >3cm | 3 | 3 |
| Prior recurrence rate | primary | 0 | 0 |
| | <1 rec/year | 2 | 2 |
| | >1 rec/year | 4 | 2 |
| Stage | Ta | 0 | 0 |
| | T1 | 1 | 4 |
| Concomitant CIS | No | 0 | 0 |
| | Yes | 1 | 6 |
| Grade | G1 | 0 | 0 |
| | G2 | 1 | 0 |
| | G3 | 2 | 5 |
| **Total Score** | | **0-17** | **0-23** |

| Recurrence points | Risk of recurrence at 1 year | Risk of recurrence at 5 years |
|---|---|---|
| 0 | 15% | 31% |
| 1-4 | 24% | 46% |
| 5-9 | 38% | 62% |
| 10-17 | 61% | 78% |
| **Progression points** | **Risk of progression at 1 year** | **Risk of progression at 5 years** |
| 0 | 0.2% | 0.8% |
| 2-6 | 1% | 6% |
| 7-13 | 5% | 17% |
| 14-23 | 17% | 45% |

**Muscle Invasive Bladder Cancer**

Most patients who present and are diagnosed with bladder cancer have a non-muscle invasive bladder cancer. However, up to 25% have muscle-invasive bladder cancer (MIBC) where cancer cells are detected within the muscularis mucosa at the time of TURBT. Tumours that only extend to the muscle layer are staged T2, those that extend into the perivesical fat T3 and those that directly invade other organs or the pelvic side wall T47.

The significance of this is that MIBC cannot be cured with endoscopic treatments alone and consideration needs to be made for radical therapy. Even with radical treatment, 5-year survival rates with MIBC can be as low as 50%.

**Treatment options**

**1. Radical Cystectomy:** Radical Cystectomy involves the surgical removal of the bladder for the purposes of treating a muscle invasive bladder cancer. In men, the prostate gland and seminal vesicles are also removed. The urethra is removed if tumour is detected on urethral biopsies. In women, the uterus, urethra and adjacent vaginal tissues are removed. The ovaries can usually be left in situ. For both men and women, the regional lymph nodes are also removed as these have a potential prognostic benefit for the patient.

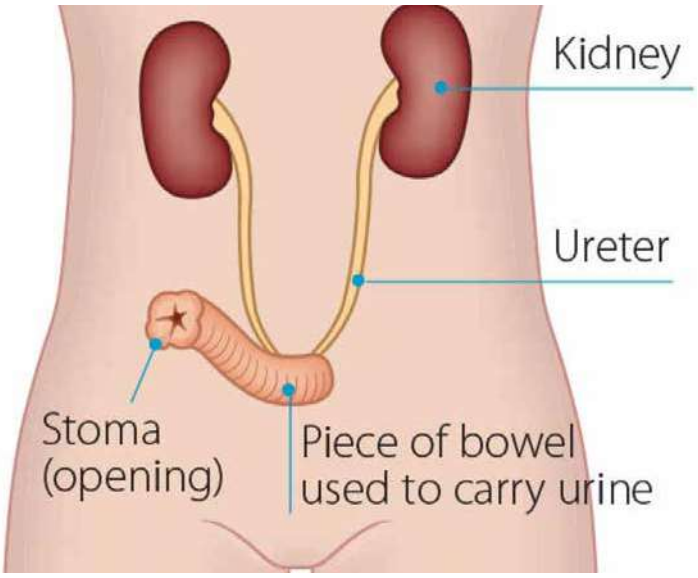



Image of Ileal Conduit from Irish Cancer Society https://www.cancer.ie/cancer-information-and-support/cancer-types/bladder-cancer/treatment-for-bladder-cancer/surgery-for-muscle-invasive-bladder-cancer

Radcial cycstectomy is a morbid operation. Up to 45% of patients will develop some complication after radical cystectomy and ileal conduit formation. Functional abnormalities relate to issues with absorption due to the removal of the segment of small bowel. The main complications include vitamin B12 deficiency, metabolic acidosis, deterioration of renal function, urinary tract infections, anastomotic complications such as stenosis and stoma complications such as stoma prolapse, stoma retraction and stoma stenosis.

**2. Neoadjuvant chemotherapy:** The addition of neoadjuvant chemotherapy (NAC) has been shown to account for a 5% improvement in overall survival in patients undergoing RC8. The original trials used the MVAC regimen (Methotrexate-Vinblastine-Adriamycin-Cisplatin) but more commonly a combination of Gemcitabine and Cisplatin are used. Cisplatin has risks of ototoxicity and nephrotoxicity and thus is unsuitable for patients with hearing difficulties or renal impairment. Some centres substitute Carboplatin in place of Cisplatin, but the evidence for this regimen is lacking. NAC should be commenced as soon as possible while the micro metastatic burden is low, and should be followed by definitive surgery ideally within 6 weeks

**3. Urinary Reservoir reconstruction:** A challenge with RC is what to do with urine afterwards. A reservoir for the urine needs to be created and a method of emptying that urine developed.

**a. Ileal Conduit**

The ileal conduit is the most performed method of urinary diversion in Ireland and the UK. This involves isolating a segment of approximately 15cm of distal ileum proximal to the ileocecal valve and disconnecting this for the contiguous bowel. The bowel is anastomosed to restore

continuity. The isolated segment of bowel is closed at one end to create a pouch and the ureters are then anastomosed to the bowel. This is then exteriorised on to the abdominal wall as a urostomy, most commonly in the right iliac fossa.

**b. Other methods**

The Studer neobladder uses a longer segment of small bowel which is isolated in the same manner as above and the ureters are anastomosed to it. This is then anastomosed to the residual urethra to allow per urethra voiding, thus negating the need for a bag. Patients void by carefully controlled relaxation of the pelvic floor muscles but may also need to pass a catheter on occasion. This is contraindicated in patients were bladder cancer was detected in the urethra.

**c. Bladder preservation strategies**

A small proportion of patients would prefer to retain their bladder or other medical comorbidities precludes radical surgery. Survival rates with these are less than with radical surgery

**4. Trimodal Therapy:** Trimodal therapy utilises TURBT, radiotherapy and chemotherapy to maximally achieve local bladder cancer control. In carefully selected patients, outcomes can match those of radical cystectomy. Outcomes are best achieved with a maximal TURBT, where all visible tumour is removed, with radio sensitising chemotherapy in advance of radiotherapy.

**5. Radiotherapy:** External beam radiotherapy should only be considered in patients who are unfit for cystectomy. It should not be offered as a primary therapy

**6. Endoscopic Management:** Patients with unresectable disease may still present with symptoms including bleeding and ureteric obstruction. Endoscopic resection and diathermy of bleeding tumour can Improve quality of life but does not include quantity.

**a. Surveillance after Radical Cystectomy**

Following a patient after radical cystectomy involves CT scanning of the thorax abdomen and pelvis, at an interval determined by the final histology to identify the development of metastases or other problems as a result of the treatment. If their urethra is still in situ, a urethroscopy with washings for cytology is also be performed.

**Advanced and Metastatic Bladder Cancer**

Metastatic bladder cancer has a poor prognosis and median survival even with cisplatin-based chemotherapy regimens is only up to 14 months. Checkpoint inhibitors such as pembrolizumab can be used in the second line setting for suitable patients

**Conclusion**

Bladder cancer should be considered as 2 distinct diseases albeit on a continuum. Most present with haematuria. Nonmuscle invasive disease (NMIBC) can be completely managed endoscopically with the occasional use of intravesical treatments. Strict adherence to a surveillance regimen is required to help prevent recurrence or progression. Muscle Invasive disease is much more aggressive and is optimally treated with radical cystoprostatectomy and ileal conduit formation after neoadjuvant chemotherapy. Long term follow-up is required to monitor for cancer recurrence and functional deterioration.

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