Bladder Neoplasms: Non-Muscle Invasive Bladder Cancer

Editors:

Sima Porten, MD, MPH

Authors:

Brant A. Inman, MD, MS, FRSC; Yair Lotan, MD; Eugene Pietzake, MD; Bogdana Schmidt, MD

Last Updated:

Friday, March 3, 2023

1. Introduction

Tumors and proliferative disorders of the urinary bladder are among the most common oncological issues managed by urologists. In this core topic, we will review basic bladder anatomy, benign bladder lesions that can cause patient symptoms or that can mimic cancer, and non-invasive bladder cancer.

1.1 Key Words

Follicular cystitis; Eosinophilic cystitis; Granulomatous cystitis; Bilharzial/schistosomal cystitis; Malakoplakia; Amyloidosis; Cystitis cystica et glandularis; Squamous metaplasia; Nephrogenic adenoma; Inflammatory Myofibroblastic Tumor; Postoperative Spindle Cell Nodule; Leiomyoma; Paraganglioma; Hemangioma; Bladder cancer; Urothelial carcinoma; Transurethral resection of bladder; Narrow band imaging; Hexaminolevulinate; BCG

2. General Considerations

2.1 Vascular and Lymphatic Anatomy of the Bladder

The blood supply to the bladder derives from the **superior and inferior vesical arteries** which are branches of the anterior division of the internal iliac artery. The venous return from the bladder occurs through the **inferior and superior vesical veins**, which in turn drain into the internal iliac vein. Lymphatic drainage from the bladder occurs first to **level I nodes (internal iliac, obturator, and external iliac), then to level II nodes (common iliac, presacral)**, and finally to **level III nodes (paracaval, para-aortic,** and **interaortocaval**). Bladder tumors may spread directly to level II nodes (skipping the level I nodes) in about 7% of cases but do not usually skip to level III nodes without first affecting level I or II nodes. **Standard pelvic lymphadenectomy (PLND) includes level I nodes, extended PLND includes level I and II nodes, super-extended PLND includes level I, II and III nodes.**[1]

2.2 The Urothelium

The urothelium is the epithelium that lines the urinary tract and extends from the tip of the renal papillae to the urethra.[2] It typically has **3-6 layers of cells** that are comprised of (from basement membrane to lumen) **basal cells, intermediate cells, and umbrella cells**. The urothelium is the **most impermeable of all human epithelia** and is also very inert (does not react with substances), a characteristic that arises due to three distinct factors: (i) a glycosaminoglycan layer on top of umbrella cells (ii) tight junctions between umbrella cells (iii) uroplakin proteins in the apical umbrella cell membrane that form plaques and hinges. **Bladder cancer is thought to arise from the basal cells in some cases (CIS, muscle-invasive urothelial carcinoma, and squamous cell carcinoma) and intermediate cells in some cases (non-invasive urothelial carcinoma).**[3]

3. Benign Urothelial Tumors

3.1 Inflammatory Disorders of the Bladder

3.1.1 Follicular Cystitis

Follicular cystitis has the appearance of **yellowish papules** , usually multiple and clumped in groups, arising from the urothelium.[4] Microscopically, the papules are comprised of clusters of inflammatory cells, usually predominated by lymphocytes. **Follicular cystitis is commonly seen in patients that have been treated with BCG and in those with recurrent UTIs**. It is an asymptomatic condition and thus, typically an incidental finding at cystoscopy and does not usually require treatment.

3.1.2 Eosinophilic Cystitis

Eosinophilic cystitis is an **allergic reaction** occurring in the bladder. It presents as a **red patch** arising from the urothelium.[5] Microscopically, the urothelium is loaded with eosinophils. **Irritative lower urinary tract symptoms are the most common clinical presentation**. Triggers for the allergic reaction are often subtle but can include suture and mesh material used in pelvic surgery. Treatment consists of **bladder relaxants (anticholinergics and β3 agonists), oral antihistamines**, and occasionally even **oral**

steroids. While the condition is usually controllable with medication, it can progress to the point where transurethral resection of the bladder (TURB), bladder augmentation, or cystectomy are required.

3.1.3 Granulomatous Cystitis

Granulomatous cystitis is the clinical presentation of **mycobacterial bladder infection**. In Western countries, intravesical BCG therapy is the most common cause but genitourinary infection by mycobacterium tuberculosis is a cause seen in the developing world (**approximately 20% of new TB cases demonstrate a GU component**).[6] Cystoscopically, the bladder appears red and inflamed, usually with a reduced bladder capacity. Microscopically, the bladder is highly inflamed and loaded with **granulomas**. BCG-related granulomatous cystitis is treated with **isoniazid (300 mg PO daily)** and **pyridoxine (vitamin B6, 25 mg PO daily)** for 3 months. Bladder relaxants may also be prescribed, and occasionally severe bladder contracture results, necessitating cystectomy. The **risk of BCG cystitis** in patients undergoing BCG therapy is approximately **1 in 200** and can be minimized by omitting BCG treatments while patients are experiencing gross hematuria (thereby reducing the risk of hematogenous dissemination of BCG). **Genitourinary TB, on the other hand, requires consultation with an infectious disease specialist and typically is treated with anti-tuberculous drugs** (4-drug regimen for two months followed by 2 for an additional four months).[7] Public health involvement is required for contact tracing and possible quarantine.

3.1.4 Bilharzial/Schistosomal Cystitis

Bilharzial cystitis is caused by parasitic infection of the bladder by Schistosomal species (***S. haematobium*** **and** ***S. mansoni***).[8] **The parasites make their way to the liver where they mature before migrating to the mesenteric and pelvic veins where they begin producing ova for 5-25 years.**The ova cause chronic granulomatous inflammation in tissues, including the bladder. **Bladder manifestations** of schistosomiasis include **hyperplasia, calcification, ulcers, scarring/fibrosis, and keratinizing squamous metaplasia.**The lesions are usually located at the dome or posterior bladder. Approximately **1-5% of cases of bilharzial cystitis will develop bladder cancer. Histology in these cases is most commonly squamous cell carcinoma, but occasionally adenocarcinoma may be observed.**

3.1.5 Bladder Malakoplakia

Malakoplakia is a rare disorder, **more common in immunosuppressed patients** , that presents with irritative LUTS and occasionally with ureteral obstruction[9] Cystoscopically, it appears as **brownish plaques** in the bladder. Microscopically, it appears as a mixed inflammatory process with **granular macrophages (von Hansemann cells)** containing **targetoid inclusions** known as **Michaelis–Gutmann bodies** (which are believed to be undigested intracellular bacteria). The cause is postulated to be **defective macrophage lysosomal digestion of bacteria**, which is normally a cGMP-dependent process. Treatment consists **primarily of transurethral resection/biopsy followed by a prolonged course of antibiotics** (1st line = quinolones, 2nd line = rifampin or trimethoprim). **Drugs that activate cGMP** (bethanechol and vitamin C) may be of benefit.

3.1.6 Bladder Amyloidosis

Bladder amyloidosis is caused by an accumulation of precipitated protein within the bladder wall.[9] The proteinaceous deposit typically appears **nodular or plaque-like, often yellowish** at cystoscopy, and cannot reliably be differentiated from tumor. Microscopically, the protein deposit is seen as a **pinkish deposit that exhibits yellow-green birefringence under polarized light and positive Congo red staining.**The two main types of amyloidosis are AA and AL, although several other types exist. The second letter in the amyloidosis classification refers to protein fibril that the amyloid plaque is derived from. For example, AL amyloid derives from immunoglobulin light chain protein while AA derives from the serum amyloid A protein. **Most bladder amyloidosis is AL type. Transurethral bladder biopsy is required to make the initial diagnosis**. Subsequently, **referral to an amyloidosis expert is required to rule out other organ involvement and to rule out a discrete cause**, such as, multiple myeloma. Periodic TURBTs may be required to debulk the amyloid plaques. Patients with a high volume of bladder amyloidosis or those recurring frequently with amyloid plaques in the bladder can be treated with **intravesical DMSO** (50 mL of 50% solution for 30 min every 2 weeks for 3-12 months) to dissolve the unwanted protein. Cystectomy is occasionally required.

3.2. Benign Proliferative Disorders of the Bladder

3.2.1 Cystitis Cystica et Glandularis (CCEG) and Intestinal Metaplasia (IM)

There is a family of related conditions characterized by abnormal but benign gland development in the bladder: **cystitis glandularis, cystitis cystica,** and **intestinal metaplasia**. Cystoscopically, these lesions appear as **red inflammatory polypoid areas** in the bladder. While CCEG and IM are often found in patients with bladder adenocarcinomas, **it is not clear whether these lesions are actually premalignant** (the best studies suggest that they are not). Treatment is primarily directed at symptom management, with transurethral resection or biopsy required to make the diagnosis. Because the long-term outcome of these lesions is in doubt, **periodic (every year or two) surveillance with cystoscopy or urinalysis** might be prudent.[10]

3.2.2 Squamous Metaplasia

Squamous metaplasia occurs when the urothelium changes to resemble a squamous epithelium. There are two types of squamous metaplasia, **keratinizing** (associated with thick keratin scaling, a.k.a. leukoplakia) and **non-keratinizing** (no keratin scaling).[11] **Non-keratinizing squamous metaplasia is benign** and commonly noted as a **whitish plaque** in females extending from the urethra to the trigone. **Keratinizing squamous metaplasia**, on the other hand, is considered **premalignant** since it is occasionally associated with **squamous cell carcinomas** (though the evidence for its premalignancy is relatively poor). It is treated with **transurethral resection. Periodic (1-2 years) surveillance with cystoscopy or urinalysis may be considered**.

3.2.3 Urothelial Hyperplasia

Urothelial hyperplasia is a benign disorder that mimics low-grade NMIBC cystoscopically.[12] **Microscopically, it is bland and lacks the characteristic features of cancer**. This lesion is **premalignant with 25-50% of patients developing bladder cancer** at some later point. Diagnosis and treatment are done with **TURBT. Annual cystoscopic surveillance** is warranted.

3.2.4 Nephrogenic Adenoma/Metaplasia

Nephrogenic metaplasia is a benign neoplasm that most commonly affects the bladder.[13] Cystoscopically the lesion is not distinguishable from bladder cancer but **microscopically it has the appearance of renal parenchyma. Treatment is transurethral resection**. Recurrence occurs in about a third of cases.

3.2.5 Inflammatory Myofibroblastic Tumor (IMT) and Postoperative Spindle Cell Nodule (PSCN)

IMT is a lesion that presents as a **bladder mass** in a patient with **irritative LUTS or hematuria**. It has many names including **inflammatory pseudotumor, pseudosarcomatous fibromyxoid tumor,** and **nodular fasciitis**.[14] PSCN is essentially a variant of IMT and is distinguished clinically from it because it **occurs in patients that have previously undergone bladder surgery** (usually weeks to months before the diagnosis). Cystoscopically it is not distinguishable from a bladder cancer but microscopically it is composed of spindle cells that are myofibroblasts occurring in a background of inflammation. A key immunohistochemical feature seems to be **ALK-1 positivity**. TURBT is the diagnostic and therapeutic modality of choice for these lesions. **About 10% of these lesions will recur.**

3.2.6 Bladder Leiomyoma

Bladder leiomyomas are small firm tumors arising from the smooth detrusor muscle and are the **most common benign soft tissue neoplasm of the bladder**.[15] Cystoscopically they appear as **sub-urothelial humps** and microscopically as a **benign smooth muscle tumor.** Diagnosis can be made at **TURBT,** but **partial cystectomy** is often required to remove the neoplasm since they **arise from the deep detrusor muscle** and can be quite large.

3.2.7 Bladder Paraganglioma

Paragangliomas can occur in the bladder and, as with adrenal pheochromocytomas, **they tend to occur in young people**.[16] **Women are affected 3 times more commonly than men. Hematuria and hypertension**, occasionally occurring as **micturitional crises**, are common presenting signs. **Patients should undergo paraganglioma staging workup including DOTATE-PET (preferred), FDG-PET, or MIBG-SPECT prior to treatment**. Patients should also be screened for hereditary paraganglioma/pheochromocytoma syndromes, most commonly caused by mutations in succinate dehydrogenase genes. Occasionally a urologist is surprised by intraoperative hypertensive crisis during TURBT and paraganglioma should be suspected. Treatment ranges from **TURBT** to **partial or radical cystectomy**, depending on the extent and location of the tumor. When the diagnosis is known, pheochromocytoma precautions, such as those taken at the time of adrenalectomy for pheochromocytoma, should be **enacted**.

3.2.8 Bladder Hemangioma

Hemangiomas are benign vascular tumors of the bladder and **tend to occur in patients < 30 years of age**.[17] Bladder hemangiomas usually present with hematuria. **Multiple hemangiomas raise the possibility of Sturge-Weber** and related syndromes. These lesions are diagnosed and treated with **TURBT** with an extremely **low probability of recurrence**.

4. Bladder Cancer

4.1 Epidemiology

Bladder cancer is the fourth most common cancer in men and the fifth most common malignancy overall.[18,19] In 2021 in the United States, 83,730 new cases of bladder urothelial carcinoma and 17,200 deaths from bladder cancer are expected to **occur**.[20,21,22] **The male to female ratio is 4:1** , with an age standardized incidence rate of 10/100,000 for males and 2.5/100,000 for females.[23] Approximately **1 in 26 males** and **1 in 87 females** will develop bladder cancer over the course of their life.[23] There is a distinct

increase in incidence with age such that **men over 70 have a 3.7% probability of developing bladder cancer compared with 0.92% of men 60 to 69 and 0.38% for men 40 to 59**[23] Furthermore, Caucasians are more likely to develop bladder cancer than other ethnic groups.

4.2 Etiology

4.2.1 Acquired Factors

See references [24,25]

Bladder cancer has several known risk factors, the majority of which are acquired (**Table 1**).

Table 1: Risk Factors for Bladder Cancer	
Tobacco Smoke	
Current smoker (RR = 4)	Attributable risk = 50-60% of bladder cancers are caused by smoking Important susceptibility gene: NAT2
Former smoker (RR = 2)	Rising pack-years exposure increases: - Risk of developing bladder cancer - Risk of having high stage and grade - Recurrence and progression rates - Mortality rate
Occupational Exposures	
Aromatic hydrocarbons	**Examples**: benzo[a]pyrene, benzene, coal tar, bitumens, diesel exhaust **Uses**: industrial chemistry, asphalt **Occupations**: metal processing, truck drivers, oil and coal production
Aromatic amines	**Examples**: 2-toluidine, 2-naphthylamine, 4-aminobiphenyl, aniline **Uses**: dyes **Occupations**: textiles, painter, hairdresser, chemical plant
N-nitrosamines	**Examples**: N'-nitrosonornicotine, 4-(methylnitrosamino)-1-(3-pyridyl), 1-butanone **Uses**: rubber, tobacco curing, preservative **Occupations**: smokers, rubber, and latex manufacturing
Other	**Examples**: formaldehyde
Arsenic	
Blackfoot disease	Associated with Arsenic in drinking water. Risk is compounded by smoking and nutritional status Seen in Taiwan: presents with urothelial tumors, cardiovascular problems, hyperkeratosis

4.2.2 Genetic Factors

There are also several inherited tumor syndromes associated with bladder cancer development (**Table 2**). Patients that have a strong family history of cancer, that have a phenotype similar to those listed in **Table 2**, or that have bladder cancers occurring at a young age and without known risk factors should be referred to a geneticist for consideration of genetic testing. All the syndromes in **Table 2** are **autosomal dominant**.

Table 2. Genetic Factors associated with Bladder Cancer

Syndrome	Gene(s)	Key features
Lynch	• MSH2 (60%) • MLH1 (30%) • MSH6 (8%) • PMS2 (1%)	• Colon cancer (80%) • Endometrial cancer (80%) • Gastric cancer • Ovarian cancer • Urothelial carcinomas (15% upper tract > bladder)
Muir-Torre (variant of Lynch)	• MSH2 (90%) • MLH1 (10%)	• Sebaceous gland carcinomas and adenomas (100%) • Colon cancer (60%) • Urothelial carcinoma (20%) • Small bowel (5%) • Breast (5%)
Peutz-Jeghers	• STK11	• GI hamartomas (100%) • Melanotic macules (100%) • Intussusception (>50%) • Colon cancer (40%) • Breast cancer (7%) • Lung cancer (5%) • Pancreatic/Biliary cancer (1%) • Sex cord stromal tumors
Cowden	• PTEN • KLLN	• Mucocutaneous hamartomas (100%) • Breast cancer (80%) • Lhermitte-Duclos brain tumor (30%) • Thyroid cancer (20%) • Endometrial cancer (20%) • Kidney cancer (15%) • Colon cancer (10%) • Bladder cancer (<5%)* • Melanoma • Macrocephaly
Bannayan-Riley-Ruvalcaba syndrome (variant of Cowden)	• PTEN	• Macrocephaly/Macrosomia • Multiple benign tumors • Hamartomas of the small and large intestine • Dark freckles on the penis in males. • Developmental delays • Hemangiomas • Multinodular goiter/thyroid adenoma, thyroid cancer

Li-Fraumeni	• P53 • CHEK2	• Soft tissue sarcoma • Breast cancer • Bladder cancer • Adrenocortical carcinoma • Leukemia
Costello	• HRAS	• Papillomas (peri-oral) • Rhabdomyosarcoma • Neuroblastoma • Bladder cancer
Neurofibromatosis	• NF1 (neurofibromin) • NF2 (merlin)	• Neurofibromas • Lisch nodules • Scoliosis • Café au lait spots • Acoustic neuromas • Schwannomas • Meningiomas

There are also genes that are associated with an increased bladder cancer risk but that do not fit into a specific inherited syndrome. Many of these susceptibility genes are associated with detoxification processes used to metabolize carcinogens, in particular by the liver. Two important examples are the **N-acetyltransferases** (NAT1 and NAT2 genes) and the **glutathione S-transferases** (GST genes).

4.2.3 Molecular Biology

Traditionally, bladder cancers have been described as arising from two separate pathways: a **non-invasive pathway** characterized by **mutations in oncogenes FGFR3 and PIK3CA as well as loss of heterozygosity on chromosome 9q**; and an **invasive pathway** characterized by **mutations in the TP53 and RB1**[26] **tumor suppressor genes**. More recently, several teams have evaluated RNA expression in bladder cancer and have developed “molecular subtypes” that differ in gene expression, prognosis, and treatment response. In NMIBC, the UROMOL project has developed the largest and most thorough evaluation of these subtypes.[27,28] In their analysis, there were 4 classes of NMIBC.

Table 3: UROMOL 2021 summary of molecular subtypes with genetic characteristics and associated clinical phenotype data

UROMOL 2021	Class 1	Class 2a	Class 2b	Class 3
Key genetic characteristic	Early cell cycle	Chromosomal instability	Stem cell like	Immune-depleted
Genetic alterations	RAS FGFR3 High uroplakin	DDR genes P53 APOBEC	EMT genes	Cytokeratin 5 FGFR3 Low uroplakin
Recurrence	Low	High	Intermediate	Intermediate
Progression	Low	High	Intermediate	Low
Immune infiltration	Intermediate	Intermediate	High	Low

DDR = DNA damage repair

EMT = epithelial-mesenchymal transition

4.3 Signs and Symptoms

Hematuria is the most common presenting symptom in patients with bladder cancer. Bladder cancer is found on initial evaluation in **13-34.5% of patients with gross (macroscopic) hematuria and in 0.5-10.5% of patients with microscopic hematuria** .[29,30,31,32,33,34] **Irritative voiding symptoms** are also a symptom of bladder cancer, especially **carcinoma in situ (CIS).** These cancers can manifest with primary symptoms, such as urgency, dysuria, frequency and nocturia, or be misdiagnosed as recurrent bacterial cystitis. The latter is more common in females and may, in part, underlie the worse prognosis observed for females with bladder cancer, when compared to males.

Approximately **80% of patients with CIS present with irritative voiding symptoms**, and the **presence of these symptoms doubles the risk of harboring CIS (5% vs 10%) among patients with hematuria**.[30,34] However, both hematuria and voiding symptoms are seen commonly with other urologic conditions such as enlarged prostates, urinary tract infection and urolithiasis and may result in diagnostic difficulties in many patients. Review the **AUA guideline for microhematuria management**.[35]

4.4 Non-Muscle Invasive Bladder Cancer (NMIBC)

4.4.1 Diagnostic Tests (Cystoscopy, Urine tests, Imaging)

Patients suspected of having bladder cancer due to hematuria or symptoms should first undergo office **cystoscopy**.[36] In specific situations, **initial cystoscopy may be performed under anesthesia at the time of biopsy if imaging or cytology is highly suggestive of malignancy** Not all tumors are readily visible on conventional white light (WL) cystoscopy, and CIS is notoriously challenging to distinguish from normal urothelium or inflamed mucosa. **Biopsy or resection in the operating room is the next typical diagnostic and therapeutic step.**

The most used adjunct for identification of bladder cancer is use of **cytology** to detect neoplastic cells in the urine, a test that was originally described in 1945. However, **cytology has low sensitivity for identification of low-grade tumors, can be difficult to interpret in patients with inflammation and suffers from operator-dependent variability. Urine-based tumor markers** depend on detection of altered proteins in the urine or genetic changes in cells but are **not currently recommended for initial hematuria evaluation by the AUA or EAU guideline panels due to poor specificity and high cost**. However, urinary cytology may be used for patients with persistent microhematuria after a negative work-up who have irritative voiding symptoms or risk factors for CIS.

Imaging is frequently performed in patients with hematuria for evaluation of the kidneys and ureters since it can detect pathologies such as renal cell carcinoma, urothelial carcinoma in the pelvicaliceal system or ureter, urolithiasis, and renal infection. **CT urography** (non-contrast, contrast, delayed imaging) is the single best imaging modality for evaluation of urinary stones, renal and peri-renal infection, and associated complications. In patients with known non-muscle invasive bladder cancer, imaging can be used to rule out upper tract involvement (< 5% probability) and to rule out nodal or distant metastases (rare). **Retrograde pyelography**, done at cystoscopy or TURBT, is another acceptable method of screening the upper **urinary tracts for urothelial cancer**. If there are suspicious filling defects on retrograde pyelography, then **subsequent ureteroscopy (+/- biopsy and selective cytologies) should be performed.**

4.4.2 Staging and Grading Systems

Bladder cancers are staged using the 8th edition of the TNM/AJCC system (Table 4).[37] Clinical stages are denoted by a lower case “c” prior to the T stage, pathological stages by a lower case “p”, and post chemotherapy or radiotherapy stages by a lower case “y”. **Bladder cancers are graded using the 2016 WHO/ISUP grading system (Table 5)**.[38]

A few important points about staging warrant mention. First, **tumors that occur in a bladder diverticulum cannot be staged as T2** since bladder diverticula do not typically contain muscle. Second, **perivesical lymph nodes are considered regional lymph nodes**. Third, **invasion of the prostate by urothelial carcinoma** can take two forms: 1) **Direct invasion through the bladder and into the prostatic stroma is staged as T4a bladder cancer**, while 2) **intraurethral prostatic stromal invasion is staged at T2 urethral cancer.**

Table 4. TNM Staging of Bladder Cancer

Stage	Characteristics
Tx	Unknown
T0	No Carrier
Ta	Non-invasive
Tis	Carcinoma in situ
T1	Invades lamina propria
T2	T2a – Invades detrusor muscle superficially T2b – Invades detrusor muscle deeply
T3	T3a – Invades peri-vesical fat microscopically T3b – Invades peri-vesical fat macroscopically
T4	T4a – Invades prostate stroma (ie direct invasion and not only prostatic ducts) or vagina/uterus T4b – Invades pelvic side wall or abdominal wall
Nx	Unknown
N0	No Cancer in nodes
N1	1 positive pelvic node in the true pelvis (internal iliac, obturator, external iliac, presacral, perivesical)
N2	≥ 2 positive pelvic nodes in the true pelvis
N3	Positive common iliac nodes
Mx	Unknown
M0	No metastases
M1a	Non-regional nodal metastases
M1b	Other distant metastases

Table 5. 2016 World Health Organization/ International Society of Urologic Pathologists: Classification of Non-Muscle Invasive Urothelial Neoplasia
Urothelial proliferation of uncertain malignant potential (hyperplasia)
Urothelial papilloma
Inverted urothelial papilloma
Urothelial dysplasia
Papillary urothelial neoplasm of low malignant potential
Urothelial CIS
Non-muscle invasive low-grade papillary urothelial carcinoma
Non-muscle invasive high-grade papillary urothelial carcinoma

4.5 Transurethral Resection (TURBT)

TURBT is the primary way that bladder tumors are diagnosed and treated. It is generally performed under general anesthesia although may be performed under spinal anesthesia in select patients. **Small tumors** can be removed with **cold cup biopsy forceps** and the biopsy crater and surrounding urothelium (important due to **field effect**) can be fulgurated. **Larger tumors** require the use of an **endoscopic resectoscope**. Modern resectoscopes are either **monopolar (used with water or glycine solution)** or **bipolar (used with saline solution)** and most allow the continuous flow of irrigant in and out of the bladder during tumor resection, which improves visualization.

Large or nodular tumors should be resected in steps and submitted as separate specimens. The first step is to resect the endoluminal part of the tumor so that it is flush with the normal adjacent bladder wall. The bladder is then irrigated free of tumor chips and the second step of resecting deeper into the bladder wall occurs. **These deeper chips are sent separately for pathology to aid in the identification of lamina propria or muscle invasion**, which can be very difficult if a single large cup full of tumor is submitted for analysis.

En-bloc resection of tumors has been reported since 1997 and aims to remove the whole tumor with surrounding stroma and underlying muscularis propria in a single specimen. It can be performed using an endoscopic resection loop or knife, laser, or button. Potential advantages include improved pathology assessment, decreased rate of perforation, and avoiding tumor fragmentation and spillage. A meta-analysis of over 4000 patients and 13 RCTs found that en-bloc TURBT was associated with improved rate of detrusor muscle in the specimen, lower rate of tumor presence at re-resection, and lower risk of bladder perforation[41]. These findings suggest potential for reducing early re-resection but a larger randomized study is necessary to assess recurrence and overall oncologic efficacy.

Several aspects of performing and reporting TURBT steps have been associated with improved outcomes and are considered indicators of high-quality TURBT. The **inclusion of detrusor muscle in the specimen** and **instillation of intravesical chemotherapy** have been consistently associated with endpoints such as disease recurrence and progression across retrospective series[40]. A study of almost 3000 patients found that use of a bladder diagram for documenting lesions, inclusion of detrusor muscle in the TURBT specimen, and use of post-TURBT intravesical chemotherapy were associated with lower rates of recurrence at first cystoscopy and less residual tumor at repeat TURBT[41].

Checklists have been shown to improve outcomes with TURBT[42] and checklist items that should be documented in the operative note are shown below.

Table 6. Checklist of data to include in a TURBT Operative Note	
1	Describe number of bladder tumors
2	Describe size of bladder tumors (largest diameter and aggregate diameter)
3	Describe tumor morphology (nodular, papillary, flat, sessile)
4	Describe recurrent versus primary tumors
5	Assess for CIS (suspicious or not)
6	Assess AJCC clinical stage (cTa, cT1, cTis, cT2, cT3, cT4)
7	Report bimanual exam findings
8	Report whether resection was visually complete
9	Report whether muscle was visually resected
10	Report presence of absence of perforation
Additional items	
11	Use of immediate postoperative chemotherapy (drug, dose, dwell time)
12	Diagram of tumor location(s)

4.5.1 Bimanual Examination

Bimanual examination should be performed in patients that have large nodular tumors. **A palpable mass after TURBT represents extra-vesical extension (cT3) of tumor until proven otherwise while a fixed palpable mass raises the possibility of pelvic side wall or adjacent organ invasion (cT4a/b)**Abdominal fullness or an increase in girth after TURBT should raise concern for intraperitoneal **bladder perforation and a cystogram** should be performed in the OR to rule it out.

4.5.2 Hexaminolevulinate (HAL) and Narrow Band Imaging (NBI)

Two technologies are currently available that may increase the effectiveness of TURBT, **hexaminolevulinate (HAL) blue light TUR** and **Narrow Band Imaging (NBI)**.[43,44] Blue Light Cystoscopy (BLC) with Cysview (Photocure, Inc.) uses a photosensitizing agent, HAL, with preferential intracellular accumulation of photoactive porphyrins in malignant versus non-malignant cells (**Figure 3 and Figure 4**). **HAL cystoscopy requires pre-procedure intravesical instillation of HAL that stays in the bladder for 1-3 hours prior to cystoscopy.** After excitation with blue light illumination, cancer cells fluoresce resulting in better tumor visualization.

A recent meta-analysis evaluated BLC in 14 randomized controlled trials including 6 with an older agent 5-ALA and 9 with the current agent HAL including over 2900 patients.[45] **The use of BLC was associated with fewer recurrences at 12 months with a HR 0.75 (0.62-0.92)**. A separate meta-analysis found that reduction in recurrence applied to both primary and recurrent tumors and that **BLC significantly improved detection of carcinoma in situ (CIS) as compared with WL.**[46] While most studies were underpowered to assess for progression, the meta-analysis found a reduced rate of progression in patients undergoing BLC. Based on available data, the **AUA guidelines for NMIBC states that "in a patient with NMIBC, a clinician should offer blue light cystoscopy at the time of TURBT, if available, to increase detection and decrease recurrence (Moderate Recommendation; Grade B)."**[47]

Recently, blue light fluorescent cystoscopy was approved by FDA for use in clinic for surveillance of bladder cancer.[48] In a prospective multicenter trial of **304 patients undergoing surveillance for NMIBC, 63 had confirmed recurrence and 13 of the 63 patients (20.6%, 95% CI 11.5-32.7) recurrence was seen only with blue light flexible cystoscopy (p <0.0001) including 5 cases of CIS. The procedure was safe and none of the 12 adverse events during surveillance were serious**Some representative videos of blue light flexible cystoscopy are available.

Current indications for rigid and flexible blue light cystoscopy stratified by AUA risk category of NMIBC (see **Table 7**).[49,50]

Table 7: Current Indications for Rigid or Flexible Blue Light Cystoscopy, stratified by AUA Risk Category for NMIBC

	Low Risk	Intermediate Risk	High Risk
First TURBT (OR)	Rigid	Rigid	Rigid
Biopsy and fulguration	Flexible		
Repeat TURBT		Rigid	Rigid
Initial surveillance at 3 months	Flexible	Flexible	Flexible
At follow-ups for 2 years	Flexible	Flexible	Flexible
Prior to intravesical therapy to check for residual disease		Flexible	Flexible
To determine BCG response, particularly in CIS			Flexible or Rigid
To adjudicate patients with positive cytology or equivalent white light cystoscopy findings	Flexible or Rigid	Flexible or Rigid	Flexible or Rigid

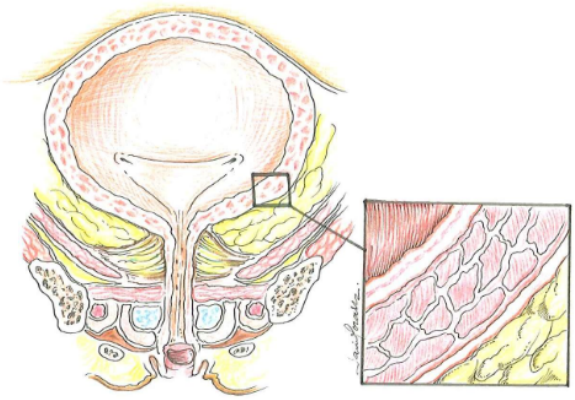

Figure 1: Cross-sectional schematic image of the bladder and its respective layers including muscularis propria.

Figure 2: Schematic diagram of bladder tumor of increasing depth of invasion. The layers of the bladder include the superficial urothelium (yellow), lamina propria (blue), muscularis propria (red) and serosa (second yellow). The corresponding tumor stages from left to right are CIS, pTa, pT1, pT2, pT3.

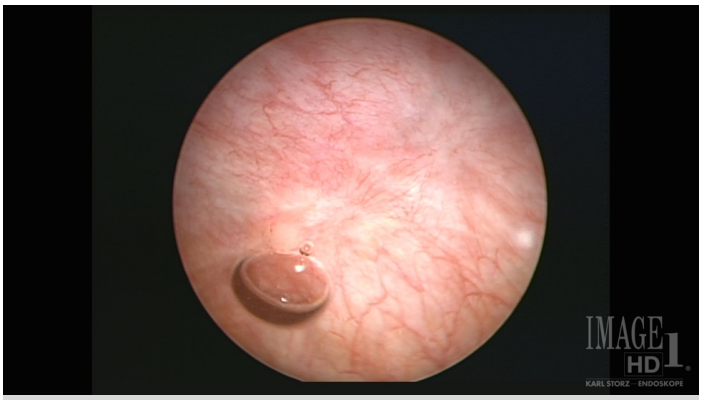

Figure 3A: White light Cystoscopy

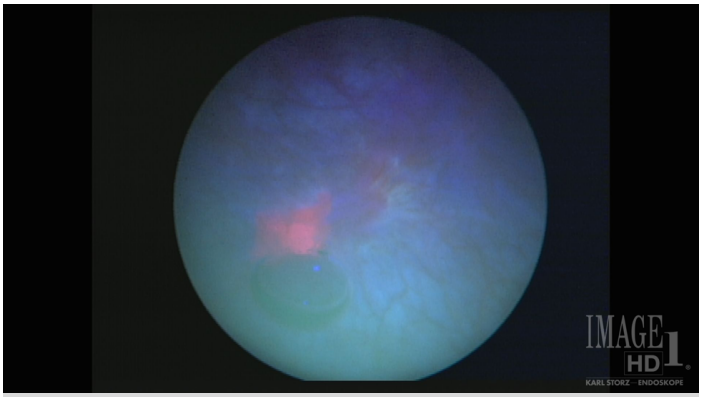

Figure 3B: Blue light Cystoscopy

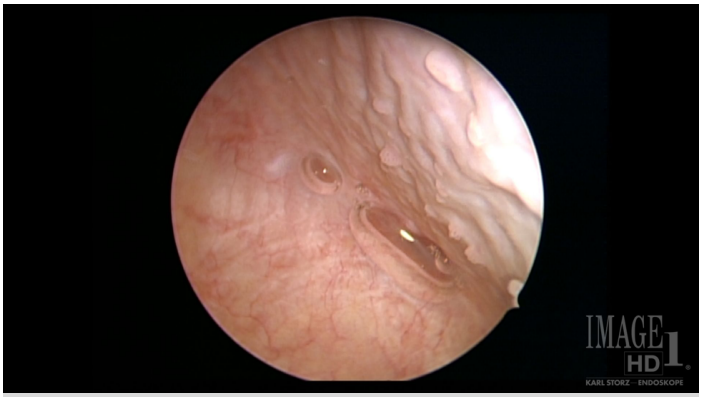

Figure 4A: White light Cystoscopy

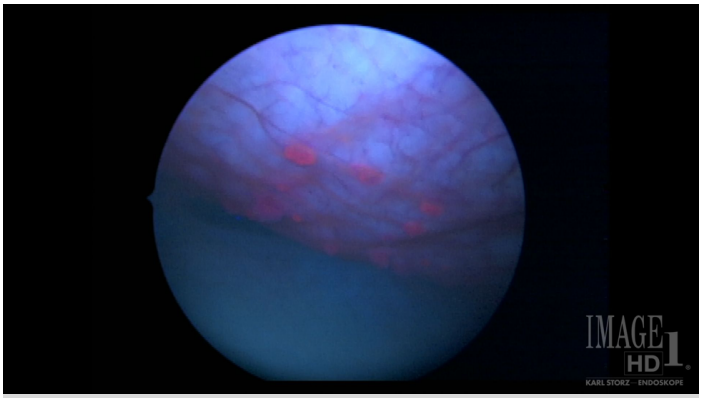

Figure 4B: Blue light Cystoscopy

NBI is an optical image enhancement technology that splits typical white light cystoscopy into two short wavelengths of light (blue and green) (**Figure 5 and Figure 6**). This process is activated by pressing a button on the endoscope camera and results in an image where vascular and delicate structures are better visualized. NBI also increases the detection of sub-clinical bladder tumors. A meta-analysis of NBI including 6 trials with 1084 patients found that NBI-TUR was associated with improvements in the 3-month recurrence risk, 1-year recurrence risk and 2-year recurrence risk compared with WL-TURB.[47] Based on available data, the AUA guidelines for NMIBC states **that "in a patient with NMIBC, a clinician may consider use of NBI to increase detection and decrease recurrence (Moderate Recommendation; Grade C)."**[47,52]

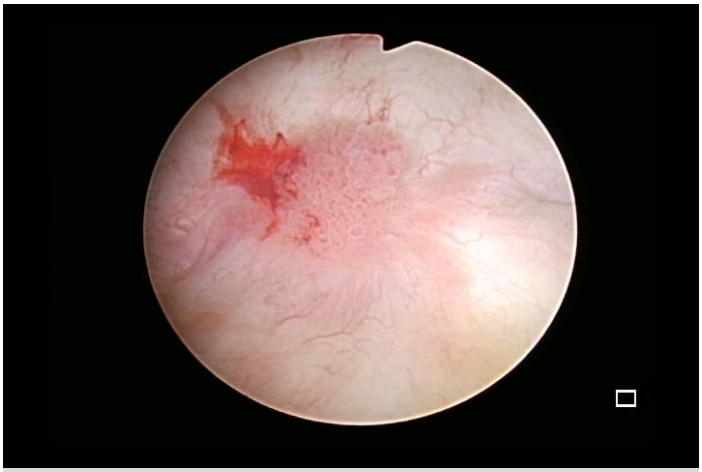

Figure 5A: White light Cystoscopy

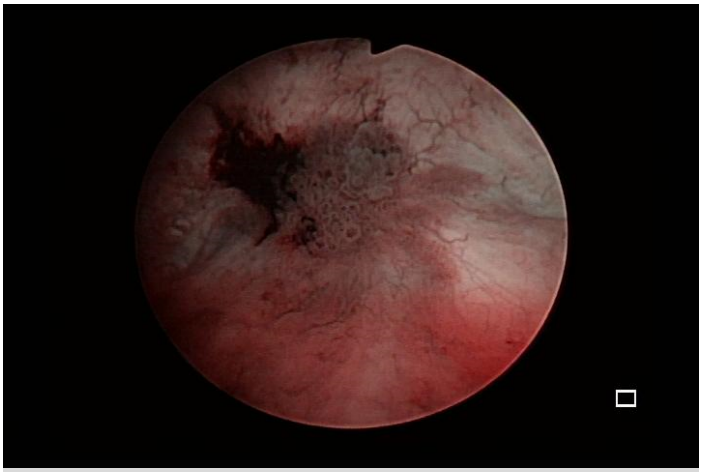

Figure 5B: Cystoscopy with NBI

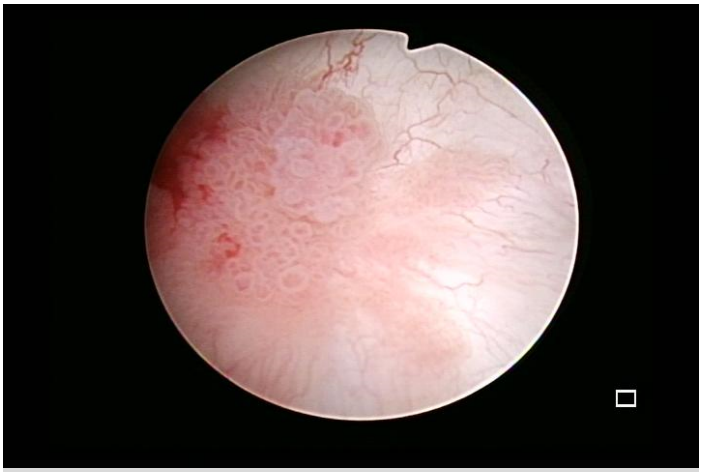

Figure 6A: White light Cystoscopy

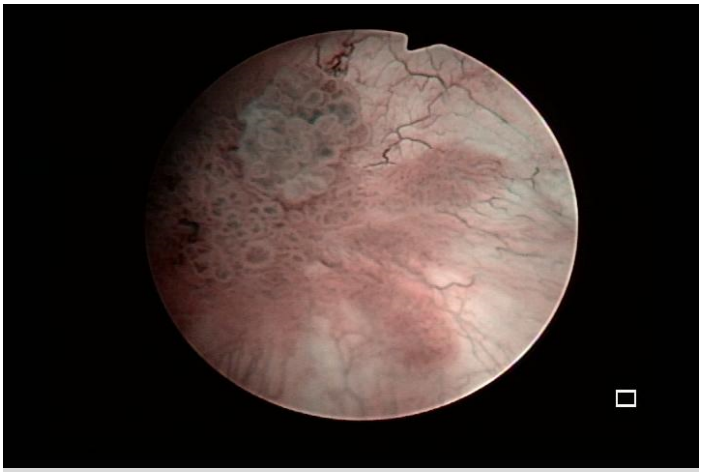

Figure 6B: Cystoscopy with NBI

4.5.3 Second-look TURBT

A second-look (repeat) TURBT is sometimes done **within 2-6 weeks of the first TURBT**. The indications for this include: **(i) Incomplete first TURBT, (ii) Large (> 3 cm) or highly multifocal tumor, (iii) High grade Ta tumor, and (iv) pT1 tumor with or without muscle in the original specimen**.

Second-look TURBT in patients with high-grade lesions demonstrated residual disease in half of the Ta tumors and upstaging in 15%; for T1 tumors, 48% had persistent NMIBC and 30% were upstaged to muscle invasion.[37]

The AUA guidelines recommend that in a patient with **high-risk, high-grade Ta tumors, a clinician should consider performing repeat transurethral resection of the primary tumor site within six weeks of the initial TURBT.** In a patient with **T1 disease**, a clinician should perform repeat **transurethral resection of the primary tumor site to include muscularis propria within six weeks of the initial TURBT**.

4.5.4 Complications of TURBT

Important complications of TURBT are noted in the **Table 8**.

Table 8. Complications of TURBT

Complication	Rate	Management
UTI	3%	1. Urinalysis and culture 2. Antibiotics
Bleeding requiring intervention or transfusion	2%	1. IV fluids +/- blood transfusion 2. Reverse systemic blood thinners 3. Manual bedside clot evacuation 4. 3-way Foley + continuous bladder irrigation 5. Clot evacuation and fulguration in operating room 6. Prothrombotic bladder irrigants 7. Consider systemic agents like Amicar 8. Angioembolization of bladder 9. Cystectomy
Bladder perforation	Any 2% Intraperitoneal 0.4% Extraperitoneal 1.6%	1. Stop resection 2. Place large (>20 F) Foley catheter 3. Do not perform continuous bladder irrigation 4. Do not administer postoperative chemotherapy 5. Start empiric antibiotics 6. Observe in hospital overnight and possibly longer 7. Laparotomy and bladder repair if (NB: open repair may increase the risk of tumor seeding): Very large intra-peritoneal rupture Large amount of iatrogenic ascites Pending intra-abdominal sepsis 8. Periodic imaging to rule out extra-vesical seeding
TUR syndrome	< 1%	Extremely rare with saline TURBT
Mortality	< 1%	

4.6 Recurrence and Progression

Bladder cancer has a high propensity for recurrence and **progression is strongly dependent on stage and grade. Low-grade Ta tumors are associated with a high rate of tumor recurrence (15-70% at one year)** but low rate of progression to higher stage disease with **less than 5% progressing to muscle invasive disease. High-grade Ta** tumors have between a **13-40% chance of progressing to lamina propria invasion**, and between **6-25% chance of becoming muscle invasive**. (**Figure 1 and Figure 2**)

T1 tumors comprise approximately one quarter of all non-muscle invasive tumors at initial presentation. They have worse malignant potential than Ta tumors in terms of **recurrence (80%) and progression (50% within three years)**.

Bladder CIS is a **noninvasive, high-grade tumor** by definition. CIS most commonly occurs concurrently with other bladder tumors and is associated **with high rates of recurrence (82%) and progression (42-83%)** especially if not treated with adjuvant intravesical therapy.

4.7 Risk Stratification

There are several tools used to predict risk of recurrence and progression of bladder cancer. The European Organization for Research and Treatment of Cancer **(EORTC) risk calculator**, based on the combined data from seven trials involving patients with NMIBC uses factors such **tumor size, number of tumors, grade, stage, presence of CIS and prior recurrence rate to develop a score and predict rate of recurrence and progression**.[44] A second risk stratification tool is that developed by the Spanish Urological Club for Oncological Treatment/Club Urologico Espanol de Tratamiento Oncologico (**CUETO**)[53] using similar features. The **AUA NMIBC guidelines use these factors but also takes into consideration lymphovascular invasion, prostatic urethral involvement, variant histology, and poor response to BCG**[54] **to stratify patients to low, intermediate and high risk (Table 9)**.[47] The patients risk determines need for adjuvant therapies as well as intensity of these therapies. It also helps guide recommendations regarding surveillance.

Table 9: AUA Guidelines Risk Stratification for NMIBC

Low Risk	*Intermediate Risk*	*High Risk*
LG solitary Ta ≤ 3cm	Recurrence within 1 year, LG Ta	HG T1
PUNLMP	Solitary LG Ta > 3cm	Any recurrent, HG Ta
	LG Ta, multifocal	HG Ta, >3cm (or multifocal)
	HG Ta, ≤ 3cm	Any CIS
	LG T1	Any BCG failure in HG patient
		Any variant histology
		Any LVI
		Any HG prostatic urethral involvement

LG = low grade;
PUNLMP = papillary urothelial neoplasm of low malignant potential;
HG = high grade;
CIS=carcinoma *in situ*;
LVI = lymphovascular invasion

4.8 Therapies for reducing recurrence and progression

4.8.1 Perioperative Intravesical Chemotherapy (IVC)

Immediate postoperative intravesical chemotherapy refers to the intravesical administration of an antineoplastic agent **within 24 hours of TURBT**.[55] **This treatment has been shown to reduce the bladder cancer recurrence rate by about 35%.**[56] **Anthracyclines** (epirubicin, doxorubicin, pirarubicin) and **mitomycin C** have been used.

A randomized trial comparing postoperative intravesical instillation of gemcitabine (2 g in 100 mL of saline) (n = 201) to saline (100 mL) (n = 205) for 1 hour immediately following TURBT found cancer recurrence within 4.0 years was 35% vs. 47%, respectively[57] **Among the 215 patients with low-grade NMIBC, the 4-year cancer recurrence rates were 34% in the gemcitabine group and 54% in the saline group (hazard ratio, 0.53; 95% CI, 0.35-0.81; P = .001 by 1-sided log-rank test for time to recurrence).** Adverse effects were no different between the gemcitabine and saline group, suggesting that intravesical gemcitabine is extremely safe. With this effectiveness, safety profile and at a fraction of the cost of mitomycin C (5%), gemcitabine should be considered as the intravesical agent of choice in this setting.

The AUA guidelines state that in a patient with **suspected or known low- or intermediate-risk bladder cancer, a clinician should consider administration of a single postoperative instillation of intravesical chemotherapy within 24 hours of TURBT**[54] **Immediate postoperative intravesical chemotherapy may not be effective for patients that have recurred more than once in the past year, those with CIS, and those with high grade T1 tumors.**

Patients with bladder perforations **should not** receive perioperative intravesical chemotherapy since systemic toxicities and severe cystitis reactions may develop. Additionally, patients with incomplete resections **should not** receive perioperative intravesical chemotherapy.

4.8.2 Chemoablative Intravesical Therapy

While most treatments for NMIBC are given as adjuvant therapy after a complete TURBT has removed all papillary disease, TURBT is surgical procedure that often requires general anesthesia and associated **complications** (see table 8). Recognition of potential detrimental side effects of TURBT and concerns of repetitive anesthesia for elderly and co-morbid patients has led to a renewed interest in investigating chemoablative approaches as a therapeutic alternative to TURBT.

Chemoablation (sometimes called chemoresection) has long been used in NMIBC clinical trials where an incomplete TURBT is performed so that the tumor ablative capabilities of novel intravesical therapies can be assessed on a “marker lesion”[58] Recently, a randomized study of 120 patients with a history of low grade or high-grade Ta disease compared intravesical mitomycin (40 mg/40 ml) three times a week for 2 weeks vs. TURBT (or office fulguration) followed by adjuvant intravesical therapy for 6 weeks[59]. The investigators found that this short term intensive chemoablative approach had a complete response rate of 57% (95%CI 43-70) and lower urinary related side effects compared to endoscopic treatment and adjuvant therapy. Single arm chemoablative trial data for a reverse thermal hydrogel formulation of mitomycin given once weekly instillation for 6 weeks demonstrated a complete response rate of 65% (95%CI 52,76.7) in patients with intermediate risk low grade NMIBC[60]. Further randomized trials are ongoing comparing this hydrogel formulation of mitomycin against TURBT.

The precise role for chemoablation within the management paradigm of patients with recurrent low grade NMIBC compared to other alternative approaches to TURBT, such as active surveillance and office cystoscopic fulguration, remain undefined.

4.8.3 Adjuvant Intravesical Therapy

Intravesical therapies can also be applied as adjuvant therapy **(usually started 2-6 weeks after last TURBT)** to **prevent the recurrence and progression of bladder cancer**. Indications for adjuvant intravesical therapy are: (i) **NMIBC with high risk of recurrence** (ii) **NMIBC with high risk of progression** (iii) **Carcinoma in situ** (iv) **Residual tumor** (rare indication for small volume tumors, TURBT almost always preferred). Of note, the risk of recurrence and progression can be estimated using the **EORTC NMIBC** prediction tool, and **adjuvant intravesical therapy is reserved for intermediate and high-risk patients**.[44]

Of note, **BCG should not be administered in the setting of active urinary tract infection, traumatic catheterization, or gross hematuria** to minimize the risk of systemic absorption and disseminated BCG infection.

The AUA guidelines state that in a low-risk patient, a clinician should not administer induction intravesical therapy. In an intermediate-risk patient a clinician should consider administration of a six-week course of induction intravesical chemotherapy or immunotherapy with BCG. In a high-risk patient with newly diagnosed CIS, high-grade T1, or high-risk Ta urothelial carcinoma, a clinician should administer a six-week induction course of BCG.[54]

Commonly used intravesical immunotherapeutic agents are described in **Table 10**.[61,62,63,64,65,66,67,68,69,70] For BCG, it is important to note that there are several different strains and **efficacy appears to be strain-dependent but there is insufficient evidence of superiority of any strain.** The standard induction course is the same for immunotherapy and chemotherapy: the agent **is instilled**

intravesically weekly for a total of 6 doses and then cystoscopy is performed 6 weeks later to assess for response. **Patients must retain the drug for two hours for peak efficacy**. Since urine production during treatment will dilute the drug and fill the bladder (making it hard for the patient to hold the drug in), **patients should not drink for 4-6 hours prior to treatment**.

In a quest to make **intravesical mitomycin C more effective ("optimized mitomycin C")**, several modifications have been found useful: (i) Dehydration for 8 hours prior to treatment (ii) Alkalinization of the urine (oral sodium bicarbonate 1.3 g, 12h, 3-6h, and 30 min prior) (iii) increasing drug concentration to 2 mg/mL (40 mg in 20 mL) (iv) Electromotive drug administration (EMDA) (v) Bladder hyperthermia. **The most common maintenance schedule for chemotherapy is once monthly for 1 year with variable improvements in recurrence-free survival observed across trials**.[71]

Clinical trials have demonstrated benefit for maintenance therapy for both mitomycin C and BCG. The most common maintenance schedule for BCG is the **Lamm/SWOG regimen (triplets of BCG given at 3, 6, 12, 18, 24, 30 and 36 months) which was associated with a 19% improvement in the 5-year recurrence-free survival (41% vs. 60%) and 6%_ improvement in the 5-year worsening-free survival [no progression including pT2 or greater, use of cystectomy, systemic chemotherapy, or radiation therapy; 70% vs. 76%, p=0.04]**.[72]

EORTC 30962 recommends full dose BCG maintenance for three years for high-risk patients.[63] For intermediate-risk patients, full dose one year maintenance is non-inferior to three years at reducing recurrence and there was no difference in recurrence-free survival was observed between full or 1/3 dose at 1 or 3 years. Currently, **there is insufficient evidence to recommend using BCG in combination with other intravesical agents**.[54]

BCG efficacy is reduced in patients that are immunosuppressed, **but evidence suggests that it can be safely administered** (usually with careful procedural surveillance) in such situations. **BCG may be less effective in patients on warfarin**, presumably secondary to inhibition of the fibronectin binding that is required for BCG entry into the urothelium. **Similar observations have been made for statin drugs**. Certain antibiotics (quinolones, rifampin, isoniazid) are toxic to BCG bacteria **but do not appreciably reduce BCG side effects if given concurrently**. Furthermore, isoniazid has been associated with transient liver toxicity and therefore prophylactic isoniazid is not recommended.

BCG induction followed by maintenance therapy has been shown to be superior to epirubicin and mitomycin C in high-risk patients with respect to reducing recurrence, bladder cancer metastasis, and death (progression). **BCG should be considered first line therapy for CIS since the response rate is double that of chemotherapy**. **For intermediate risk patients, BCG and chemotherapy appear similar in efficacy.**

A recent study evaluated the literature regarding treatment of intermediate-risk patients[73] including eight studies (of which 3 were meta-analyses) which evaluated BCG and intravesical chemotherapy.[62,63,64,65,74,75,76,77,78] BCG induction with/without maintenance significantly lowered the risk of disease recurrence by 40–59% in 5 studies. There were no differences in recurrence between BCG induction only and intravesical chemotherapy in 2 meta-analyses. One study by Malmström et al. demonstrated a 32% reduction in disease recurrence when BCG maintenance was used in patients who had previously received intravesical chemotherapy.[65] Seven studies reported no difference in disease progression between BCG and intravesical chemotherapy, while two studies suggest that induction with maintenance BCG reduces the risk of disease progression by 19–38%.[63] As noted above, the European Organisation for Research and Treatment of Cancer (EORTC) 30962 trial randomized patients to maintenance for 1 year or 3 years with full dose or 1/3 dose.[63] In intermediate-risk patients, 3 years of maintenance was more effective than 1 year maintenance in patients receiving 1/3 dose (HR: 1.35; 95% CI, 1.03–1.79; $p = 0.0318$) but not in patients receiving full dose BCG (HR: 0.88; 95% CI, 0.64–1.21; $p = 0.4380$).[63]

A systemic review evaluated the utility of maintenance intravesical chemotherapy[71] including 16 RCTs. The most commonly studied intravesical chemotherapy agents used in maintenance regimens were epirubicin, doxorubicin, and mitomycin C. There was considerable heterogeneity within these trials in terms of trial design, chemotherapeutic agents in trial regimens, overall sample size, number of patients enrolled with intermediate- or high-risk NMIBC, and length of follow-up, thereby making direct comparisons between trials (eg, via meta-analysis) difficult. Of the 16 trials, 13 reported no significant improvement in recurrence for patients receiving maintenance compared with no maintenance, and none of the trials demonstrated a significant impact on progression or survival.

Although BCG is the standard of care as described above for some patients with non-muscle invasive bladder cancer, **three supply shortages have impacted BCG supply in the past decade**. In the US, the only source of intravesical BCG is the TICE® BCG strain manufactured by Merck & Co and increased global demand has resulted in supply constraints. Different strategies have been proposed for judicious use of BCG in times of shortage, including using intravesical chemotherapy, upfront radical cystectomy, and splitting BCG dosing. To assess the clinical feasibility of splitting dosing Brooks et. al evaluated the shelf-life stability and found BCG viability remained constant for at least 8 hours after reconstitution and remained at level of one-third dose up to 72 hours,[79] demonstrating that this strategy can be practically employed in a clinical setting.

Clinical trials are evaluating different strains of BCG as well as novel immunotherapies for NMIBC, but currently it remains the

standard of care for many patients and given limited supply, shortages may continue to occur. Up to date information regarding current BCG availability and best practices in times of shortage can be accessed at the following link: **https://www.auanet.org/about-us/bcg-shortage-info**

Disease recurrence after BCG falls within four categories: BCG refractory, BCG relapsing, BCG intolerant, and BCG unresponsive.[62]

1. **BCG refractory** describes patients who have **persistent disease after 6 months of BCG therapy or who have progression of disease at 3 months** (such as Ta/CIS to T1). Most guidelines recommend **assessment at 6 months** since many patients who do not respond at 3 months will respond by 6 months.[80]
2. **BCG relapsing** describes **patients who recur after BCG treatment. This can be early (within 12 months), intermediate (12-24 months), or late (>24 months)**.
3. **BCG intolerance** describes disease persistence secondary to **inability to receive adequate BCG due to toxicity/side effects**.
4. **BCG unresponsive** describes patients who are BCG refractory or those who relapse **within 6 months of treatment**. There is no additional benefit to more BCG treatment in BCG-unresponsive patients and these are the patients for whom cystectomy is indication or enrollment onto trials of novel therapeutics.

Up to 50% of high risk NMIBC patients will ultimately have recurrence following BCG treatment. The standard of care for patients with recurrence despite BCG is radical cystectomy. Salvage intravesical therapy with chemotherapy agents, systemic immunotherapy, and clinical trials are alternative options based on disease characteristics albeit at a higher risk of recurrence and progression

Patients with CIS in particular should be carefully counseled that up to 12% will have lymph node metastases based on retrospective series[81]. Alternative treatments are reviewed in **Table 10**. Similarly, patients treated initially with a chemotherapeutic can be offered BCG. Unfortunately, if first-line intravesical therapy fails, patients tend to have poor response rates to second-line therapy. The 2-year recurrence and progression rates for these patients are typically around 60-80% and 10-20%, respectively. Gemcitabine appears to be the most active single agent in those with disease recurrence after BCG with a 2-year recurrence free survival of 21%[82]. The **combination of gemcitabine and docetaxel** appears to be even more active with a 2-year recurrence-free survival of 46%. The gemcitabine/docetaxel combination is commonly administered as follows: gemcitabine 1g in 50 mL water (pH adjusted) x 1 hour, drain bladder, docetaxel 37.5 mg in 50 mL saline x 1-2 hours. For those achieving an initial complete response to gemcitabine and docetaxel, once monthly maintenance instillations may reduce recurrence risk[83,84]. Of note, there is no level I data as regards gemcitabine and docetaxel in this setting.

A new intravesical agent that is being considered by the FDA is **nadoferagene firadenovec**, a replication incompetent type 5 adenovirus designed to infect the bladder and produce the anticancer cytokine i**nterferon α_{2b}**. In order to improve the efficiency of viral infection of the urothelium, a polyamide surfactant called **Syn3** is administered concurrently with the virus. In the pivotal trial, 157 BCG-unresponsive patients received intravesical nadoferagene firadenovec (3 x 1010 viral particles per mL, 75 mL, 1 hour dwell time, q3 months x 5 doses) and 60% of patients achieved a complete response and that was durable to 1 year in 50% of cases. Progression to MIBC occurred in 3% of patients and serious adverse events were rare (2%).

Another intravesical approach being considered by the FDA is the combination of BCG with ALT-803, an IL-15 superagonist that promotes CD8+ T cell and natural killer (NK) cell activation. Preliminary data demonstrated that 71% (59/83) of evaluable patients with CIS achieved a complete response at either 3- or 6-month follow-up and 34% (28 of 83) remained disease-free at 18-month follow-up. While promising, longer-term follow-up is needed to know whether responses to ALT-803 plus BCG remain durable and to better understand the additive contribution of ALT-803 to the BCG that is given as full induction with SWOG style maintenance.

Intravesical oncolytic viruses are also being explored for the treatment of NMIBC. The furthest along in development is CG0070, a replication-competent oncolytic adenovirus with reported direct cytotoxicity from replication within Rb-defective bladder cancer cells that may induce immunogenic cell death. CG0070 is currently under investigation alone and in combination with immune checkpoint inhibitors.

Table 10. Medications for NMIBC

	DRUG	DOSE	MECHANISM OF ACTION	SIDE-EFFECTS
INTRAVESICAL IMMUNOTHERAPIES				

Immunotherapies	• Bacillus Calmette-Guerin (BCG)
	• TICE
	• Armand-Frappier
	• Connaught
		• 50 mg, 50 mL
		• 120 mg, 50 mL
		• 81 mg, 50 mL
			• Toll-like receptor 2, 4, and 9 agonist
			  • activates innate immunity
			  • activates adaptive immunity
				• Inflammatory cystitis (most have mild cystitis)
				• Severe BCG cystitis (2-5%)
				• Flu-like symptoms (10-15%)
				• Fever (5%)
				• Granulomatous prostatitis (1%)
				<u>Rare but serious</u>:
				• BCG Sepsis (0.5%)

	Interferon α2b	• 50 MU
		• 50 mL
			• JAK-STAT pathway activation
			• Stimulates apoptosis
			• Immunoregulatory cytokine
			  • activates innate immunity
			  • activates adaptive immunity
				• Since it is usually given with BCG, the side effects below are those that are increased in incidence over BCG alone:
				• Flu-like symptoms (15-20%)
				• Fever (10%)

	Nadoferagene firadenovec	• 3×10^{10} VP/mL, 75 mL, q3 months	• Immunological gene therapy with type 5 adenovirus • Infects bladder and causes Interferon α2b production by bladder	• Irritative LUTS (60%, most minor)
INTRAVESICAL CHEMOTHERAPIES				
Anthracyclines	Valrubicin	• 800 mg • 75 mL	• Intercalating DNA strands (inhibits DNA synthesis) • Inhibits topoisomerase II (inhibits DNA	• Urgency/frequency (30-60%, most mild) • Hematuria (10-20%) • Chemical cystitis,
	Doxorubicin	• 50 mg • 50 mL		

Anthracyclines	Epirubicin	• 50 mg • 50 mL	synthesis) • Oxygen free radical generation (damages cells) • Histone eviction (impairs DNA damage response)	severe (1-3%) <u>Rare but serious</u> (if systemic absorption): • Cardiotoxicity • Myelosuppression
	Pirarubicin	• 30 mg • 50 mL		
Alkylating agents	Mitomycin C	• 40 mg • 20 mL (Optimized:1.3 g $NaHCO_3$ 12h, 3-6h, 30 min prior)	DNA/RNA crosslinking (inhibits DNA/RNA synthesis)	• Urgency/frequency (30-50%, most mild) • Hematuria (5-20%) • Pain (15%) • Rash & itch (10%) • Allergy (5%) • Chemical cystitis, severe (1-3%) • Encrustation cystitis after TURBT <u>Rare but serious</u> (if systemic absorption): • Myelosuppression • Severe skin reaction if spilled on skin (MMC) • Mucositis and neurotoxicity (ThioTEPA)
	ThioTEPA	• 60 mg • 30 mL		
Nucleoside analog	Gemcitabine	• 2 g • 100 mL	Pyrimidine analog, masquerades as cytidine, incorporates into replicating DNA and leads to masked chain termination	• Urgency/frequency (10-20%, most mild) • Pain (10%) • Hematuria (5%) • Rash & itch (5%) • Chemical cystitis, severe (1-3%) <u>Rare but serious</u> (if systemic absorption): • Myelosuppression • Pulmonary fibrosis
Taxanes	Nab-Paclitaxel	• 500 mg • 100 mL	Stabilizes microtubule polymer and prevent	• Urgency/frequency (20-40%, most mild) • Hematuria (10%) <u>Rare but serious</u> (if systemic absorption):

Taxanes	Docetaxel	• 75 mg • 100 mL	disassembly (inhibits mitosis)	systemic absorption). • Myelosuppression • Hand-foot syndrome • Change in color of nails
SYSTEMIC THERAPIES				
Immune checkpoint inhibitors	Pembrolizumab	• 200 mg q 3 weeks • 400 mg q 6 weeks	Blocks the PD-1 receptor and prevents it from interacting with PD-L1 and PD-L2 ligands	Immune-related • Dermatitis (20%) • Endocrinitis (10%) • Pneumonitis (8%) • Colitis (2%) • Hepatitis (1%) • Nephritis (0.5%)

4.8.4 Adjuvant Systemic Therapy

In addition to intravesical therapy there is now one FDA-approved systemic option for patients with BCG-unresponsive NMIBC: **pembrolizumab**. This approval was based on early results from[85] the KEYNOTE-057 phase 2 trial of 148 BCG-unresponsive NMIBC patients treated with **pembrolizumab** (200 mg IV q 3 weeks x 2 **years**). For CIS patients (96), the complete response rate was 41% and lasted on average 16 **months**. Of the 39 patients who had a complete response, 51% experienced subsequent recurrence. Overall, 42% in this trial ended up undergoing radical cystectomy, but rates of upstaging to MIBC were very low. The key limitation of pembrolizumab is the possibility of life-threatening **immune-related adverse events**. In this trial, Grade 3 or 4 treatment-related adverse events occurred in 13% of patients with serious treatment-associated adverse events in 8%. There were no treatment-related deaths. Essentially any "-itis" can be triggered by this class of drugs and physicians must be vigilant is ensuring good follow-up care. Several ongoing trials are assessing other immune checkpoint inhibitors for NMIBC as monotherapies or in combination with other agents (e.g. KEYNOTE-676).

4.9 Surveillance

Bladder cancer has a high risk of recurrence and progression requiring life-time surveillance. The main modality used is **cystoscopic** evaluation of the bladder accompanied frequently by **cytologic evaluation of the urine**. Urine based tumor markers are also optional adjunctive tests. The National Comprehensive Cancer Network (NCCN) guidelines recommend **cystoscopic evaluation every 3-6 months** and then at increasing intervals as appropriate.[86,87] While there is no consensus on optimal follow up regimen, most guidelines recommend that the first cystoscopy following TURBT should take place at three months, since recurrence at this time is recognized as an important prognosticator for both recurrence and progression[88,89] **Higher risk patients are usually assessed cystoscopically at 3 month intervals for the first two years, and then at 6 month intervals for the next 2-3 years, and then annually thereafter**[90] For low risk tumors, however, the EAU guidelines recommend cystoscopy at 3 months and if negative then another cystoscopy at 12 months and annually thereafter for the next five years.[91] The AUA guidelines recommend that for **a low-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent surveillance cystoscopy six to nine months later, and then annually thereafter**.[54]

The surveillance cycle restarts every time a tumor is identified. If a tumor is identified on surveillance cystoscopy, the patient will require another TURBT to reassess the stage, grade, and pathological characteristics of the recurrent tumor for oncologic control of the tumor and proper patient counseling.

4.10 Upper Urinary Tract Surveillance

See references 92, 93, 94, 95, 96, 97

There is a low risk of developing urothelial carcinoma in the upper urinary tracts. **Approximately 5% of patients with bladder tumors develop upper tract urothelial carcinomas** overall with higher rates of upper tract recurrences in patients with high-risk NMIBC. **Risk factors** for upper tract malignancy include **high grade bladder tumors, tumor location near the ureteral orifices, tumor multifocality, frequent recurrences, presence of bladder CIS, ureteral stent placement in a bladder with active tumor and intravesical therapy failures** The frequency and type of imaging for surveillance depends on risk of upper tract involvement but there is no consensus.

The AUA guidelines state **that an asymptomatic patient with a history of low-risk NMIBC, a clinician should not perform routine surveillance upper tract imaging. High-risk patients should get upper tract imaging every 1 to 2 years. CT and MR urography** has replaced intravenous pyelography as the main modality due to improved sensitivity and specificity. **Retrograde pyelography may be performed at time of cystoscopy or TURBT**. In patients with renal insufficiency or contrast allergy, MR urography without gadolinium can be performed using urine as the contrast agent.

In patients with a **positive urine test** (cytology, FISH, etc.) **in the setting of a normal cystoscopy, consideration should be given to the possibility that the patient could have a urothelial carcinoma hiding somewhere in the urinary tract**, though the possibility that the urine test is falsely positive should also be considered. We recommend **repeating the urine test and, if the test is still positive, investigating further. Upper tract imaging** should be the first thing obtained if not done within the past 3 months. If a patient has a persistently positive urine test despite negative upper tract imaging and negative cystoscopy, the urologist should strongly consider **ureteroscopy, random bladder biopsies, and prostatic urethral biopsies**. However, the added value of these tests in diagnosing occult urothelial cancer patients with normal cystoscopies and imaging has not been well demonstrated. There may be added benefit of using **enhanced cystoscopy** in this setting to detect CIS however enhanced cystoscopy should not preclude random biopsies.[48]

4.11 Partial Cystectomy

Tumors occurring in a bladder diverticulum should be biopsied, but extensive transurethral resection should be avoided

because diverticuli are thin walled and bladder perforation is likely. Partial cystectomy with diverticulectomy, if feasible, is generally the treatment of choice for such tumors. **Nodular tumors occurring at the dome of the bladder** should raise the possibility of **urachal cancer** and, likewise, partial cystectomy with en bloc urachectomy and pelvic lymphadenectomy (with/without en bloc resection of the umbilicus) is the treatment of choice. **Partial cystectomy may also be indicated for solitary muscle-invasive tumors that are < 3 cm in size, not associated with CIS, and located in a favorable anatomic location**.

4.12 Radical Cystectomy

Radical cystectomy is not commonly performed for NMIBC, but there are several situations that exist where it is justifiable to consider cystectomy.

4.12.1 Small Capacity Contracted Bladder or Neurogenic Bladder

Patients that have very **small capacity contracted bladders** (from repeated TURBT or intravesical therapy) or who have **neurogenic bladders with NMIBC**, are often incontinent and miserable. Intravesical therapy is impossible to do effectively in these patients and often makes their bladder symptoms worse. Not only does cystectomy cure the vast majority of these patients, it also results in improved quality of life for most (given no further need for cystoscopy and resolution of severe urinary frequency and lower urinary tract symptoms).

4.12.2 BCG-Unresponsive High-Risk Bladder Cancer

As noted above, patients whose bladder tumors recur despite prior BCG are at very high risk of recurrence (60-80%) and progression (10-20%). Cystectomy is the most effective cancer therapy in this situation but comes with the morbidity of urinary diversion and the morbidity and mortality risks of the operation.

4.12.3 Very Large (>10 cm) Bladder Tumors

Occasionally patients will present with enormous bladder masses that occupy the majority of the bladder and that appear potentially non-muscle invasive. While some of these cases may be safely resected transurethrally, usually after multiple staged TURBTs, the bladder is often left irreparably scarred. For this reason, many of these patients are best treated with immediate cystectomy.

4.12.4 Variant Histology

The AUA guidelines recommend that **an experienced genitourinary pathologist should review the pathology of a patient with any suspicion of variant or suspected variant histology** (e.g., micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid), extensive squamous or glandular differentiation, or the presence/absence of lymphovascular invasion.[54] **Due to the high rate of upstaging associated with variant histology, a clinician should consider offering initial radical cystectomy.**

4.12.5 “Very High Risk” T1 Bladder Cancer

The AUA, NCCN, and EUA guidelines recommend that radical cystectomy be considered in select patients with T1 tumors at “very high risk” for clinical under-staging and/or treatment failure with BCG. **Risk factors include residual cT1 on restaging TUR, multiple T1 recurrences, large ≥ 3 cm tumor, extensive CIS, multi-focal disease, deep/extensive lamina propria invasion (T1b/T1e), lymphovascular invasion, prostatic urothelial carcinoma, or variant histology)**.

A recent small (n=50) feasibility study attempted to randomized newly diagnosed high risk NMIBC patient to either BCG or immediate radical cystectomy[98], while not restricted to “very high risk” patients it is illustrative of the dilemma faced in deciding between these treatments. For example, 2 (10%) patients randomized to cystectomy had pathologic upstaging to ≥pT2 disease, but most patients were over-treated with cystectomy as 25% were found to be pT0 and 50% had only pTa/pTis. Among patients randomized to BCG, 2 (9%) developed metastatic disease, 4 (17%) underwent delayed cystectomy for BCG failure, and 1 was undergoing treatment for BCG unresponsive disease at the time of publication. Clearly BCG is insufficient treatment for some patients with newly diagnosed high risk NMIBC, and this is especially true for those with “very high risk” T1 disease, so until better bladder preservation treatments become available, radical cystectomy should be discussed with these patients.

4.13 Radiation and Chemoradiation Therapy

The role of radiation or combined chemoradiation in NMIBC is evolving. One trial in high-grade T1 patients demonstrated that radiotherapy alone did not improve recurrence or progression-free survival over intravesical therapy and was associated with 5% incidence of long-term complications. Few data exist for combined chemoradiation therapy in NMIBC.

Videos

TURBT

En bloc bladder tumor resection: back to oncologic basics

Tips and Tricks - Lotan

Non-Muscle Invasive Bladder Cancer High-Yield Review

Presentations

Non-Muscle Invasive Bladder Cancer Presentation 1

References

1 ☆ Leissner J, Ghoneim MA, Abol-Enein H, Thüroff JW, Franzaring L, Fisch M, Schulze H, Managadze G, Allhoff EP, el-Baz MA, Kastendieck H, Buhtz P, KropfS,Hohenfellner R, Wolf HK. Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. J Urol.2004 Jan;171(1):139-44.

2 Lewis SA. Everything you wanted to know about the bladder epithelium but were afraid to ask. Am J Physiol Renal Physiol. 2000 Jun;278(6):F867-74.

3 ☆ Harland SJ, Kynaston H, Grigor K, Wallace DM, Beacock C, Kockelbergh R, Clawson S, Barlow T, Parmar MK, Griffiths GO; National Cancer Research Institute Bladder Clinical Studies Group. A randomized trial of radical radiotherapy for the management of pT1G3 NXM0 transitional cell carcinoma of the bladder. J Urol. 2007 Sep;178(3 Pt 1):807-813.

4 ☆ Sarma KP. On the nature of cystitis follicularis. J Urol. 1970 Nov;104(5):709-14.

5 ☆ Itano NM, Malek RS. Eosinophilic cystitis in adults. J Urol. 2001 Mar;165(3):805-7.

6 Lamm DL. Complications of bacillus Calmette-Guérin immunotherapy. Urol Clin North Am. 1992 Aug;19(3):565-72.

7 Cek M, Lenk S, Naber KG, Bishop MC, Johansen TE, Botto H, Grabe M, Lobel B, Redorta JP, Tenke P; Members of the Urinary Tract Infection (UTI) Working Group of the European Association of Urology (EAU) Guidelines Office. EAU guidelines for the management of genitourinary tuberculosis. Eur Urol. 2005 Sep;48(3):353-62.

8 Khalaf I, Shokeir A, Shalaby M. Urologic complications of genitourinary schistosomiasis. World J Urol. 2012 Feb;30(1):31-8.

9 Tirzaman O, Wahner-Roedler DL, Malek RS, Sebo TJ, Li CY, Kyle RA. Primary localized amyloidosis of the urinary bladder: a case series of 31 patients. Mayo Clin Proc. 2000 Dec;75(12):1264-8.

10 Smith AK, Hansel DE, Jones JS. Role of cystitis cysticaetglandularis and intestinal metaplasia in development of bladder carcinoma. Urology. 2008 May;71(5):915-8.

11 Ahmad I, Barnetson RJ, Krishna NS. Keratinizing squamous metaplasia of the bladder: a review. Urol Int. 2008;81(3):247-51.

12 Readal N, Epstein JI. Papillary urothelial hyperplasia: relationship to urothelial neoplasms. Pathology. 2010 Jun;42(4):360-3.

13 Young RH. Tumor-like lesions of the urinary bladder. Mod Pathol. 2009 Jun;22Suppl 2:S37-52. doi: 10.1038/modpathol.2008.201.

14 Lott S, Lopez-Beltran A, Maclennan GT, Montironi R, Cheng L. Soft tissue tumors of the urinary bladder, Part I: myofibroblastic proliferations, benign neoplasms, and tumors of uncertain malignant potential. Hum Pathol. 2007 Jun;38(6):807-23.

15 ☆ Goluboff ET, O'Toole K, Sawczuk IS. Leiomyoma of bladder: report of case and review of literature. Urology. 1994 Feb;43(2):238-41.

16 Cheng L, Leibovich BC, Cheville JC, Ramnani DM, Sebo TJ, Neumann RM, Nascimento AG, Zincke H, Bostwick DG. Paraganglioma of the urinary bladder: can biologic potential be predicted? Cancer. 2000 Feb 15;88(4):844-52.

17 Cheng L, Nascimento AG, Neumann RM, Nehra A, Cheville JC, Ramnani DM, Leibovich BC, Bostwick DG. Hemangioma of the urinary bladder. Cancer. 1999 Aug 1;86(3):498-504.

18 Siegel RL1, Miller KD2, Jemal A3. CA Cancer J Clin. 2018 Jan;68(1):7-30. doi: 10.3322/caac.21442. Epub 2018 Jan 4. Cancer statistics, 2018.

19 Ploeg M, Aben KK, Kiemeney LA. The present and future burden of urinary bladder cancer in the world. World journal of urology. 2009;27(3):289-93.

20 CA Cancer J Clin. 2016 Jan;66(1):7-30. doi: 10.3322/caac.21332. Epub 2016 Jan 7. Cancer statistics, 2016. Siegel RL, Miller KD, Jemal A.

21 American Cancer Society. Cancer Facts & Figures 2019. Atlanta: American Cancer Society; 2019.

22 Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021 Jan;71(1):7-33. doi: 10.3322/caac.21654. Epub 2021 Jan 12. Erratum in: CA Cancer J Clin. 2021 Jul;71(4):359. PMID: 33433946

23 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA: a cancer journal for clinicians. 2012;62(1):10-29.

24 † Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. JAMA. 2011 Aug 17;306(7):737-45.

Smoking is the main cause of bladder cancer.

25 Reulen RC, Kellen E, Buntinx F, Brinkman M, Zeegers MP. A meta-analysis on the association between bladder cancer and occupation. Scand J Urol Nephrol Suppl. 2008 Sep;(218):64-78.

26 Knowles MA, Hurst CD. Molecular biology of bladder cancer: new insights into pathogenesis and clinical diversity. Nat Rev Cancer. 2015 Jan;15(1):25-41.

27 Lindskrog SV, Prip F, Lamy P, et al. An integrated multi-omics analysis identifies prognostic molecular subtypes of non-muscle-invasive bladder cancer. Nat Commun. 2021;12(1):2301. Published 2021 Apr 16. doi:10.1038/s41467-021-22465-w

28 Lindskrog SV, Prip F, Lamy P, Taber A, Groeneveld CS, Birkenkamp-Demtröder K, Jensen JB, Strandgaard T, Nordentoft I, Christensen E, Sokac M, Birkbak NJ, Maretty L, Hermann GG, Petersen AC, Weyerer V, Grimm MO, Horstmann M, Sjödahl G, Höglund M, Steiniche T, Mogensen K, de Reyniès A, Nawroth R, Jordan B, Lin X, Dragicevic D, Ward DG, Goel A, Hurst CD, Raman JD, Warrick JI, Segersten U, Sikic D, van Kessel KEM, Maurer T, Meeks JJ, DeGraff DJ, Bryan RT, Knowles MA, Simic T, Hartmann A, Zwarthoff EC, Malmström PU, Malats N, Real FX, Dyrskjøt L. An integrated multi-omics analysis identifies prognostic molecular subtypes of non-muscle-invasive bladder cancer. Nat Commun. 2021 Apr 16;12(1):2301. doi: 10.1038/s41467-021-22465-w. PMID: 33863885; PMCID: PMC8052448.

29 ☆ Golin AL, Howard RS. Asymptomatic microscopic hematuria. The Journal of Urology. 1980;124(3):389-91.

30 Mohr DN, Offord KP, Owen RA, Melton LJ, 3rd. Asymptomatic microhematuria and urologic disease. A population-based study. JAMA. 1986;256(2):224-9.

31 ☆ Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. The Journal of Urology. 2000;163(2):524-7.

32 Lee LW, Davis E, Jr. Gross urinary hemorrhage: a symptom, not a disease. JAMA. 1953;153(9):782-4.

33 Varkarakis MJ, Gaeta J, Moore RH, Murphy GP. Superficial bladder tumor. Aspects of clinical progression. Urology. 1974;4(4):414-20.

34 Zincke H, Utz DC, Farrow GM. Review of Mayo Clinic experience with carcinoma in situ. Urology. 1985;26(4 Suppl):39-46. Epub 1985/10/01.

35 ☆ Barocas DA, Boorjian SA, Alvarez RD et al: Microhematuria: AUA/SUFU guideline. J Urol 2020; 204: 778.

36 Grossfeld GD, Wolf JS Jr, Litwan MS, Hricak H, Shuler CL, Agerter DC, Carroll PR. Asymptomatic microscopic hematuria in adults: summary of the AUA best practice policy recommendations. AmFam Physician. 2001 Mar 15;63(6):1145-54.

37 Brierley J, Gospodarowicz MK., Wittekind C, editors. TNM classification of malignant tumours, 8th edition. Hoboken, NJ : John Wiley & Sons, Inc., 2017.

38 Humphrey, P. A., Moch, H., Cubilla, A. L., Ulbright, T. M., & Reuter, V. E. (2016). The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part B: Prostate and Bladder Tumours. European Urology, 70(1), 106–119. https://doi.org/10.1016/j.eururo.2016.02.028

39 ☆ Yanagisawa T, Mori K, Motlagh, R, et al. En Bloc Resection for Bladder Tumors: An Updated Systematic Review and Meta-Analysis of Its Differential Effect on Safety, Recurrence and Histopathology. J. urol.. 2022;207(4):754-768. doi:10.1097/JU.0000000000002444.

40 Akand M, Muilwijk T, Raskin Y, De Vrieze M, Joniau S, Van Der Aa F. Quality Control Indicators for Transurethral Resection of Non-Muscle-Invasive Bladder Cancer. Clin Genitourin Cancer. 2019;17(4):e784-e792. doi:10.1016/j.clgc.2019.04.014

41 Paramananthan Mariappan, Allan Johnston, Luisa Padovani, Eilidh Clark, Matthew Trail, Sami Hamid, Graham Hollins, Helen Simpson, Benjamin G. Thomas, Rami Hasan, Jaimin Bhatt, Imran Ahmad, Ghulam M. Nandwani, Ian D.C. Mitchell, David Hendry, Enhanced Quality and Effectiveness of Transurethral Resection of Bladder Tumour in Non–muscle-invasive Bladder Cancer: A Multicentre Real-world Experience from Scotland's Quality Performance Indicators Programme, European Urology, Volume 78, Issue 4, 2020, 520-530, https://doi.org/10.1016/j.eururo.2020.06.051.

42 ☆ Anderson C, Weber R, Patel D, Lowrance W, Mellis A, Cookson M, Lang M, Barocas D, Chang S, Newberger E, Montgomery JS, Weizer AZ, Lee CT, Kava BR, Jackson M, Meraney A, Sjoberg D, Bochner B, Dalbagni G, Donat M, Herr H. A 10-Item Checklist Improves Reporting of Critical Procedural Elements during Transurethral Resection of Bladder Tumor. J Urol. 2016 Oct;196(4):1014-20. doi: 10.1016/j.juro.2016.03.151. Epub 2016 Apr 1. PMID: 27044571; PMCID: PMC5460769.

43 ☆ Collado A, Chéchile GE, Salvador J, Vicente J. Early complications of endoscopic treatment for superficial bladder tumors. J Urol. 2000 Nov;164(5):1529-32.

44 Sylvester RJ, van der Meijden AP, Oosterlinck W et al: 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. Eur Urol 2006;49:466.

45 ☆ Chou R, Selph S, Buckley DI, Fu R, Griffin JC, Grusing S, Gore JL. Comparative Effectiveness of Fluorescent Versus White Light Cystoscopy for Initial Diagnosis or Surveillance of Bladder Cancer on Clinical Outcomes: Systematic Review and Meta-Analysis. J Urol. 2017 Mar;197(3 Pt 1):548-558. doi: 10.1016/j.juro.2016.10.061

46 Burger M, Grossman HB, Droller M, Schmidbauer J, Hermann G, Dr?goescu O, Ray E, Fradet Y, Karl A, Burgués JP, Witjes JA, Stenzl A, Jichlinski P, Jocham D. Photodynamic Diagnosis of Non-muscle-invasive Bladder Cancer with Hexaminolevulinate Cystoscopy: A Meta-analysis of Detection and Recurrence Based on Raw Data. Eur Urol. 2013 Apr 8. Epub ahead of print. PubMed PMID: 23602406.

47 ☆ Chang SS, Boorjian SA, Chou R et al: Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016; 196: 1021.

48 ☆ Daneshmand S, Patel S, Lotan Y, Pohar K, Trabulsi E, Woods M, Downs T, Huang W, Jones J, O'Donnell M, Bivalacqua T, DeCastro J, Steinberg G, Kamat A, Resnick M, Konety B, Schoenberg M, Jones JS; Efficacy and Safety of Blue Light Flexible Cystoscopy with Hexaminolevulinate in the Surveillance of Bladder Cancer: A Phase III, Comparative, Multicenter Study. Flexible Blue Light Study Group Collaborators. J Urol. 2018 May;199(5):1158-1165. doi: 10.1016/j.juro.2017.11.096. Epub 2017 Dec 2. PMID: 29203268

49 Lotan Y, Bivalacqua TJ, Downs T, Huang W, Jones J, Kamat AM, Konety B, Malmström PU, McKiernan J, O'Donnell M, Patel S, Pohar K, Resnick M, Sankin A, Smith A, Steinberg G, Trabulsi E, Woods M, Daneshmand S. Blue light flexible cystoscopy with hexaminolevulinate in non-muscle-invasive bladder cancer: review of the clinical evidence and consensus statement on optimal use in the USA - update 2018. Nat Rev Urol. 2019 Jun;16(6):377-386. doi: 10.1038/s41585-019-0184-4. PMID: 31019310; PMCID: PMC7136177.

50 Daneshmand S, Schuckman AK, Bochner BH, Cookson MS, Downs TM, Gomella LG, Grossman HB, Kamat AM, Konety BR, Lee CT, Pohar KS, Pruthi RS, Resnick MJ, Smith ND, Witjes JA, Schoenberg MP, Steinberg GD. Hexaminolevulinate blue-light cystoscopy in non-muscle-invasive bladder cancer: review of the clinical evidence and consensus statement on appropriate use in the USA. Nat Rev Urol. 2014 Oct;11(10):589-96. doi: 10.1038/nrurol.2014.245. Epub 2014 Sep 23. PMID: 25245244.

51 Weiting Kang,#1,3 Zilian Cui,#1,3 Qianqian Chen,2,3 Dong Zhang,1 Haiyang Zhang,1 and Xunbo Jin1. Narrow band imaging-assisted transurethral resection reduces the recurrence risk of non-muscle invasive bladder cancer: A systematic review and meta-analysis. Oncotarget. 2017 Apr 4; 8(14): 23880–23890. Published online 2016 Nov 3. doi: 10.18632/oncotarget.13054. PMCID: PMC5410352. PMID: 27823975

52 ☆ Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. Chang SS, Boorjian SA, Chou R, Clark PE, Daneshmand S, Konety BR, Pruthi R, Quale DZ, Ritch CR, Seigne JD, Skinner EC, Smith ND, McKiernan JM. J Urol. 2016 Oct;196(4):1021-9.

53 ☆ Fernandez-Gomez J, Madero R, Solsona E et al: Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. J Urol 2009;182:2195.

54 ☆ Sam S. Chang, MD, MBA; Bernard H. Bochner, MD, FACS; Roger Chou, MD; Robert Dreicer, MD, MS, MACP, FASCO; Ashish M. Kamat, MD, MBBS, FACS; Seth P. Lerner, MD, FACS; Yair Lotan, MD; Joshua J. Meeks, MD, PhD; Jeff M. Michalski, MD, MBA; Todd M. Morgan, MD; Diane Z. Quale; Jonathan E. Rosenberg, MD; Anthony L. Zietman, MD; Jeffrey M. Holzbeierlein, MD, FACS. DIAGNOSIS AND TREATMENT OF NON-MUSCLE INVASIVE BLADDER CANCER: AUA/SUO GUIDELINE. American Urological Association (AUA) and Society or Urologic Oncology (SUO). 2017.

55 † Abern MR, Owusu RA, Anderson MR, Rampersaud EN, Inman BA. Perioperative intravesical chemotherapy in non-muscle-invasive bladder cancer: a systematic review and meta-analysis. J NatlComprCancNetw. 2013 Apr 1;11(4):477-84.

Good analysis of pros/cons of Perioperative intravesical chemotherapy

56 Richard J. Sylvester, Willem Oosterlinck, Sten Holmang, et al: Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy After Transurethral Resection with Transurethral Resection Alone in Patients with Stage pTa–pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation?, European Urology, Vol 69, Issue 2, February 2016, 231-244, http://dx.doi.org/10.1016/j.eururo.2015.05.050.

57 Messing EM: The BCG shortage. Bladder Cancer 2017; 3:227.

58 Bono AV, Hall RR, Denis L, Lovisolo JA, Sylvester R. Chemoresection in Ta-T1 bladder cancer. Members of the EORTC Genito-Urinary Group. Eur Urol. 1996;29(4):385-90. doi: 10.1159/000473784. PMID: 8791042.

59 Lindgren MS, Bue P, Azawi N, Blichert-Refsgaard L, Sundelin MO, Dyrskjøt L, Jensen JB. The DaBlaCa-13 Study: Short-term, Intensive Chemoresection Versus Standard Adjuvant Intravesical Instillations in Non-muscle-invasive Bladder Cancer-A Randomised Controlled Trial. Eur Urol. 2020 Dec;78(6):856-862. doi: 10.1016/j.eururo.2020.07.009. Epub 2020 Jul 28. PMID: 32736928.

60 ☆ Chevli KK, Shore ND, Trainer A, Smith AB, Saltzstein D, Ehrlich Y, Raman JD, Friedman B, D'Anna R, Morris D, Hu B, Tyson M, Sankin A, Kates M, Linehan J, Scherr D, Kester S, Verni M, Chamie K, Karsh L, Cinman A, Meads A, Lahiri S, Malinowski M, Gabai N, Raju S, Schoenberg M, Seltzer E, Huang WC. Primary Chemoablation of Low-Grade Intermediate-Risk Nonmuscle-Invasive Bladder Cancer Using UGN-102, a Mitomycin-Containing Reverse Thermal Gel (Optima II): A Phase 2b, Open-Label, Single-Arm Trial. J Urol. 2022 Jan;207(1):61-69. doi: 10.1097/JU.0000000000002186. Epub 2021 Aug 26. PMID: 34433303; PMCID: PMC8667793.

61 Brausi M, Oddens J, Sylvester R, Bono A, van de Beek C, van Andel G, GonteroP, Turkeri L, Marreaud S, Collette S, Oosterlinck W. Side Effects of BacillusCalmette-Guérin (BCG) in the Treatment of Intermediate- and High-risk Ta, T1Papillary Carcinoma of the Bladder: Results of the EORTC Genito-Urinary CancersGroupRandomised Phase 3 Study Comparing One-third Dose with Full Dose and 1 Yearwith 3 Years of Maintenance BCG. Eur Urol. 2013 Jul 24.

62 Friedrich MG, Pichlmeier U, Schwaibold H, Conrad S, Huland H. Long-term intravesical adjuvant chemotherapy further reduces recurrence rate compared with short-term intravesical chemotherapy and short-term therapy with BacillusCalmette-Guérin (BCG) in patients with non-muscle-invasive bladder carcinoma. Eur Urol. 2007 Oct;52(4):1123-29.

63 † Oddens J, Brausi M, Sylvester R, Bono A, van de Beek C, van Andel G, Gontero P, Hoeltl W, Turkeri L, Marreaud S, Collette S, Oosterlinck W. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol. 2013 Mar;63(3):462-72.

Randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma

64 Sylvester RJ, Brausi MA, Kirkels WJ, Hoeltl W, Calais Da Silva F, Powell PH, Prescott S, Kirkali Z, van de Beek C, Gorlia T, de Reijke TM; EORTC Genito-Urinary Tract Cancer Group. Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guérin, and bacillus Calmette-Guérin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. Eur Urol. 2010 May;57(5):766-73.

65 Malmström PU, Sylvester RJ, Crawford DE, Friedrich M, Krege S, Rintala E, Solsona E, Di Stasi SM, Witjes JA. An individual patient data meta-analysis ofthe long-term outcome of randomised studies comparing intravesicalmitomycinCversus bacillus Calmette-Guérin for non-muscle-invasive bladder cancer. Eur Urol. 2009 Aug;56(2):247-56.

66 † Lamm DL, Blumenstein BA, Crawford ED, Montie JE, Scardino P, Grossman HB, Stanisic TH, Smith JA Jr, Sullivan J, Sarosdy MF, et al. A randomized trial of intravesical doxorubicin and immunotherapy with bacilli Calmette-Guérin for transitional-cell carcinoma of the bladder. N Engl J Med. 1991 Oct 24;325(17):1205-9.

Main study supporting use of BCG

67 Addeo R, Caraglia M, Bellini S, Abbruzzese A, Vincenzi B, Montella L, Miragliuolo A, Guarrasi R, Lanna M, Cennamo G, Faiola V, Del Prete S. Randomized phase III trial on gemcitabine versus mytomicin in recurrent superficial bladder cancer: evaluation of efficacy and tolerance. J ClinOncol. 2010 Feb1;28(4):543-8. doi: 10.1200/JCO.2008.20.8199.

68 Au JL, Badalament RA, Wientjes MG, Young DC, Warner JA, Venema PL, Pollifrone DL, Harbrecht JD, Chin JL, Lerner SP, Miles BJ; International MitomycinCConsortium. Methods to improve efficacy of intravesicalmitomycin C: results of arandomized phase III trial. J Natl Cancer Inst. 2001 Apr 18;93(8):597-604.

69 ☆ Di Stasi SM, Giannantoni A, Stephen RL, Capelli G, Navarra P, Massoud R, Vespasiani G. Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer: a prospective randomizedstudy. J Urol. 2003 Sep;170(3):777-82.

70 Lammers RJ, Witjes JA, Inman BA, Leibovitch I, Laufer M, Nativ O, Colombo R. The role of a combined regimen with intravesical chemotherapy and hyperthermia inthe management of non-muscle-invasive bladder cancer: a systematic review. Eur Urol. 2011 Jul;60(1):81-93.

71 Tabayoyong WB, Kamat AM, O'Donnell MA, McKiernan JM, Ray-Zack MD, Palou J, Brausi M, Black PC, Williams SB. Systematic Review on the Utilization of Maintenance Intravesical Chemotherapy in the Management of Non-muscle-invasive Bladder Cancer. Eur Urol Focus. 2018 Jul;4(4):512-521. doi: 10.1016/j.euf.2018.08.019. Epub 2018 Sep 3. PMID: 30190111; PMCID: PMC7810510.

72 ☆ Lamm DL, Blumenstein BA, Crissman JD, Montie JE, Gottesman JE, Lowe BA, Sarosdy MF, Bohl RD, Grossman HB, Beck TM, Leimert JT, Crawford ED. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol. 2000 Apr;163(4):1124-9. PMID: 10737480.

73 Tan, W. S., Steinberg, G., Witjes, J. A., Li, R., Shariat, S. F., Roupret, M., Babjuk, M., Bivalacqua, T. J., Psutka, S. P., Williams, S. B., Cookson, M. S., Palou, J., & Kamat, A. M. (2022). Intermediate-risk Non–muscle-invasive Bladder Cancer: Updated Consensus Definition and Management Recommendations from the International Bladder Cancer Group. European Urology Oncology. https://doi.org/10.1016/j.euo.2022.05.005

74 Oddens JR, Sylvester RJ, Brausi MA, et al. The effect of age on the efficacy of maintenance bacillus Calmette-Guérin relative to maintenance epirubicin in patients with stage Ta T1 urothelial bladder cancer: results from EORTC Genito-urinary Group study 30911. Eur Urol 2014;66:694–701.

75 Ojea A, Nogueira JL, Solsona E, et al. A multicentre, randomised prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: low-dose bacillus Calmette-Guerin (27 mg) versus very low-dose bacillus Calmette-Guerin (13.5 mg) versus mitomycin C. Eur Urol 2007;52: 1398–406.

76 Marttila T, Järvinen R, Liukkonen T, et al. Intravesical bacillus Calmette-Guérin versus combination of epirubicin and interferona2a in reducing recurrence of non-muscle-invasive bladder carcinoma: FinnBladder-6 study. Eur Urol 2016;70:341–7.

77 Schmidt S, Kunath F, Coles B, et al. Intravesical bacillus Calmette-Guérin versus mitomycin C for Ta and T1 bladder cancer. Cochrane Database Syst Rev 2020;1:Cd011935.

78 ☆ Böhle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal metaanalysis of comparative studies on recurrence and toxicity. J Urol 2003;169:90–5.

79 Brooks N, Nagaraju S, Matulay J, Han XY, Kamat AM. Bacillus Calmette-Guérin Retains Clinically Relevant Viability for up to 72 Hours After Reconstitution: Potential Implications for Clinical Practice in Times of Shortage. Eur Urol Oncol. 2021 Oct;4(5):826-828. doi: 10.1016/j.euo.2020.03.004. Epub 2020 May 29. PMID: 32475716.

80 DL Lamm, BA Blumenstein, JD Crissman, etal: Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: A randomized Southwest Oncology Group Study J Urol 163:1124–1129,2000

81 Bruins HM, Skinner EC, Dorin RP, Ahmadi H, Djaladat H, Miranda G, Cai J, Daneshmand S. Incidence and location of lymph node metastases in patients undergoing radical cystectomy for clinical non-muscle invasive bladder cancer: results from a prospective lymph node mapping study. Urol Oncol. 2014 Jan;32(1):24.e13-9. doi: 10.1016/j.urolonc.2012.08.015. Epub 2013 Feb 6. PMID: 23395238.

82 Skinner 2013: DOI: 10.1016/j.juro.2013.04.031

83 Daniels MJ, Barry E, Milbar N, Schoenberg M, Bivalacqua TJ, Sankin A, Kates M. An evaluation of monthly maintenance therapy among patients receiving intravesical combination gemcitabine/docetaxel for nonmuscle-invasive bladder cancer. Urol Oncol. 2020 Feb;38(2):40.e17-40.e24. doi: 10.1016/j.urolonc.2019.07.022. Epub 2019 Aug 28. PMID: 31473090.

84 ☆ Steinberg RL, Thomas LJ, Brooks N, Mott SL, Vitale A, Crump T, Rao MY, Daniels MJ, Wang J, Nagaraju S, DeWolf WC, Lamm DL, Kates M, Hyndman ME, Kamat AM, Bivalacqua TJ, Nepple KG, O'Donnell MA. Multi-Institution Evaluation of Sequential Gemcitabine and Docetaxel as Rescue Therapy for Nonmuscle Invasive Bladder Cancer. J Urol. 2020 May;203(5):902-909. doi: 10.1097/JU.0000000000000688. Epub 2019 Dec 10. PMID: 31821066.

85 alar AV, Kamat AM, Kulkarni GS, Uchio EM, Boormans JL, Roumiguié M, Krieger LEM, Singer EA, Bajorin DF, Grivas P, Seo HK, Nishiyama H, Konety BR, Li H, Nam K, Kapadia E, Frenkl T, de Wit R. Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. Lancet Oncol. 2021 Jul;22(7):919-930. doi: 10.1016/S1470-2045(21)00147-9. Epub 2021 May 26. Erratum in: Lancet Oncol. 2021 Aug;22(8):e347. PMID: 34051177.

86 † ICUD-EAU International Consultation on Bladder Cancer 2012: Screening, diagnosis, and molecular markers.Kamat AM, Hegarty PK, Gee JR, Clark PE, Svatek RS, Hegarty N, Shariat SF, Xylinas E, Schmitz-Dräger BJ, Lotan Y, Jenkins LC, Droller M, van Rhijn BW, Karakiewicz PI; International Consultation on Urologic Disease-European Association of Urology Consultation on Bladder Cancer 2012. Eur Urol. 2013 Jan;63(1):4-15.

Good review on molecular markers

87 AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer; 2010.

88 ☆ Solsona E, Iborra I, Dumont R, Rubio-Briones J, Casanova J, Almenar S. The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer. The Journal of Urology. 2000;164(3 Pt 1):685-9.

89 ☆ Holmang S, Johansson SL. Stage Ta-T1 bladder cancer: the relationship between findings at first followup cystoscopy and subsequent recurrence and progression. The Journal of Urology. 2002;167(4):1634-7.

90 Sengupta S, Blute ML. The management of superficial transitional cell carcinoma of the bladder. Urology. 2006;67(3 Suppl 1):48-54.

91 Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Bohle A, Palou-Redorta J. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. European Urology. 2008;54(2):303-14.

92 ☆ Herr HW, Cookson MS, Soloway SM. Upper tract tumors in patients with primary bladder cancer followed for 15 years. The Journal of Urology. 1996;156(4):1286-7.

93 ☆ Oldbring J, Glifberg I, Mikulowski P, Hellsten S. Carcinoma of the renal pelvis and ureter following bladder carcinoma: frequency, risk factors and clinicopathological findings. The Journal of Urology. 1989;141(6):1311-3.

94 Herranz-Amo F, Diez-Cordero JM, Verdu-Tartajo F, Bueno-Chomon G, Leal-Hernandez F, Bielsa-Carrillo A. Need for intravenous urography in patients with primary transitional carcinoma of the bladder? European Urology. 1999;36(3):221-4

95 ☆ Wright JL, Hotaling J, Porter MP. Predictors of upper tract urothelial cell carcinoma after primary bladder cancer: a population based analysis. The Journal of Urology. 2009;181(3):1035-9.

96 Hurle R, Losa A, Manzetti A, Lembo A. Upper urinary tract tumors developing after treatment of superficial bladder cancer: 7-year follow-up of 591 consecutive patients. Urology. 1999;53(6):1144-8.

97 ☆ Wang LJ, Wong YC, Huang CC, Wu CH, Hung SC, Chen HW. Multidetector computerized tomography urography is more accurate than excretory urography for diagnosing transitional cell carcinoma of the upper urinary tract in adults with hematuria. The Journal of Urology 2010.183(1):48-55.

98 Catto JWF, Gordon K, Collinson M, Poad H, Twiddy M, Johnson M, Jain S, Chahal R, Simms M, Dooldeniya M, Bell R, Koenig P, Conroy S, Goodwin L, Noon AP, Croft J, Brown JM; BRAVO study group. Radical Cystectomy Against Intravesical BCG for High-Risk High-Grade Nonmuscle Invasive Bladder Cancer: Results From the Randomized Controlled BRAVO-Feasibility Study. J Clin Oncol. 2021 Jan 20;39(3):202-214. doi: 10.1200/JCO.20.01665. Epub 2020 Dec 17. PMID: 33332191; PMCID: PMC8078404.