Non-Muscle-Invasive Bladder Cancer: Review of Diagnosis and Management

ABSTRACT

Non-muscle-invasive bladder cancer (NMIBC) represents the large majority of newly diagnosed bladder tumors and represents a significant burden to both patients and the healthcare system. Although the initial standard treatment for all non-muscle-invasive tumors is surgical resection, there exist a wide variety of both surgical and medical treatment modalities based upon the tumor's specific stage and grade. Ensuring a proper diagnosis is key, and management should be tailored to the individual in order to reduce cancer recurrence and prevent progression of disease.

KEYWORDS: Bladder cancer, non-muscle-invasive, diagnosis, treatment

CME Pre-test Quiz

Introduction

Carcinoma of the bladder is the sixth most common cancer in Canada and the fourth most common malignancy in the United States, with an incidence in the United States of roughly 21 cases per 100,000 individuals.[1-3] Bladder cancer is three times more common in men than in women, and risk factors include cigarette smoking, occupational exposure to aromatic amines (such as aniline dyes), cyclophosphamide use, and prior pelvic radiotherapy. Of these, cigarette smoking is the most important risk factor, with approximately 50% of all bladder cancers resulting from tobacco use.[4]

Histologically, over 90% of bladder cancers diagnosed in Western countries are urothelial carcinoma (UC); other less commonly encountered histologic

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subtypes include squamous cell carcinoma (3%), adenocarcinoma (1.4%), and small cell carcinoma (1%).[2]

Non-muscle-invasive bladder cancer (NMIBC), previously referred to as superficial bladder cancer, is defined as disease that does not invade the muscularis propria, the deep muscular layer of the urinary bladder. Approximately 70%-75% of newly diagnosed bladder tumors can be classified as non-muscle-invasive. Of these tumors, 70% are exophytic and papillary tumors confined to the mucosal layer (Ta), 25% invade the submucosal lamina propria (T1), and 5% consist of flat high-grade lesions known as carcinoma in situ (CIS).[5,6] This review will focus on the management of non-muscle-invasive UC.

Economically, bladder cancer is a significant burden to both patients and the healthcare system as a whole. Of all malignancies, bladder cancer has the highest lifetime treatment costs per patient.[7] Additionally, although patients with non-invasive disease have a lower mortality rate than those with muscle invasion, patients with NMIBC bear the majority of the economic costs given that they represent the bulk of the disease burden. Classification of a patient's disease as non-muscle-invasive is an important distinction that affects both treatment and prognosis.

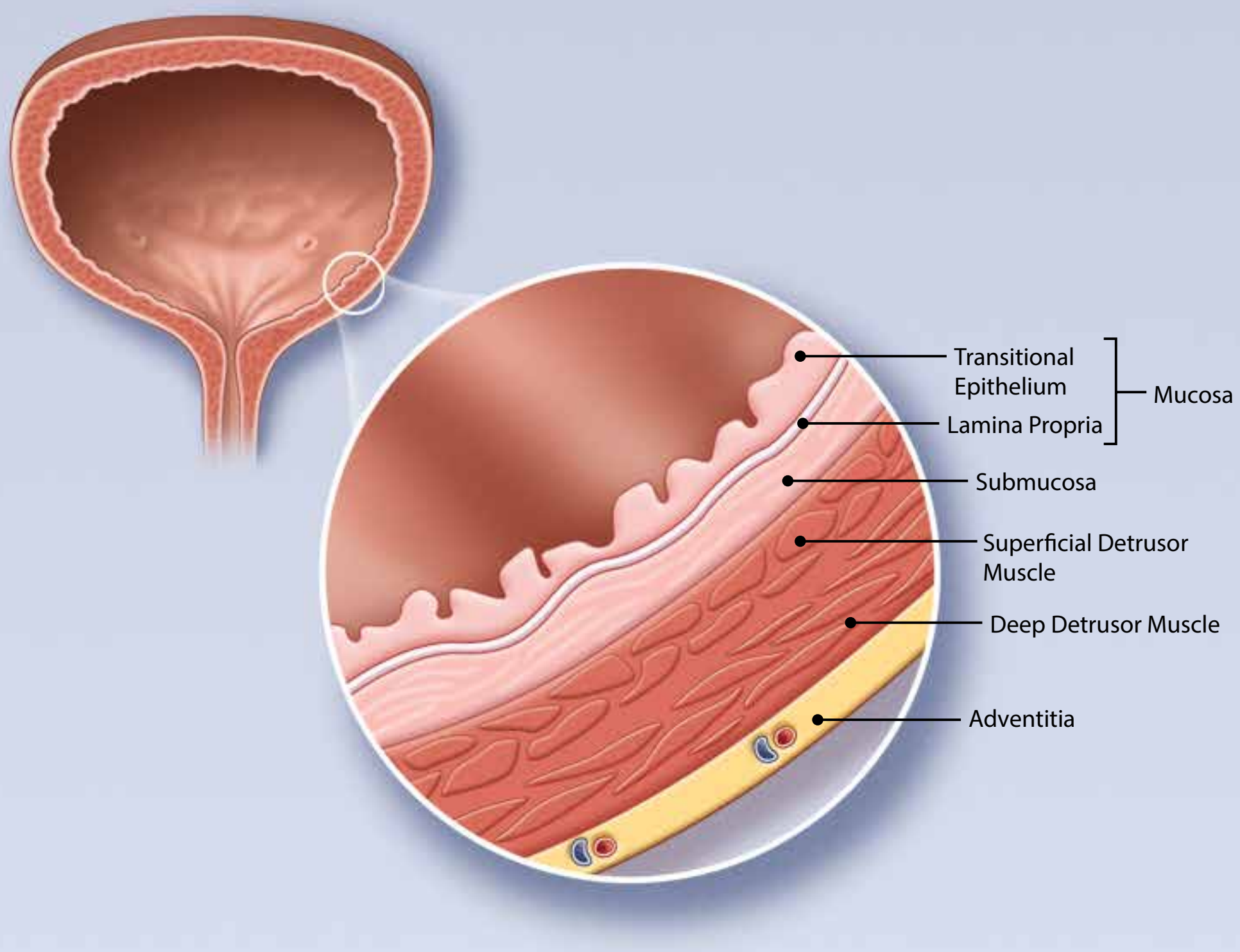
Diagnosis

For individuals who are asymptomatic, options for screening at the primary care level include urinalysis for microscopic hematuria and urine cytology. Although early detection of malignancy is key, there is insufficient evidence to recommend routine screening for bladder cancer; studies have not shown any improvement in survival for treatment of asymptomatic patients with screen-detected bladder cancer.[1,8]

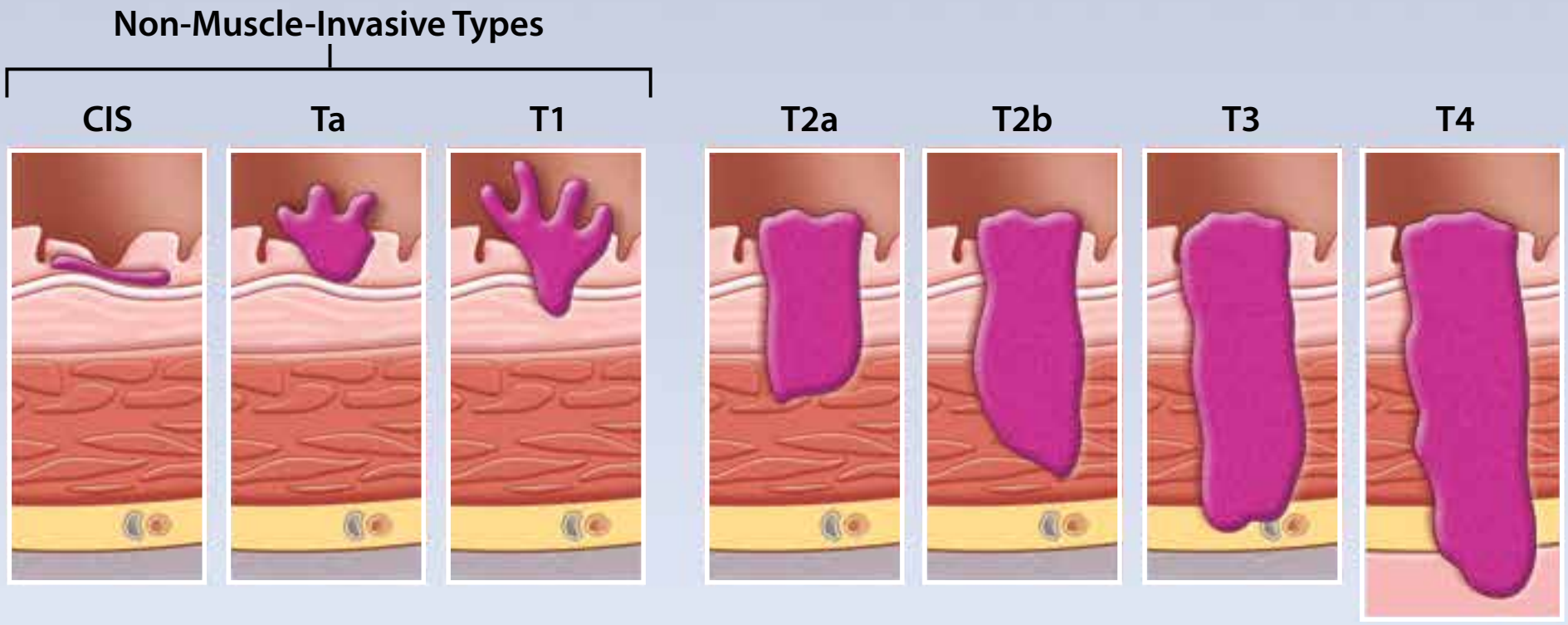
Symptomatic patients most frequently present with painless hematuria; 80% of patients diagnosed with bladder cancer will have either gross or microscopic hematuria prior to diagnosis.[4] Other less common presenting symptoms include urinary frequency, urgency, and dysuria. With more advanced disease, patients may present with upper urinary tract obstruction, flank pain, or bone pain.[2] Of note, some female patients may falsely attribute bladder cancer-related hematuria to benign causes such as menstruation or urinary tract infection. It is important to evaluate these patients comprehensively; studies have shown that women are less likely to be referred for urologic workup of hematuria than men, potentially delaying an important diagnosis.[9]

For patients with asymptomatic microscopic hematuria (AMH), the American Urological

Non-Muscle-Invasive Bladder Cancer



TNM Staging for Bladder Cancer



Association (AUA) recommends initial investigation with history and physical examination, and laboratory tests which focus on common benign causes including infection, intense exercise, menstruation and intrinsic renal disease. Once benign causes of AMH have been ruled out, urologic consultation is necessary to evaluate both the upper and lower urinary tracts as possible sources of bleeding.[10]

A POOLED ANALYSIS SHOWED THAT THE RECURRENCE OF ALL NON-MUSCLE-INVASIVE TUMORS WAS 48% WITHIN FOUR YEARS OF DIAGNOSIS.

According to the AUA, all patients with hematuria should be stratified as high or low risk for malignancy. Those with AMH are considered low risk unless they have any risk factors including age >40 years, male gender, current or prior history of cigarette smoking, chemical exposure history, prior pelvic radiation, irritative voiding symptoms, or prior urologic disease.[11] Patients with risk factors or who have gross hematuria are considered high risk and require thorough urologic evaluation. Prior to urology referral, contrast imaging of the upper urinary tract can be obtained and is usually done with computed tomography (CT) urography; other imaging modalities such as intravenous pyelography (IVP) or retrograde pyelography can also be performed.[12] Urine cytology may also be obtained (through either a voided specimen or "bladder wash") and is most useful in detecting high grade (HG) malignancy or the presence of CIS anywhere along the urinary tract.[5] Complete urologic work-up of hematuria then includes evaluation of the lower urinary tract through cystoscopy. Cystoscopy can be performed as part of the routine office evaluation by the urologist or in the operating room with retrograde ureterography if initial imaging is concerning for ureteral pathology. It is generally well tolerated and does not require an anesthetic. Complications are minor with urinary tract infection being the most common in <1% to 7.5% of patients.[13,14] Both high and low risk patients with persistent hematuria who have an initially negative evaluation should undergo repeat evaluation at 48-72 months; approximately 3% of this group will eventually be diagnosed with a urologic malignancy.[11]

If there is concern for possible metastatic disease, laboratory tests including complete blood count, blood chemistries (including alkaline phosphatase), and liver function tests should be obtained. Imaging for metastases should include chest CT and CT or magnetic resonance imaging (MRI) of

Table 1: Natural History of Non-muscle-invasive Bladder Cancer

Pathology	Probability of Recurrence in 5 Years[1]	Approximate Probability of Progression to Muscle-Invasive Disease in 5 Years[1,2]
Ta (Low Grade)	50%	Minimal (0.8% - 6%)
Ta (High Grade)	60%	Moderate (6% - 17%)
T1 (Low Grade)	50%	Moderate (6% - 17%)
T1 (High Grade)	50-70%	Moderate to High (17% - 45%)
Tis	50-90%	High (45% - 50%)

1. Clark PE, Agarwal N, Biagioli MC, et al. Bladder cancer. Journal of the National Comprehensive Cancer Network : JNCCN 2013;11:446-75.
2. Aldousari S, Kassouf W. Update on the management of non-muscle invasive bladder cancer. Canadian Urological Association journal = Journal de l'Association des urologues du Canada 2010;4:56-64.

the abdomen and pelvis. Bone scan should be performed for patients with bone pain or elevated alkaline phosphatase levels.

If a lesion is identified on cystoscopy, a transurethral resection of bladder tumor (TURBT) and bimanual exam under anesthesia (EUA) should be performed. TURBT is crucial to provide a pathologic diagnosis and provides information on tumor stage and grade. At the time of TURBT, sampling of muscle surrounding the lesion is important to assess for depth of invasion, since the depth of invasion has prognostic relevance and influences subsequent management.[2,15]

Natural History

Initial bladder tumors that are found to be non-muscle-invasive (Ta, T1, or CIS) have a propensity to recur and these recurrences may present at the same stage or at a more advanced stage.[2] A pooled analysis showed that the recurrence of all non-muscle-invasive tumors was 48% within four years of diagnosis.[16] For low-grade (LG) Ta and T1 disease specifically, the probability of recurrence in five years is approximately 50%, while high-grade (HG) Ta and T1 disease have a 60% risk. Recurrence risk of lesions with CIS is highest of all NMIBC and ranges from 50-90% within five years.

Additionally, all non-muscle-invasive tumors have the potential to progress to muscle-invasive disease, which can significantly worsen a patient's prognosis. Probability of progression is as high as 17% within one year and as high as

50% within five years for all non-muscle-invasive tumors. Low-grade papillary tumors have the lowest risk of progression whereas lesions with CIS have the highest risk.[2,17]

AFTER ALL VISIBLE LESIONS HAVE BEEN REMOVED, SUBSEQUENT TREATMENT OPTIONS DEPEND ON THE TUMOR'S CLINICAL STAGE AND GRADE.

It is important to accurately assess and stage a patient's bladder tumor given that rates of recurrence and progression depend upon the tumor's initial stage and grade. Preventing disease progression is essential in the management of NMIBC.

Treatment

Treatment of non-muscle-invasive bladder cancer can involve several therapeutic modalities. Initial standard treatment for these tumors is TURBT.[5] At the time of transurethral resection, completeness of resection is important to improve diagnostic accuracy and reduce the probability of future recurrence.[18] After all visible lesions have been removed, subsequent treatment options depend on the tumor's clinical stage and grade.

Intravesical Chemotherapy

Adjuvant intravesical (i.e. injected into the bladder) chemotherapy with Mitomycin C is recommended for the treatment of low-grade (LG) Ta tumors. Guidelines suggest instillation of a single dose of Mitomycin within 24 hours of transurethral resection.[2] After this single dose, clinicians may opt to administer induction intravesical chemotherapy for an additional 6 weeks. Studies have illustrated that adjuvant intravesical chemotherapy prophylaxis with Mitomycin C

Table 2: Recommended Follow-up of Non-muscle-invasive Bladder Cancer

Clinical Stage	Recommended Follow-up[1,2]
Ta (Low Grade)	Cystoscopy every 3 months for 1 year, then yearly until five years
Ta (High Grade), T1, CIS	Cystoscopy and urine cytology every 3 months for 2 years, every 6 months until five years, then yearly. Upper tract imaging with CT urography every 1-2 years.

1. Clark PE, Agarwal N, Biagioli MC, et al. Bladder cancer. Journal of the National Comprehensive Cancer Network : JNCCN 2013;11:446-75.
2. Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. European urology 2013;64:639-53.

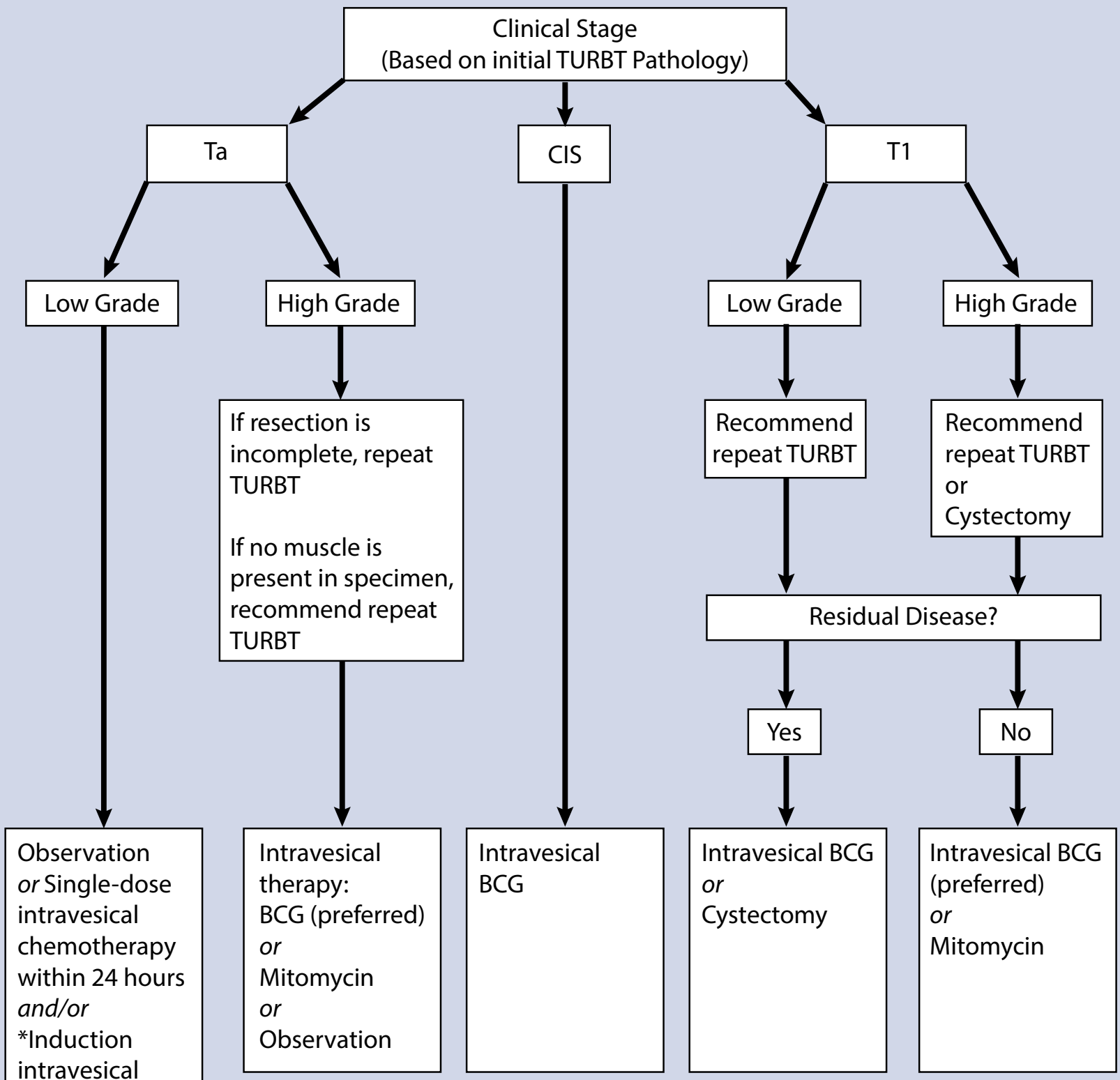
decreases the risk of recurrent non-muscle-invasive disease by 11%.[19,20]

For tumors with CIS, Bacillus Calmette-Guerin (BCG) immunotherapy has been shown to be superior to chemotherapy, but intravesical Mitomycin C can be used if a patient cannot tolerate BCG.[2]

Repeat Transurethral Resection

Transurethral resection should be repeated after initial resection for all T1 tumors regardless of grade. For high-grade (HG) Ta tumors, resection should be repeated if the initial resection was incomplete or did not contain muscle in the resection specimen.[2] Repeat resec-

Figure 1: Treatment of Non-Muscle-Invasive Bladder Cancer[1]



1. Clark PE, Agarwal N, Biagioli MC, et al. Bladder cancer. Journal of the National Comprehensive Cancer Network : JNCCN 2013;11:446-75.

*Induction therapy as defined as weekly administration for at least 6 consecutive weeks

SUMMARY OF KEY POINTS

Non-muscle-invasive bladder cancer consists of papillary tumors (Ta), tumors invading the submucosal lamina propria (T1), and flat lesions known as carcinoma in situ (CIS).

Proper management is key given the significant risk of tumor recurrence or progression to muscle-invasive disease.

Many treatment modalities exist including transurethral resection, intravesical chemotherapy, intravesical immunotherapy, and radical cystectomy; treatment choice depends on a variety of factors including tumor stage and grade.

tion for T1 and HG Ta disease is associated with a 32% improvement in recurrence-free survival.[21] Additionally, rates of identifying residual tumor at the time of repeat TURBT have been reported as high as 76%.[22] Unrecognized, higher stage disease has been identified in 9% to 49% of patients at the time of repeat resection, further emphasizing the importance of this practice in these high risk patients.[23]

Intravesical (BCG) Immunotherapy

For HG Ta and all T1 disease, adjuvant intravesical therapy is suggested after repeat TURBT to prevent tumor recurrence. Specifically, adjuvant BCG immunotherapy is preferred and reduces risk of recurrence by 61%.[24-26] BCG therapy should be administered as an initial induction course (weekly administration for at least 6 weeks) followed by maintenance therapy (weekly administration for 3 weeks approximately every 3-6 months) for a total of 3 years of adjuvant treatment.

For tumors with CIS, intravesical BCG immunotherapy is recommended as the therapy of choice after initial TURBT.[27] The optimal course of BCG immunotherapy involves weekly instillations given once a week for 6 weeks followed by maintenance BCG administration.[28]

Although highly effective, BCG therapy has an important side effect profile to be aware of. The most common local toxicity associated with BCG therapy is BCG-induced cystitis, which may result in irritative voiding symptoms in approximately 90% of patients. Less common local side effects include ureteral obstruction and contracted bladder, granulomatous prostatitis, and epididymitis or epididymo-orchitis. The most common systemic side effects include flu-like signs and symptoms which are generally not serious. A rare but concerning systemic toxicity to be aware of is BCG sepsis, which is associated with traumatic catheterization or instillation too soon after TURBT.[4]

CME

Post-test Quiz

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Early Radical Cystectomy

Radical cystectomy, although an aggressive and potentially morbid procedure, can be a treatment option for select cases of NMIBC. For HG T1 disease, early radical cystectomy instead of re-resection is an option that increases survival if patients are at a particularly high risk of progressing to muscle-invasive disease.[29,30] Additionally, in the event that residual T1 disease (HG or LG) remains after repeat resection, early radical cystectomy is a reasonable treatment option. Similarly, for all T1 disease (regardless of grade), if there is residual disease or disease recurrence after initial BCG immunotherapy, recommended options include repeat BCG induction or early radical cystectomy.[2]

Follow-up

Follow-up is similar to diagnosis and involves surveillance of both the upper and lower urinary tracts. If a tumor is identified at any point during treatment or follow-up, management and surveillance must restart and mimics protocols following initial tumor diagnosis. Recommended initial follow-up for NMIBC depends upon both grade and stage. For LG Ta disease, office cystoscopy is recommended every three months for one year. Surveillance cystoscopy can then be performed at increasing interval but at least yearly for a total of 5 years.

For cancers that are HG Ta, T1 (any grade), or CIS, recommended follow-up involves cystoscopy and urine cytology every 3 months for two years, every 6 months until 5 years, then yearly. Upper tract imaging with CT urography should also be performed every 1-2 years. Urinary urothelial tumor markers (through NMP22 or UroVysion, for example) can be considered as well.[2,5] Upper urinary tract imaging surveillance is important given that the risk of an upper tract tumor following an initial bladder cancer diagnosis is 2-4%.[31] Regardless of tumor type, strict adherence to the recommended follow-up plan is important to prevent disease recurrence and progression.

CLINICAL PEARLS

The gold standard for the complete work-up of hematuria is office cystoscopy and imaging of the upper urinary tract.

Initial standard treatment of non-muscle-invasive bladder tumors is TURBT; at the time of resection, sampling of muscle surrounding the lesion is important to accurately assess depth of invasion.

Issues in Elderly Patients

Bladder cancer is common in older adults, with a mean age at diagnosis of 70 years. With increasing age there are several important considerations. First, competing causes of mortality sometimes change the risk-benefit ratio in favour of less aggressive initial approaches to treatment (e.g. intravesical therapy rather than radical cystectomy). In a similar vein, many older adults prioritize quality of life over survival. In the case of bladder cancer, this often shifts preferences towards less invasive treatment approaches.[32] Second, comorbidities and functional limitations that are commonly seen with increasing age increase the perioperative morbidity and mortality of radical cystectomy but do not generally increases the risk of TURBT or intravesical therapy. However, functional and/or cognitive impairments can make it more difficult to adhere to 24 months of maintenance BCG and regular surveillance. These factors need to be considered when adapting bladder cancer treatment and follow-up to older adults.

Conclusion

Non-muscle-invasive bladder cancer can be challenging to manage and can require multiple modes of therapy which are both costly and labor intensive. Diagnostic accuracy is important in order to tailor treatment accordingly and reduce cancer recurrence and prevent disease progression.

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