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Curr Opin Oncol. Author manuscript; available in PMC 2017 May 01.

Published in final edited form as:

Curr Opin Oncol. 2016 May ; 28(3): 210–215. doi:10.1097/CCO.0000000000000278.

Natural Biology and Management of Non-Muscle Invasive Bladder Cancer

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Abstract

Purpose of review—To review the natural biology of non-invasive bladder cancer and its management strategies while summarizing the most recent advances in the field.

Recent findings—Non-muscle invasive bladder cancer (NMIBC) has a tendency to recur and progress. Risk stratification has helped triage patients but improved tools, including biomarkers, are still needed. Enhanced endoscopy with photodynamic imaging, narrow band imaging, optical coherence tomography, and confocal laser endomicroscopy show promise for diagnosis, risk stratification, and disease monitoring. Attempts at better treatment, especially in refractory high-risk cases, include the addition of intravesical hyperthermia, combination and sequential therapy with existing agents, and the use novel agents such as Mycobacterial cell wall extract. New data is emerging regarding the potential role of active surveillance in low-risk patients.

Summary—NMIBC represents a variety of disease states and continues to pose management challenges. As our understanding of tumor biology improves and technology advances, achieving better outcomes through individualized care may be possible.

Keywords

bladder cancer; non-invasive; risk stratification; management; review

INTRODUCTION

Bladder cancer will account for an estimated 74,000 new cancer diagnoses and 16,000 deaths in the United States in 2015 [1]. Non-muscle invasive bladder cancer (NMIBC), characterized by its tendency to recur and in certain high-risk populations progress,

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Conflicts of interest:
Dr Clark - Galil National head of a registry trial and on a scientific advisory board. Genentech - on a data safety monitoring board for a phase three clinical trial. The remaining authors have no conflicts of interest.

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represents a heterogeneous collection of diseases that remains difficult to treat. Most patients may be managed with bladder sparing therapies while some require timely cystectomy. Advancements in our understanding of tumor biology, endoscopic technology, and intravesical therapy are promising but are overall slow to develop and leave significant room for improvement. This article will review the natural biology and recent updates in NMIBC management.

NATURAL BIOLOGY

NMIBC pathology may range from low grade to high grade with lesions in situ (CIS), surface tumors (Ta), or lamina propria (T1) invasion, each with varying oncologic outcomes. An ongoing challenge in this disease is that 50–90% of patients experience recurrence [2] and up to a third will progress [3], necessitating accurate risk stratification.

Recurrent tumors are dangerous and some host factors have been correlated with negative outcomes. In a high-risk superficial bladder cancer population of over 7000 subjects, nearly 40% recurred without progression, a third progressed, and over 12% experienced bladder cancer related mortality [3]. Invasion into the lamina propria was the only factor predictive of recurrence while risk of progression and mortality were associated with female gender, African American race, undifferentiated grade, CIS and T stage.

Risk stratification

Biological aggressiveness is variable in NMIBC and treatment choices differ based on risk stratification. The European Organisation for Research and Treatment of Cancer (EORTC) risk tables and Spanish Urological Club for Oncological Treatment (CUETO) scoring model provide templates for defining risk categories in NMIBC [4,5]. The EORTC study, based on data from 7 trials, found that number of tumors, tumor size and prior recurrence predicted recurrence while progression was influenced by T stage and grade as well as presence of CIS [4]. However, very few patients were treated with BCG in this study. Therefore, CUETO developed a scoring model that evaluates short- and long-term recurrence and progression risk in BCG-treated patients only, based on 4 trials involving over a thousand patients [5]. Gender, age, grade, tumor status, multiplicity and CIS predicted recurrence while those same factors and T stage were associated with progression. However, Xylinas et al. evaluated the accuracy of these scoring systems in a retrospective analysis and found that both models overestimated risk of recurrence and progression [6]. Newer, more accurate tools, perhaps incorporating biomarkers, are therefore clearly needed.

Risk stratification is utilized in the guidelines issued by the National Comprehensive Cancer Network (NCCN)[3], European Association of Urology (EAU)[7], and American Urological Association (AUA)[8] (Table 1). Of note is the recommendation for radical cystectomy (RC) among high-risk patients. According to the NCCN, RC should be offered for high grade, T1 disease and in patients with recurrent or persistent NMIBC following intravesical therapy [3]. Similarly, the EAU and AUA recommend RC for high risk, recurrent disease [7,8].

While low-risk and high-risk tumors have been well delineated in the various guidelines, there is a paucity of data regarding the definition and optimal management of intermediate

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risk NMIBC. Therefore, the International Bladder Cancer Group (IBCG) reviewed available evidence and proposed a treatment algorithm for patients with intermediate risk disease [9]. Recurrent and/or multiple low-grade Ta tumors, which constitute “intermediate risk”, were stratified and treated according to factors such as tumor multiplicity, size >3 cm, timing of recurrence <1 year, and frequency of recurrence >1 per year. The authors stressed the importance of individualizing patient management based on appropriate disease classification. One way of customizing care is through the use of molecular markers from voided urine or resected tissue, although consistent, strong evidence to recommend routine use is currently lacking. A promising marker, Ki-67, an indicator of cell proliferation, has recently been shown to significantly correlate with tumor progression and recurrence in NMIBC [10].

Impact of tobacco use

Smoking remains the most important risk factor in the development of bladder cancer [11]. Risk is greater with increased tobacco consumption and, in fact, the risk attributable to cigarette smoking has increased over time in the United States, perhaps reflecting changes in cigarette composition [12] or altered work or environmental related exposures. Smoking cessation is known to decrease bladder cancer risk [12]. In a survey about smoking cessation published in 2010, only 20% of American urologists always provided this service while the majority never counseled patients [13]. However, Bassett et al. conducted a more recent survey from a stratified, random sample of bladder cancer survivors and found urologists to be an important source of information regarding the causal relationship between smoking and bladder cancer [14]. Active smokers cited smoking as a risk factor more commonly than never smokers and more frequently implicated tobacco use in their own cancers.

DIAGNOSIS AND STAGING

Cystoscopy with transurethral resection (TUR) of all visible tumors remains the standard of care in the diagnosis, staging, and treatment of bladder cancer. In patients with CIS or suspected muscle invasion, evaluation of the urethra is imperative. Repeat resection, especially in high-risk patients, is indicated given the known impact on tumor recurrence and progression [15,16]. Also key is obtaining muscle and acquiring a thorough pathologic review, both of which have been shown to impact bladder cancer specific survival for all tumor grades [17].

Resection may be performed using monopolar or bipolar electrocautery. Ventakatramani et al. found there was no difference in complications, including bleeding, obturator reflex, operative time, or hyponatremia, although use of bipolar electrocautery resulted in decreased cautery artifact [18]

Enhanced endoscopy

Technology continues to improve and the development of photodynamic diagnosis using intravesical administration of specialized dyes has augmented the ability to find early recurrent NMIBC. Cysview™, or “Blue Light Cystoscopy”, has been shown to detect significantly more Ta, T1, and CIS than the standard white light cystoscopy (WLC) [19].

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Cysview is the most well studied of the novel technologies and repeat TUR for high risk NMIBC has resulted in decreased tumor recurrence when compared to WLC [20,21]. Additionally, Cysview is safe [22] and cost-effective [19].

Narrow-band imaging (NBI), which is FDA approved for use in NMIBC, has been shown to better delineate bladder tumors due to increased visualization of the more highly vascularized neoplastic tissue [23]. A randomized controlled trial (RCT) comparing restaging NBI-TUR vs conventional WLC restaging demonstrated decreased recurrence rate in 126 patients followed for 3 years in those randomized to the NBI [24]. A more recent randomized study by Herr showed significantly decreased early and late tumor recurrences at 2 years following second look TUR using NBI when compared to conventional WLC in patients with high-risk NMIBC [25*].

Optical coherence tomography (OCT) is a promising, emerging technology for several urologic cancers including bladder, prostate, and kidney [26]. High resolution, cross-sectional imaging is useful in the diagnosis and treatment of bladder cancer, although depth of penetration is limited (2mm) and the procedure is time consuming with a steep learning curve [27–29].

Confocal laser endomicroscopy (CLE) also provides real-time, ultrahigh resolution imaging and can be used for diagnosis of disease in other organ systems [29]. Images are obtained following the administration of intravenous fluorescein dye and placement of a fiber optic probe through the endoscope. CLE can differentiate low-grade from high-grade tumors making it a useful adjunct to WLC [30]. More recently, CLE has also shown promise in the diagnosis and management of upper tract urothelial carcinoma [31]. CLE is not yet FDA approved for bladder cancer, although it has been cleared for ophthalmic and gastrointestinal procedures.

INTRAVESICAL THERAPY

Intravesical therapy allows local delivery of high concentrations of therapeutic agents to eradicate remaining malignant cells following TURBT and is also used prophylactically to induce a local immune response reducing the likelihood of future bladder tumor recurrence. The decision to use intravesical therapy is contingent upon patient risk factors and the probability of future bladder tumor recurrence. Several notable studies evaluating novel concepts in intravesical therapy have been published over the last year.

Regional Hyperthermia

The synergistic effect of combining hyperthermia with chemotherapy or radiation has been exploited for the treatment of invasive sarcomas and pelvic tumors for years [32,33]. More recently, uses of intravesical conductive and intracavitary hyperthermia for NMIBC have been reported [34–36]. The three techniques for regional hyperthermia in bladder cancer utilize 70 to 120 MHz antennas, intracavitary radiofrequency hyperthermia with a 916 MHz antenna, and intravesical conductive therapy using a heated perfusate. Geijsen et al. reported their prospective experience with regional 70MHz hyperthermia in patients with NMIBC [37**]. Twenty patients with intermediate to high-risk disease were treated with intravesical

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mitomycin C (40 mg) combined with regional hyperthermia in 6 weekly sessions followed by a maintenance period of 1 year. Fourteen patients completed the induction period and 4 dropped out due to toxicity. The 24-month recurrence free survival rate was robust at 78%.

Response to BCG and cytokine levels

Previous studies evaluating predictors of a durable response to BCG have centered predominantly on tumor markers [38]. However, it is increasingly evident that a more important predictor of BCG response is the host immune system [39]. Kamat et al. recently published the results of a prospective clinical trial evaluating 130 intermediate and high-risk bladder cancer patients and developed a nomogram predicting the probability of recurrence based on changes in IL-2, IL-4, IL-8, IL-18, IL-1ra, TRAIL, IFN-γ, IL-12, and TNF-α; they found this to be the best predictor of BCG response [40].

BCG Refractory Disease

Intravesical Gemcitabine with Mitomycin C—Many patients with recurrent, BCG-refractory high-risk NMIBC consider radical cystectomy, yet many others either refuse or are not medically fit. In these instances, further intravesical therapy should be considered. Emerging data has suggested that gemcitabine alone may be effective in the setting of BCG failure [41–43]. In a recent retrospective analysis of 27 patients, Cockerill et al. report a favorable and durable RFS of 15.2 months [44]. A multi-institutional analysis for sequential intravesical gemcitabine with MMC found that patients with high-grade NMIBC or BCG refractory disease had a 2 year RFS of nearly 40% [45].

Sequential combination of Mitomycin C plus BCG—A randomized prospective trial by Solsana et al. in patients with intermediate and high-risk NMIBC found the sequential combination of MMC with BCG to be more effective but more toxic that BCG alone [46**]. The 5-year disease free interval was significantly improved with combination therapy and this was especially evident in patients with recurrent T1 tumors. However, given the significnatly increased local toxicity experienced by the combination group, the authors suggest that only patients with recurrent T1 disease should be offered this therapy given that they have the highest likelihood of recurrence.

Intravesical Docetaxel—Systemically administered docetaxel has some efficacy in metastatic bladder cancer leading investigators to posit whether locally administered docetaxel might improve outcomes, and several studies have evaluated its utility in the treatment of BCG-refractory NMIBC. A recent phase I clinical trial by Barlow et al. studied 54 patients with 6 weekly instillations of intravesical docetaxel [47]. An impressive 59% of patients achieved a complete response, with 18 going on to receive further maintenance therapy. The 5-year disease-specific and overall survival rates were 85% and 71%, respectively.

Mycobacterial cell wall extract (MCWE)—Because BCG is a live attenuated culture preparation of the *Mycobacterium bovis* bacillus, it can be associated with systemic side effects, which on occasion can be quite severe. MCWE from *Mycobacterium phlei* is comparable in composition to BCG but does not contain any live bacterial elements, and

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thus may lessen the risk of systemic toxicity. A multi-institutional clinical trial evaluating the use of mycobacterial cell wall-DNA complex (MCC) – which is essentially MCWE without a mercury-based preservative called *thiomersal* – in BCG-naïve and -refractory patients with CIS, showed a 46% complete response rate at 12 weeks [48]. After 18 months, almost a third of these participants remained disease free. A phase III trial evaluating the one year disease free survival rate of MCC among BCG-refractory, CIS, or recurrent high grade NMIBC is currently underway (ClinicalTrial.gov; no. NCT00406068). As novel techniques like MCC emerge and standard therapies are refined, we can anticipate additional prospective studies evaluating their clinical utility and hopefully yielding improved outcomes in NMIBC.

SURVEILLANCE AND FOLLOW UP

Because low-risk tumors typically pose only a mild health risk to patients, observation of these low-risk bladder tumors may be a safe alternative. Soloway et al. published the first report of patients with NMIBC for whom their primary treatment strategy was observation [49]. In this retrospective review, 32 patients had their tumor recurrence managed expectantly for an average of 10 months from 1992 to 2002. All but 3 (7%) had low-grade noninvasive recurrences after their period of observation ended. No patients experienced progression to muscle invasion. Gofrit et al. published a retrospective review in which they successfully observed 28 patients with low-risk NMIBC for an average of 13.5 months [50]. Main reasons for terminating surveillance were the appearance of additional tumors (n=19), excessive tumor growth (n=9) and hematuria (n=1). All recurrent tumors were low grade and noninvasive. In a separate analysis of 22 patients managed expectantly, only 2 patients (9%) had evidence of progression after an average of 17 months [51]. Furthermore, Hernandez et al. reported the successful observation of 64 patients with NMIBC for an average of 10.3 months and, while no patient progressed to muscle invasive disease, 6.5% of patients progressed to a higher stage and 16.2% to a higher grade [52]. Compared to historical controls matched for clinical characteristics, the authors found no significant differences in progression rates. Although methodological limitations existed, this was the first and only prospective analysis of observation for low risk bladder cancer. It should be noted, however, that the small sample size of these studies speaks to the highly selective nature of these patients selected for surveillance.

Taken together, observation of low risk bladder cancer is increasingly recognized as a reasonable treatment strategy for patients who clearly have tumors that pose very little risk of harm. However, high quality studies assessing if surveillance can reduce treatment related morbidity and lower medical costs without compromising oncologic efficacy are lacking.

CONCLUSION

While management of NMIBC continues to evolve, timely detection, appropriate risk stratification, and individualized treatment remain crucial. Recent advances in endoscopic tumor detection, coupled with improved intravesical therapies, have helped tailor treatment. Smoking cessation plays a key role in tumor prevention and urologists are instrumental in relaying information to patients. Further, well-designed clinical trials are needed to enhance

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risk stratification and treatment options for those patients refractory to current therapy and those patients who may qualify for expectant management.

Acknowledgments

None

Financial Support:

This work was in part supported by NIH/NCI Grant 5T32CA106183 (MDT)

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Key Points

Risk stratification is a key component in the management of NMIBC although available tools are imperfect. Molecular markers may prove beneficial for individualizing treatment and predicting tumor recurrence and progression.

Urologists are a vital source of information for patients regarding the association between smoking and bladder cancer, particularly among active smokers striving to quit.

Enhanced endoscopy using Cysview™, NBI, OCT, and CLE improves disease detection and has been a useful adjunct to standard WLC.

In select patients with low risk NMIBC, observation is increasingly recognized as a reasonable treatment strategy although additional prospective studies are needed.

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Table 1

Tumor risk stratification based on the EAU guidelines.

Low-Risk	Intermediate-Risk	High-Risk
Primary, solitary, Ta, low-grade, <3 cm, no CIS	Tumors not categorized as low-grade or high-grade	T1, high-grade, CIS, or multiple and recurrent and >3 cm