Patient management – non muscle invasive bladder cancer

Buakuma, P., Dewar, G., Pandian, S. and Madaan, S.

Non Muscle Invasive Bladder Cancer

P Buakuma, G Dewar, SK Pandian, S Madaan,

Department of Urology & Nephrology, Darent Valley Hospital, Dartford, Kent, UK.

Abstract

Non-muscle invasive bladder cancer (NMIBC) is the more common type of bladder cancer (75%). However, within this group of cancer, there is a spectrum of disease, with low grade, low risk tumours which rarely recur or progress at one end of the spectrum, to high grade, high risk tumours that have a significant risk of recurrence and progression to muscle invasive bladder cancer (MIBC).

Management involves risk-adapted strategies of Cystoscopy based surgery, including TURBT (Transurethral Resection of Bladder Tumour), Cystoscopy surveillance, including Check Flexible Cystoscopy (performed under local anaesthesia), and intra-vesical Chemo / Immunotherapy with the goal of preserving the bladder when it is safe to do so.

Rarely, high risk NMIBC may require more radical treatment including radical cystectomy and appropriate urinary diversion. However, the local recurrence and long-term survival rates are much better when compared to radical treatment for MIBC.

Introduction

Bladder cancer (BC) is the most common malignancy of the urinary tract[1]. It is the 11th most commonly diagnosed cancer in the world[2]. In the UK, it is the seventh most common cancer. The Worldwide age standardised incidence rate (per 100,000 person-years) is 8.9 for men and 2.2 for women (2008 data)[2]. Worldwide, BC is the 14th leading cause of cancer deaths, age-

standardised mortality rate (per 100.000 person-years) was 3.3 for men versus 0.9 for women in 2008. BC causes 5,369 deaths per year in the UK and has a survival rate of 50% at 10 years[3]. BC incidence and mortality rates vary across different countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments[4]. Smoking is the most established risk factor for BC, while other risk factors include occupational exposure to aromatic amines and hydrocarbons. Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1) and are classified as Non-muscle invasive bladder cancer (NMIBC). They have a high prevalence due to long-term survival in many cases and lower risk of cancer specific mortality compared to T2-4 tumours, which are classified as Muscle invasive bladder cancer (MIBC)[1, 5].

Pathophysiology and Types

The bladder is lined with transitional epithelium which is composed of layers of epithelia allowing the bladder to expand as it fills with urine. Most cancers of the bladder are epithelial-derived[2]. Pathological subtypes of epithelial bladder cancers include:

- Transitional Cell Carcinoma-this is the most common epithelial subtype (>90%)
- Squamous Cell Carcinoma (5%)
- Adenocarcinoma (<2%)

Non-epithelial-derived cancers such as lymphomas and sarcomas also make up a small proportion of cancers.

Risk Factors

The incidence of bladder tumours increases with age, with the majority of cases being diagnosed in those over the age of 50. There are number of modifiable risk factors which should be identified in the patients social, occupational and travel history[6]. In western

countries, smoking is the single biggest modifiable risk factor for developing bladder cancer with smokers having a 2-6 times greater risk[7]. One meta-analysis of epidemiological studies demonstrated that 50% of male and 34.8% of female patients who developed bladder cancer had a smoking history[8]. The risk increases with the number of pack years smoked; and although quitting smoking reduces the ongoing risk of developing bladder cancer, cessation does not reduce risk to the level of lifelong non-smokers[9].

Occupational exposure to carcinogenic chemicals such as aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons found in paint, rubber and dye manufacturing have been proven to have a contributing factor in 10% of cases[10]. Chronic irritation of the bladder leads to an increased risk of developing squamous cell carcinoma; this can be due to long-term catheterization or bladder stones. In regions of the world with endemic levels of Schistosomiasis, chronic infection from this parasite leads to chronic cystitis[11]. Squamous Cell Carcinoma accounts for 75% of bladder cancers in these regions[12].

Clinical Presentation

Patients with NMIBC commonly present with gross, painless, visible haematuria (VH)[6]. They may also present as non-visible haematuria (NVH), usually picked up on routine urinalysis using dipstix examination (Figure 3). Patients may also complain of Lower Urinary Tract Symptoms (LUTS) of storage, including frequency and urgency and sometimes dysuria, especially in the presence of carcinoma in situ (CIS) of the bladder. It is important to note that storage LUTS may also be the presenting symptoms in patients with urinary tract infections (UTIs). However, it is useful to remember that the diagnosis of UTI does not automatically exclude a bladder cancer, as both could be present in the same patient.

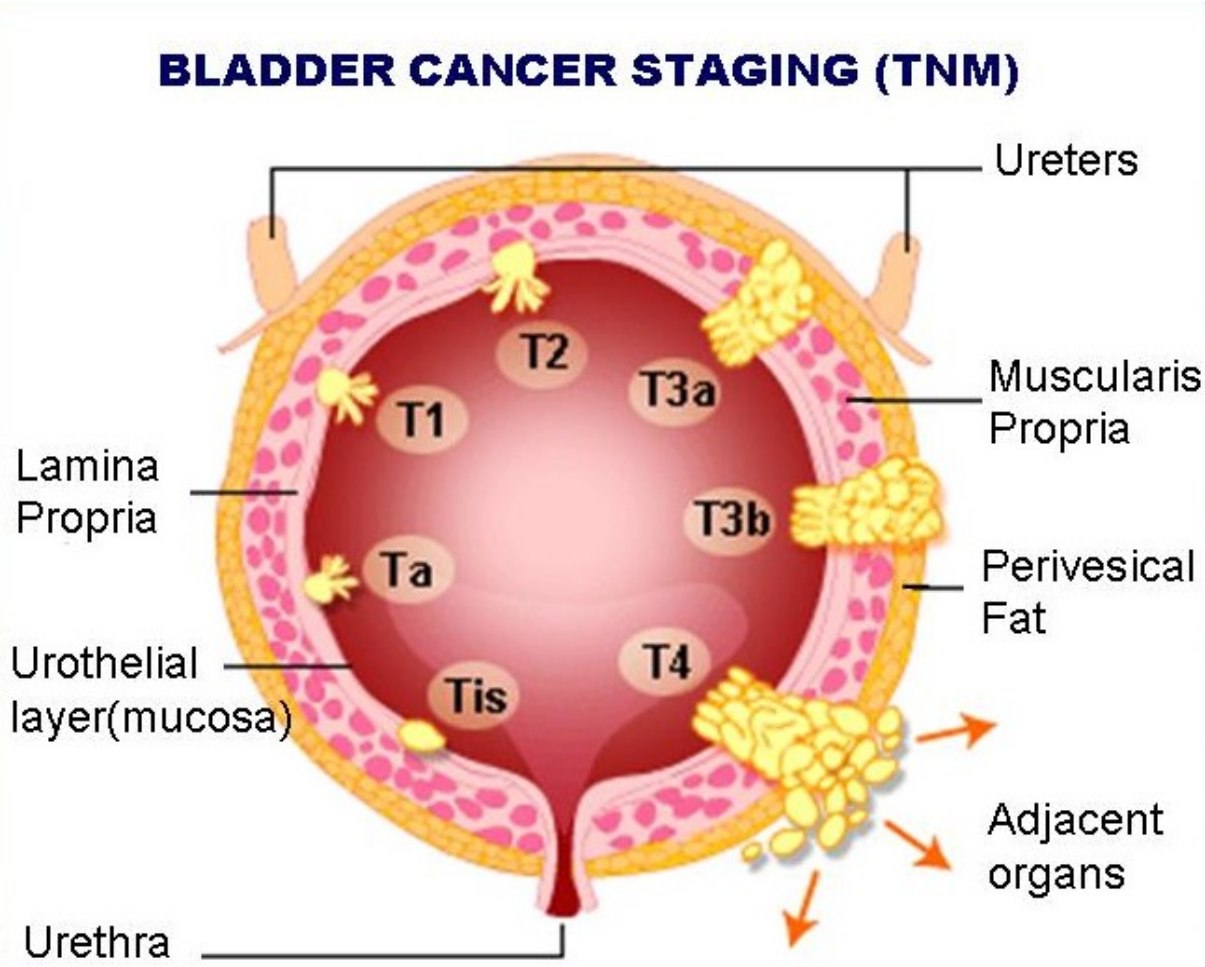

Figure 1 – TNM staging of Bladder Cancer – also demonstrating the different layers of bladder histology and their relation to bladder cancer staging

Heamaturia Clinic and Investigations

Patients with both VH and NVH are referred by the GPs via the 2 week wait pathway to the Rapid Access Haematuria clinic. This is provided in the form of a “One-Stop” service during which clinicians take a detailed history, perform thorough clinical examination and carry out investigations, (summarized in figure 2). This allows the patient to be informed of their diagnosis on the same day of their initial out-patient appointment and reduces the anxiety and delay for both, the patients and clinicians who are planning their management.

In addition to the information given in Figure 2, a detailed history taking regarding VH should also include the timing of its occurrence in relation to the urinary stream, which may give clues to the possible site of the underlying pathology. Initial haematuria refers to patient seeing blood at the beginning of micturition. This may suggest a possible urethral pathology. Mixed haematuria implies the presence of blood mixed throughout the urinary stream, which may indicate that the pathology is possibly in the upper urinary tract (kidneys, ureters) or bladder. Terminal haematuria is seen at the end of voiding urine suggesting that the underlying pathology is possibly in the bladder neck or prostate.

Clinical examination of the patient may reveal useful information including other pathology. Supra-pubic tenderness may suggest cystitis related to UTI. A palpable bladder may be found, if the patient is in retention of urine. Renal angle fullness may suggest hydronephrosis or a renal mass, which will be typically bi-manually palpable and / or ballotable. Just tenderness in the renal angle may suggest pyelonephritis. Genital examination may reveal phimosis and / or meatal stenosis. Digital Rectal Examination (DRE) is an integral part of the abdominal examination and may reveal nodule(s) or hardness in the prostate suggestive of malignancy or a smooth, firm enlargement of the prostate suggestive of BPE (Benign Prostatic Enlargement), which is the most common cause of visible haematuria in a man. Tenderness in the prostate may suggest prostatitis.

The mainstay of investigations is imagining and endoscopy. Flexible cystoscopy (Figure 4) allows direct visualization of bladder tumours. Small tumours and suspicious areas in the bladder mucosa may be biopsied and biopsy sites diathermied, under flexible cystoscopy guidance.

HISTORY TAKING

- **Visible haematuria** (onset, duration, painful / painless, volume, any clots?)
- **Non-visible haematuria** (diagnosis setting e.g. Routine medical at work)
- **LUTS** (frequency, urgency, dysuria, voiding difficulty - clot retention of urine)
- **Systemic symptoms** (tiredness, weakness, loss of appetite / weight, bone pain)
- **Risk factors** (smoking, occupation – mechanics, factory / industry workers, hair dressers)
- **Current medications** (anticoagulants)

EXAMINATION

- **General examination** (anaemia, dehydration, heart rate, BP)
- **Systematic examination** (abdomen, external genitalia, rectal / vaginal examination)

INVESTIGATIONS

- **Urinalysis - Dipstix testing** (blood, protein, leucocytes, nitrites, pH)
- **MSSU (Mid-stream specimen of urine) –** M, C&S (microscopy, culture & sensitivity)
- **Blood tests** (FBC, U&Es, PSA in men)
- **Urine Cytology** (usually not required during initial investigation)
- **US-KUB** – for patients < 50 years of age with NVH
- **CTU** – in all patients with VH and in patients > 50 years of age with NVH
- **Flexible Cystoscopy** – in all patients with VH and patients > 50 years of age with NVH
- **Urinary Biomarkers** – BTA (Bladder Tumour Antigen); NMP-22 (Nuclear Matrix Protein); UroVysion (FISH assay – Fluorescent in situ Hybridization assay)

Figure 2- The progress of patient through the rapid access haematuria clinic

Figure 3 – Urine Dipstix for testing – reagents change colour with positive tests

Figure 4 – Flexible Cystoscope – commonly used in out-patient setting

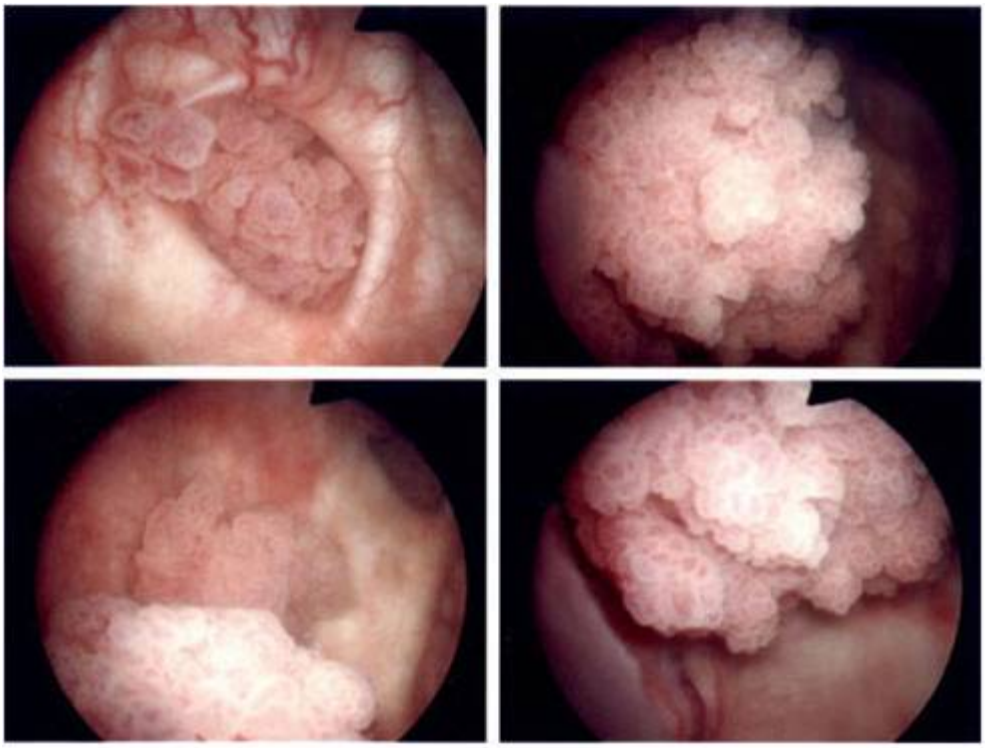

Figure 5 - Different appearances of Non-muscle invasive bladder cancer at Cystoscopy

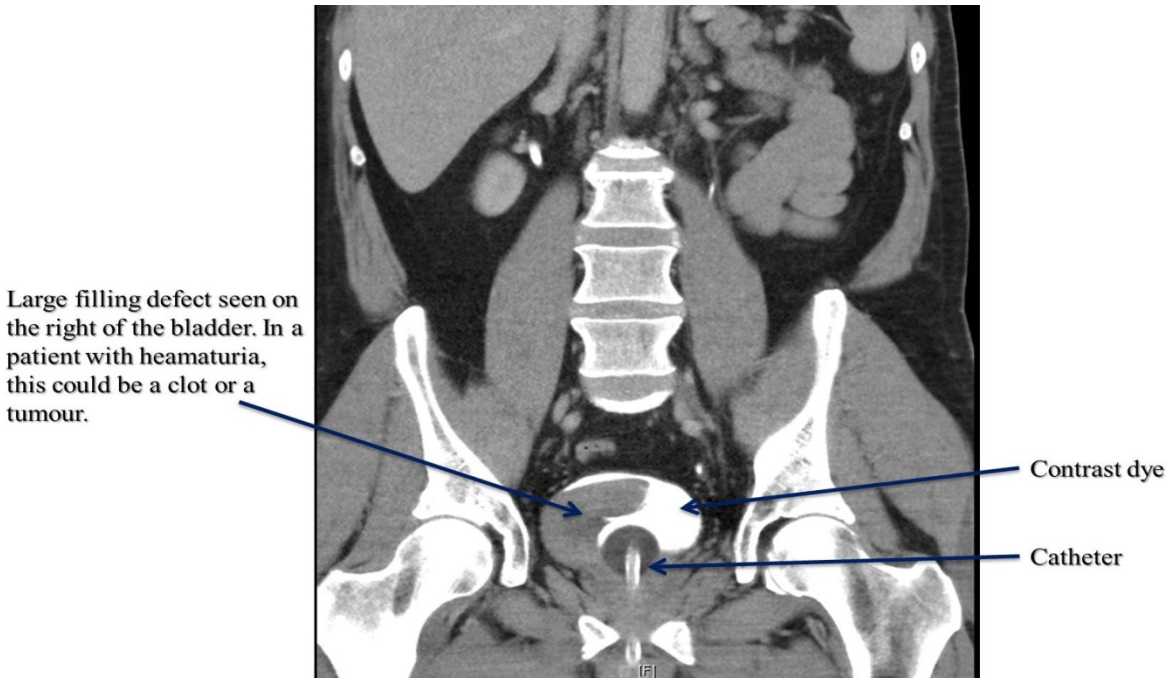

Figure 6 – CT-IVU appearance of a bladder cancer

Urine Cytology

Urine cytology forms part of routine initial evaluation of VH and NVH in some centres. However, in many centres, including ours, it is reserved as a second line investigation, if the initial investigations fail to demonstrate a cause for haematuria. The criticism about urine cytology is due its low sensitivity to detect low risk NMIBC, especially. It has a relatively higher sensitivity for high risk NMIBC. However, the specificity to detect NMIBC is much higher for urine cytology i.e. there is not many false positive results. So, if a patient has positive urine cytology, it is almost certain that there is Urothelial Carcinoma (UC) somewhere within the urinary tract, not necessarily bladder or urethra but may be in the ureters or kidneys. Thus, urine cytology can be judiciously used in the diagnosis and / or follow-up of patients with high risk NMIBC.

The Urinary Biomarkers, BTA, NMP-22 and UroVysion may be used instead of or along with urine cytology to aid the diagnosis of NMIBC[13].

Initial Management
(TURBT + Intra-vesical Mitomycin C)

In the event a suspicious lesion identified during cystoscopy, the patient would need to be urgently scheduled to have a Trans-Urethral Resection of Bladder Tumour (TURBT). This procedure is both therapeutic and diagnostic. It is the best way to get the lesion pathologically assessed to confirm the extent of disease. The detrusor muscle should ideally be included in the specimen sent for Histopathological examination, especially, to ensure that the cancer isn't muscle invasive. Absence of detrusor muscle in a biopsy has been linked to a greater risk of the patient having residual disease[14].

The European Association of Urology (EUA) guidelines states that a bimanual examination should be carried out after a TURBT to assess for the presence of residual masses or

thickening of the bladder which may indicate muscle invasive disease, while immobility of the bladder and pelvic organs may suggest T4 disease[14]. Immediately after the TURBT a single dose of intra-vesical chemotherapy is ideally given to the patient. The chemotherapy drug commonly used is Mitomycin C (MM-C). Mitomycin C is a drug which is isolated from the culture of Streptomyces caespitosus[6]. It's mechanism of action is alkylation and cross-linking of DNA strands which results in cancer cell death. MM-C is a large molecule and this prevents its systemic uptake thus limiting its effects to the local area of administration. The general complications that can arise from intra-vesical chemotherapy are LUTS of storage, skin desquamation and skin rash in the short term, but in the long term patients could potentially end up with bladder fibrosis and contracture[6, 14].

Staging

Bladder cancer is staged (Figure 1) using the Tumour, Node, Metastases system (2002). Union International Centre le Cancer, updated it in 2009[14, 15]. Non-muscle invasive cancer (NMIBC), sometimes referred to as "Superficial bladder cancer" are tumours of stages: Ta, T1 and Tis which are confined to the bladder mucosa, including the lamina propria (T1) (Table 1, Figures 1). Tumours which invade the bladder muscle, and deeper are staged T2 and greater (Figure 1).

T – Primary Tumour	
Ta	Papillary Tumours confined to Epithelial Mucosa
T1	Tumours Invading Sub epithelial Tissue (i.e. lamina propria)
Tis	Carcinoma in situ – flat high-grade tumours confined to the mucosa appear as inflammatory lesions.

Table 1- TNM staging of Non-muscle Invasive Bladder Cancer

Papillary non-muscle invasive bladder tumours are graded based on the degree of differentiation. The older WHO classification (1973) used a numerical system for grading tumours:

- Urothelial papilloma
- Grade 1: well differentiated (G1)
- Grade 2: moderate differentiated (G2)
- Grade 3: poorly differentiated (G3)

More recently the World Health Organization (WHO) in 2004 reclassified these tumours as below:

- Urothelial papilloma (completely benign lesion)
- Papillary urothelial neoplasm of low malignant potential (PUNLMP)
- Low-grade (LG) papillary urothelial carcinoma
- High-grade (HG) papillary urothelial carcinoma

This older grading system is still frequently seen in clinical practice and some units use both systems in parallel. The two systems are not equivalent with Grade 1 tumours becoming Papillary urothelial neoplasm of low malignant potential (PUNLMP) or Low-grade (LG) papillary urothelial carcinoma, Grade 2 tumours assigned to Low-Grade or High-Grade and all previous Grade 3 tumours are now High-Grade (Table 2).

PUNLMP	Low Grade	High Grade
Grade 1	Grade 2	Grade 3

Table 2 - Comparison of WHO grading 1973 and 2004 [10, 11]

Carcinoma in Situ is subdivided into three clinical types:

- Primary: isolated CIS with no previous or concurrent papillary tumours and no previous CIS
- Secondary: CIS detected during follow-up of patients with a previous tumour that was not CIS
- Concurrent: CIS in the presence of any other urothelial tumour in the bladder

Follow up & Further Management

Bladder cancer has a high recurrence rate (50–70%) therefore it is important to follow up patients regularly to identify patients who would require further therapy[6]. This surveillance mainly involves a repeat cystoscopy every 3-6 months depending on risk stratification. Patients are divided into either the low, intermediate and high risk groups. Divisions are made using the pathological report of the specimens collected during TURBT and the number and size of tumours visualized[14]. This division is used to aid disease management (Table 3) and determine length of follow-up.

The follow-up regime mentioned in Table 3 is based on the National Institute for Clinical Excellence (NICE) guidelines[16] for NMIBC (2015). Some Urologists are however uncomfortable to discharge patients in the low risk group after only 12 months follow-up. They prefer to continue cystoscopy surveillance on an annual basis for up to 5 years as was hitherto practiced in the UK.

Risk Group	Histology	Follow Up
Low	solitary pTaG1/ pTaG2 (low grade) - diameter of less than 3 cm Papillary urothelial neoplasm of low malignant potential	Cystoscopy surveillance for 12 months
Intermediate	solitary pTaG1/ pTaG2 (low grade) - diameter of more than 3 cm multifocal pTaG1/ pTaG2 (low grade) pTaG2 (high grade) low-risk non-muscle-invasive bladder cancer recurring within 12 months of last tumour occurrence	Intravesical MMC - weekly x 6 Cystoscopy surveillance for 5 years
High	pTaG3 pT1G2/pT1G3 pTis (Cis) aggressive variants e.g. micro papillary or nested variants	2nd TURBT to exclude muscle invasive disease Either: Intravescial maintenance BCG then Cystoscopy surveillance for 10 years or Radical Cystectomy

P = Pathological - this information is obtained from histology rather than clinical examination or imaging

Table 3 -Management and Follow up Plan for NMIBC[16]

The follow-up of NMIBC involves cystoscopy surveillance for a period of 5-10 years but patients with intermediate and high risk disease also receive adjuvant intra-vesical treatment once muscle invasive disease has been excluded. This can be in the form of chemotherapy (MM-C), as mentioned earlier in this article or in the form of immunomodulators. The most commonly used immunomodulator is BCG - *Bacillus Calmette-Guérin*[17]. BCG is a vaccine that was initially developed to prevent tuberculosis but has been found to be useful in the treatment of bladder cancer. It's mechanism of action in the bladder is not completely

understood. However, it is thought that the vaccine stimulates a local immune response [6] against the tumour cells via the promotion of pro-inflammatory cytokines (e.g. IL-1, IL-6, IL-8 and TNF - tumour necrosis factor). Complications related to BCG use include, cystitis, granulomatous prostatitis, disseminated tuberculosis, BCG sepsis and death. BCG induction consists of 6 doses given weekly. Studies have shown that giving further maintenance BCG for up to 3 years improves the response[18].

NICE recommends that patients with High Risk NMIBC should be offered the choice of primary cystectomy or BCG and the benefits and risks of both options discussed[16]. For patients who are refractory to BCG or not-tolerant, radical cystectomy is the treatment of choice. However those patients who are unfit or have decided against radical cystectomy may be offered alternative options depending on local policies. These can include further BCG induction therapy or device assisted intravesical chemotherapy in the form hyperthermia MMC or electromotive drug administration of MMC.

If cystectomy is performed, urinary diversion is done either through an ileal conduit (non-continent diversion) or the formation of a neobladder or abdominal pouch (continent diversion). Both forms of diversions require the use of a section of bowel which could lead to complications such as electrolyte disturbances, sepsis, and malabsorption of vitamins, bowel obstruction and the formation of renal calculi.

Recurrence & Progression

Recurrence involves the formation of a new lesion of the same histological grade, whereas progression means that the tumour has advanced in its pathological stage. Various factors are used when determining prognosis and the risk of recurrence or progression (Figure 5). The most important of these are histology and grade of the tumour. Carcinoma-in-situ is associated with a greater chance of progression to invasive disease.

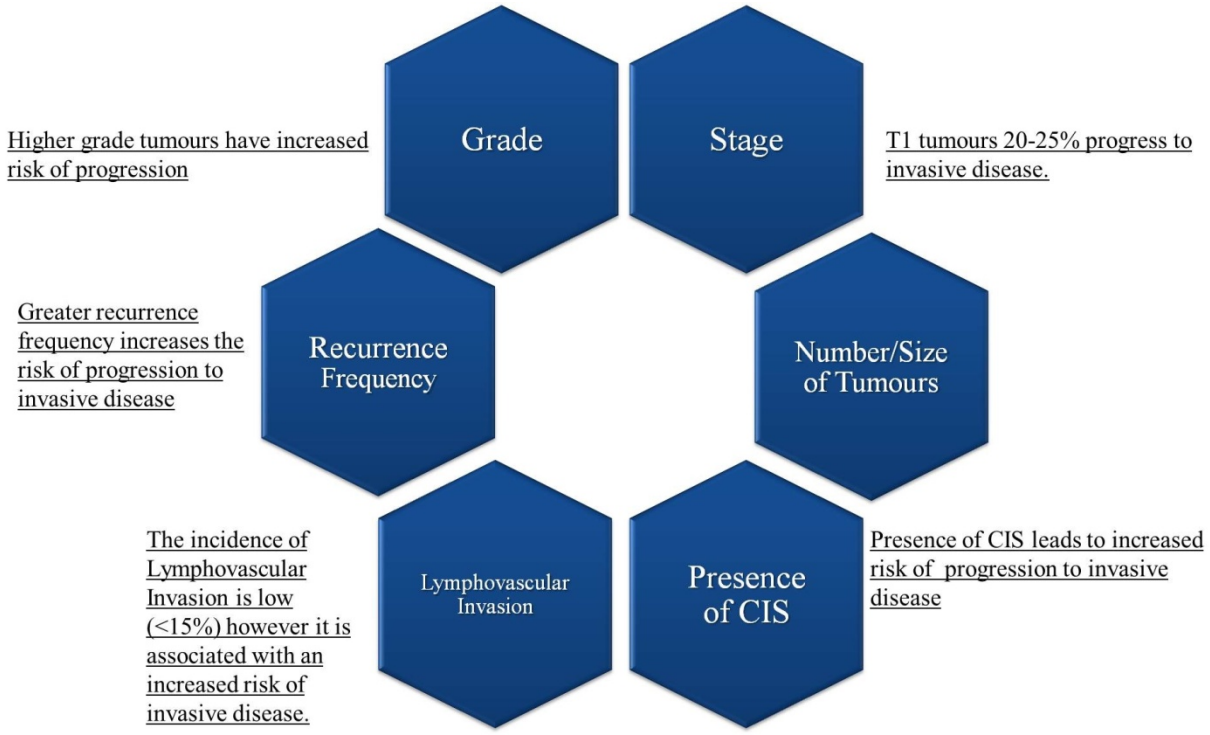

Figure 7 - Factors used to assess prognosis [19, 20]

Risk progression scores have been developed in order to predict disease recurrence and progression however; these do not include patients with the presence of CIS alone[16]. CIS is only included in patients with concurrent papillary disease. Recurrence and progression scores are given with regards to tumour grade/number, size, previous recurrence and presence of CIS[20]. The scores are then added up (Tables 4 & 5).

Factor		Recurrence Score	Progression Score
Number of Tumours	2-7	3	3
	>7	6	3
Tumour diameter	>3 cm	3	3
Prior recurrence rate	< 1 recurrence/year	2	2
	> 1 recurrence/year	4	2
Category	T1	1	4
Concurrent CIS	Yes	1	6
Grade	G2	1	0
	G3	2	5
Total Score		**0-17**	**0-23**

Recurrence score	Probability of Recurrence at 5 years	Progression Score	Probability of Progression at 5 years
0	15%	**0**	0.2%
1-4	24%	**2-6**	1%
5-9	38%	**7-13**	5%
10-17	61%	**14-23**	17%

Table 4, 5 - Probability of recurrence and progression[20]

Conclusion

NMIBC should be considered in patients presenting with VH and / or NVH. Those at risk should be investigated quickly at the two week wait haematuria rapid-access clinic. Late detection and management could potentially lead to muscle-invasive disease with greater morbidity and mortality. Therefore it is imperative for patients to undergo imaging and cystoscopy as quickly as possible for a definitive diagnosis and to plan definitive treatment such as TURBT. Patients are risk stratified based on their histopathology results. Further management including appropriate intra-vesical adjuvant MMC or BCG treatment and cystoscopy surveillance is based on the risk group that the patient belongs to. The aim of the treatment for NMIBC in general, is to preserve the bladder. However, some patients who have high risk or progressive disease may opt for or need radical cystectomy followed by an appropriate form of urinary diversion.

Multiple Choice Questions

1. A 67 year old British man presents with frank painless haematuria. Which of the follow risk factors is most important to establish whilst taking the history?

    a) History of recurrent UTIs

    b) Smoking

    c) Hyperparathyroidism

    d) Occupational exposure to aromatic amines

    e) Schistosomiasis

2. The patient's GP decides to refer him for further investigation. What is the gold standard investigation for this patient?

    a) CT Urogram

    b) Urinary Biomarkers

    c) USS KUB

    d) Renal Function Tests

    e) Cystoscopy

3. A 71 year old male patient is referred to Urology. Investigation demonstrates a papillary lesion visualized within the bladder. A biopsy is taken which is sent for histology. This shows that the tumour invades the lamina propria but does not invade the superficial muscle. Which of following tumour stages best describes these results?

    a) Ta

    b) Tis

    c) T1

    d) T2

    e) T3

4. A 65 year old female patient undergoes TURBT and is given the diagnosis of a pTaG2 (high grade) bladder tumour. She is given an intravesical dose of Mitomycin C. Which of the following is the most appropriate regime of surveillance for reoccurrence?

    a) No follow-up required

    b) Cystoscopy surveillance for 12 months

    c) Further maintenance MMC and Cystoscopy surveillance for 12 months

    d) Further maintenance MMC and Cystoscopy surveillance for 5 years

    e) 2nd TURBT, Intravescial BCG and Cystoscopy surveillance for 10 years

5. A 60 year old patient with high risk disease undergoes a second TURBT which shows disease progression. The histology report grades the lesions as muscle invasive. What would be the most appropriate management option for this patient?

    a) No further management required

    b) Repeat cystoscopy in 3 months

    c) Verify eligibility for radical cystectomy.

    d) Repeat course of intravesical BCG

    e) Palliative radiotherapy

Multiple Choice Answers

1. Answer B

D is also important to ask about however it is not the most important risk factor associated with Non muscle invasive bladder cancer. E is relevant in patients who have migrated or travelled to countries where schistomiasis is prevalent.

2. Answer E

Cystoscopy allows direct visualization of the tumour and is also the only way to diagnose CIS.

3. Answer C

T1 disease is defined as tumours invading sub epithelial tissue but that does not invade the superficial muscle layer.

4. Answer D

The patient's disease would fall into the intermediate risk group. A is incorrect as every risk group is followed up, B is for the low Risk group, D is for the intermediate risk group, E is for the high risk group and C doesn't fit any of the risk groups

5. Answer C

A and B are incorrect given the progression of high grade disease. E is incorrect as the question stem hasn't indicated that the patient is at the stage of palliative therapy yet.

References

1. Marko Babjuk, Willem Oosterlinck, Richard Sylvester, Eero Kaasinen, Andreas Bo¨ hle, Juan Palou-Redorta. EAU Guidelines on Non-Muscle-Invasive Urothelial Carcinoma of the Bladder. European urology (2 0 0 8) **54:** 303–314
2. Ferlay J, Bray F, Forman D, et al. GLOBOCAN 2008 v1.2, Cancer Incidence and MortalityWorldwide: IARC Cancer Base No. 10 2010, International Agency for Research on Cancer: Lyon, France. http://www.iarc.fr/en/publications/eresources/cancerbases/index.php
3. Bladder Cancer Statistics. Cancer Research UK. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer [Accessed October 15, 216AD].
4. Steinmaus C, Ferreccio C, Acevedo J, et al. Increased lung and bladder cancer incidence in adults after in utero and early-life arsenic exposure. Cancer Epidemiol Biomarkers Prev 2014 Aug; **23(8):**1529-38.
5. Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol 2013 Feb; **63(2):**234-41. http://www.ncbi.nlm.nih.gov/pubmed/22877502
6. Kaufman, D.S., Shipley, W.U. & Feldman, A.S., 2009. Bladder cancer. The Lancet, 374(9685), pp.239–249. Available at: http://dx.doi.org/10.1016/S0140-6736(09)60491-8.
7. Freedman, N.D., 2011. Association Between Smoking and Risk of Bladder Cancer Among Men and Women. JAMA, 306(7), p.737. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3441175.
8. Zeegers, M. et al., 2000. The impact of characteristics of cigarette smoking on urinary tract cancer risk: a meta-analysis of epidemiologic studies. Cancer, 89, pp.630–639.

9. van Osch, F.H. et al., 2016. Quantified relations between exposure to tobacco smoking and bladder cancer risk: a meta-analysis of 89 observational studies. International journal of epidemiology, 45(3), pp.857–70. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27097748.
10. Reulen, R.C. et al., 2008. A meta-analysis on the association between bladder cancer and occupation. Scandinavian journal of urology and nephrology. Supplementum, (218), pp.64–78. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18815919.
11. Mostafa, M.H., Sheweita, S.A. & O'Connor, P.J., 1999. Relationship between schistosomiasis and bladder cancer. Clinical microbiology reviews, 12(1), pp.97–111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9880476.
12. El-Bolkainy, M.N. et al., 1981. The impact of schistosomiasis on the pathology of bladder carcinoma. Cancer, 48(12), pp.2643–8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7306921.
13. Chou, R. et al., 2015. Urinary biomarkers for diagnosis of bladder cancer: A systematic review and meta-analysis. Annals of Internal Medicine, 163(12), pp.922–931.
14. Morgan, T.M. & Clark, P.E., 2015. Bladder cancer. European Urology Guidelines, 22(3), pp.242–249.
15. Sobin LH, Gospodariwicz M, Wittekind C, eds. TNM classification of malignant tumours. UICC International Union against Cancer. 7th edn. Wiley-Blackwell, 2009 Dec; pp. 262-265.
16. NICE, 2015. Bladder Cancer: diagnosis and managment. , (February). Available at: https://www.nice.org.uk/guidance/ng2/resources/bladder-cancer-diagnosis-and-management-of-bladder-cancer-51036766405.

17. Shelley, M. et al., 2000. Intravesical Bacillus Calmette-Gu□rin in Ta and T1 bladder cancer. Cochrane Database of Systematic Reviews, (4). Available at: http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=2009823087&site=ehost-live.

18. Crawford, E.D. et al., 2003. Southwest Oncology Group studies in bladder cancer. Cancer, 97(S8), pp.2099–2108. Available at: http://doi.wiley.com/10.1002/cncr.11286.

19. Chade, D.C. et al., 2010. Clinical Outcomes of Primary Bladder Carcinoma in Situ in a Contemporary Series. J Urol, 184(1), pp.74–80.

20. Sylvester, R.J. et al., 2006. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. European urology, 49(3), pp.466-5-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16442208.