Review

DOI: 10.4274/uob.galenos.2020.1549

Bull Urooncol 2020;19:167-174

Non-muscle Invasive Bladder Cancer: Identifying Patients to Consider Timely, Initial Cystectomy

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Abstract

Non-muscle invasive bladder cancer is a heterogeneous disease with widely varying risks of recurrence and progression to muscle invasion. Risk stratification within current treatment guidelines are an attempt to address this heterogeneity. This heterogeneity stems from a number of pathologic characteristics as well as recurrence status. Radical cystectomy, while the definitive, curative therapy for muscle invasive disease, is not often utilized for non-muscle invasive disease, even when it may be a superior option to bladder-sparing therapy. A majority of American Urologists have been reported to defer cystectomy for less invasive therapies when it is a guideline driven option. Both cystectomy and bladder-sparing therapy have excellent oncologic outcomes, but very different morbidity and mortality profiles. Timely, initial cystectomy provides improved oncologic outcomes for patients with high-risk non-muscle invasive bladder cancer, as opposed to delayed cystectomy following prolonged, failed bladder-sparing therapy. Patient selection is paramount when considering timely, initial cystectomy, given the increased rates of morbidity and mortality. The heterogeneity of non-muscle invasive pathologic characteristics includes a number of factors that may help differentiate patients who would benefit from a timely, initial cystectomy as opposed to bladder-sparing therapy. A rapidly evolving understanding of bladder cancer biology may help improve risk stratification and further aid in the selection of patients for timely, initial cystectomy.

Keywords: Early cystectomy, high-risk bladder cancer, non-muscle invasive bladder cancer, timely cystectomy

Introduction

Bladder cancer burdens the healthcare system as the sixth most commonly diagnosed cancer in the United States (US), with the highest per patient cost of any cancer in the US (1,2). These statistics are even more troublesome as the incidence and death rate of bladder cancer have remained remarkably unchanged from 1985 (20.7 and 4.7 per 100,000) to 2016 (19.4 and 4.4 per 100,000) based on the SEER Medicare Dataset (2).

Approximately 75% of bladder cancers are non-muscle invasive bladder cancer (NMIBC) at diagnosis (3). This predominance for non-muscle invasive disease complicates the treatment algorithm due to its heterogeneity of risk and treatment options. Treatment of NMIBC by the American Urological Association (AUA) Guidelines relies on risk stratification based on tumor characteristics and recurrence status. The applicability of these treatment algorithms has improved with the current guidelines by the introduction of, and emphasis on, risk re-stratification at every subsequent recurrence, treatment and transurethral resection of a bladder tumor (TURBT) (4).

Treatment of NMIBC and Early Cystectomy

Both recurrence and progression rates vary widely for low, intermediate and high-risk NMIBC, with the overall risk of recurrence as high as 70% within the first year, and the lifetime risk of progression to muscle invasive disease between 10-50% (5,6). This variability reflects the range of factors that contribute to the AUA risk stratification, namely the depth of tumor invasion, presence of lymphovascular invasion (LVI), concomitant carcinoma *in situ* (CIS), tumor size and location, tumor biology including a number of potential variants and recurrence status (5,7,8,9,10). However, these factors represent an incomplete list, as molecular and genetic factors will help determine more effective therapeutic strategies on an individual basis (11,12).

This heterogeneity within the NMIBC cohort, though complicating, emphasizes the need to categorize patients who may bear increased risk from bladder-sparing, intravesical therapy and thus may benefit from timely, initial, up front cystectomy. It should be noted that repeat TURBT, when indicated, is essential for appropriate risk stratification, and has been associated with decreased mortality and increased rates of tumor upstaging (13).

Guideline-directed treatment of NMIBC includes complete resection of all visible tumor and risk-guided surveillance, and may include intravesical instillation of immunotherapy [Bacillus Calmette-Guerin (BCG)] or chemotherapy, re-resection of the primary tumor site, or radical cystectomy (4,14). There is no argument that bladder-sparing techniques serve as the backbone

Cite this article as: Koch GE, Chang SS. Non-muscle Invasive Bladder Cancer: Identifying Patients to Consider Timely, Initial Cystectomy. Bull Urooncol 2020;19(4):167-174

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Received: 08.01.2020 **Accepted:** 11.05.2020

of NMIBC therapy. Both induction and maintenance courses of intravesical BCG have been shown to decrease recurrence and progression of NMIBC when compared to TURBT alone or to TURBT plus intravesical chemotherapy (15,16,17,18).

Regarding BCG for patients with high-grade invasion into the lamina propria NMIBC (T1), multiple retrospective analyses have demonstrated BCG's efficacy. In a series of 126 patients with T1 disease, Brake et al. (19) reported a recurrence-free rate of 86% at 53 months following 1 or 2 cycles of induction BCG. These successes were re-demonstrated by Novotny in a group of 63 patients who underwent a combination of induction and maintenance BCG regimens showing a recurrence in 25% and progression in 13% of patients. Canter also showed a decrease in progression to 8.6% with the addition of adjuvant BCG (20).

Given these results for BCG, and realizing the morbidity of radical cystectomy, up front bladder removal, even for high-risk NMIBC patient, is not often considered (21). This holds true for BCG refractory NMIBC, which carries an approximately 80% chance of treatment failure or progression, as evidenced by one survey in which 80% of American Urologists would not recommend a radical cystectomy for a patient with NMIBC refractory to two induction courses of BCG (22). This lack of adoption is likely multifactorial, but worrisome given the excellent, albeit retrospective data, supporting upfront, timely radical cystectomy versus delayed cystectomy following failed bladder-sparing therapy. Herr and Sogani (23) reviewed 90 patients with high-risk NMIBC who underwent cystectomy. Of the patients whose cystectomy was within 2 years of BCG initiation, 15-year cancer-specific survival was 69%, versus 29% in those who underwent cystectomy more than 2 years after BCG initiation. While none of these patients underwent cystectomy prior to progression to muscle invasion, Jäger et al. (24) showed a similar result in strictly high-risk NMIBC patients, with a ten-year overall survival of 79% in patients who underwent cystectomy within 6-12 months of their initial TURBT as opposed to 62% for cystectomy after 12 months. Raj et al. (25) then compared Herr's original group to a more contemporary cohort that underwent early cystectomy for recurrent T1 disease, showing an improved disease-specific survival favoring early cystectomy, which was then echoed by Denzinger et al. (26) in a similar population. Denzinger et al. (26), Hautmann et al. (27) and Stöckle et al. (28) have all reported similar findings in patients who either underwent early radical cystectomy for high-risk non-muscle invasive disease versus delayed cystectomy following failure of bladder-sparing therapy, showing five-year disease-specific survivals of 90% compared to 62% and ten-year disease-specific survivals of 78-79% compared to 51%-65%, favoring early cystectomy.

Given the excellent outcomes from both bladder-sparing BCG, and from timely, initial cystectomy, it is unsurprising that a recent meta-analysis showed mixed results regarding the differences in cancer-specific survival for bladder-sparing therapy versus timely cystectomy for patients with high-risk T1 NMIBC (29). In this analysis, cancer-specific survival showed no significant difference between upfront cystectomy versus intravesical therapy at 2, 5 and 10-years; it favored cystectomy at 15-years, however with significant variability of the data. Overall survival on the other hand favored bladder-sparing intravesical therapy at 2, 5 and 10-years, with insufficient data for 15 years. It should be noted that these results reflect both a heterogeneous group of studies, and include complete responders to intravesical therapy, thus decreasing the power of the meta-analysis to detect differences between immediate versus delayed cystectomy. The true denominator of those who never received cystectomy and instead received alternative, likely ineffective, intravesical therapies is unknown and likely underestimated.

Outside of oncologic outcomes, any discussion of radical cystectomy should also take into account both the advantages of cystectomy's improved staging and the disadvantages of its increased morbidity and mortality. Accurate staging is paramount when discussing the potential treatment options available for bladder cancer given the strong evidence for radical cystectomy for muscle invasion (30). Unfortunately, staging is often not as technically straightforward as the dichotomy of "muscle invasive or not". More than 20% of patients initially diagnosed with T1 NMIBC have been found to be incorrectly staged on repeat TURBT (31). This is echoed by the rates of pathologic upstaging at the time of radical cystectomy, which have found previously T1 NMIBC patients to be reclassified as muscle-invasive in 25-50% of cases, with 15% of patients found to harboring lymph-node positive disease at the time of cystectomy for NMIBC (32,33).

Radical cystectomy is not without risk, which may account for the reported reluctance to recommend extirpative therapy, even when indicated (22). Contemporary series have reported the 90-day morbidly of radical cystectomy to be between 27-60% when genitourinary, gastrointestinal, infectious and wound related complications are considered, regardless of an open versus robotic surgical approach, with mortality often cited between 3-5% (21,34,35). Outside of the perioperative risk, there has been controversy regarding quality of life outcomes after radical cystectomy. Yang et al. (36) found both genitourinary and sexual outcomes to be negatively impacted by radical cystectomy over bladder-sparing therapy. Interestingly, these results were significant regardless of continent versus incontinent urinary diversion. On the other hand, Kulkarni et al. (37) examined quality-adjusted life expectancy and found upfront radical cystectomy to have better outcomes than radical cystectomy following failure of bladder-sparing therapy.

Considering both the advantages and disadvantages of radical cystectomy weighed against the effectiveness of bladder-sparing therapy, discussing the criteria for choosing the NMIBC patient appropriate for a timely, upfront cystectomy is essential. This patient may be chosen before or following re-staging TURBT. Unsurprisingly, this question has long been the focus of multiple research groups in an attempt to optimize the NMIBC treatment pathway. Risk stratification and predictive modeling have both been employed to this end. AUA Guidelines serve as a framework for this discussion, categorizing patients based on the pathologic features of TURBT specimens and conferring "high risk" status on any specimen with high-grade lamina propria invasion, variant pathology, CIS, multifocality or large size of a high-grade tumor, high-grade recurrences/BCG failure or prostatic specimens and LVI (4). Both the European Organization for Research and Treatment of Cancer (EORTC) and the Club Urologico Español de Tratamiento Oncologico have devised predictive models to help improve risk stratification and thus

guide treatment decisions for NMIBC. Unfortunately, neither of these have shown much practical use for the modern patient, as both cohorts included patients without routine re-staging TURBT, did not categorize based on LVI or variant histology, and overall did not follow current treatment algorithms (6,38). These shortcomings were demonstrated in a multi-institutional external validation study showing both prediction tools to have poor discrimination between progression and recurrence, with low positive predictive values and a tendency to overestimate the risk of disease progression for high-risk NMIBC (39).

Lacking a contemporary tool to aid in the decision for timely, upfront cystectomy, tumor characteristics must be taken in turn. Substaging the level of invasion of the lamina propria, as defined by the current American Joint Committee on Cancer Staging (AJCCS), has been a focus of much research. Both identification of muscularis mucosa involvement as well as the depth of lamina propria invasion have been identified to carry prognostic value (40). When T1 disease is subclassified into "superficial" versus "deep" invasion, Holmang et al. (8) showed a significant difference in both progression (36% vs 58%) and disease-specific mortality (23% vs 45%). Rouprêt et al. (41) reported a similar finding, showing improved recurrence-free, progression-free and cancer-specific survival for T1a over T1b NMIBC. Further subdividing T1 tumors into T1a, T1b, or T1c depending on the depth of invasion above, into, or beyond the muscularis mucosa, respectively, has also been consistently associated with increased progression and decreased survival for deeper T1 subclasses (5,42). Extent of muscularis mucosa invasion has also been proposed as a subclassification of T1 disease, although the exact definition of "extent" has not yet been standardized. Indeed, the most recent update to the AJCCS guidelines recommends an attempt at quantification of lamina propria invasion, although no specific strategy or metric is defined (43). Even though muscularis mucosa involvement has previously been discussed as a potentially useful measurement to subcategorize T1 NMIBC, its adoption has not been widely implemented, as its identification is extremely inconsistent. Muscularis mucosa is often scattered and discontinuous, and its reported detection rate ranges from 6 to 76% (44,45). Using depth of invasion with a tangible, easily defined cutoff for microinvasion has been more readily adopted and shown improved prediction of progression, over the EORTC calculator, and an association with progression-free survival, depending on the cut-off used (10,40). Even more recently, aggregate linear length of invasive carcinoma has been reported as an independent predictor of progression to muscle invasion in a recent study by Leivo et al. (46). While it is clear that sub-classification of lamina propria invasion has prognostic value, and will likely someday factor more directly into the decision to recommend timely cystectomy over bladder-sparing therapy, the lack of widespread validation and adoption of a single, definitive strategy for sub-classifying pure T1 NMIBC limits its current clinical application.

LVI provides another pathologic characteristic with the potential to help differentiate the patient who may benefit from a timely, initial radical cystectomy for non-muscle invasive disease. For MIBC, the presence of LVI is well established as a poor prognostic factor, and has been associated with advanced stage, grade and lymph-node involvement as well as decreased recurrence-free survival, cancer-specific survival and overall survival (47,48,49). For NMIBC, large, multicenter cohorts have also shown independent associations with recurrence-free survival, progression-free survival and cancer-specific survival, and have been further confirmed by a 4.000 patient meta-analysis (50,51,52). Unfortunately, LVI proves difficult to implement as a widespread metric due to technical challenges. Certain tissue processing artifacts like tissue retraction can complicate the identification of LVI (53). Furthermore, LVI in TURBT specimens only represents a small sample of the total tumor burden and thus it may be missed, or conversely overestimated in the overall tumor burden. Accordingly, concordance between TURBT and cystectomy specimens ranges from 18-79% with a negative predictive value of 50-70% (54,55,56). However, even considering these technical barriers to standardization, a recent meta-analysis and systematic review found that LVI in NMIBC tripled the risk of progression to MIBC and doubled the risk of disease recurrence. Furthermore, this evidence was so strong that the authors recommended LVI for inclusion in the TNM staging criteria for bladder cancer (57).

At diagnosis, approximately 10% of bladder cancer patients are found to have CIS, which represents a high-risk form of NMIBC, regardless of whether it presents as a discrete lesion, or synchronous with other non-muscle invasive lesions (4). At the time of cystectomy, specimens with CIS are understaged in up to 48% of non-muscle invasive cases, and the risk of pathologic upstaging in T1 NMIBC with synchronous CIS is 55% compared to 6% in high-risk T1 disease without CIS (58,59). The rate of progression in the presence of CIS also poses a major risk for NMIBC patients. In one study of NMIBC patients undergoing BCG therapy, 81% of whom had CIS, 53% of patients showed disease progression while on BCG therapy (60). This has been reproduced multiple times, demonstrating a strong association between CIS and progression to muscle invasion in 40-80% of cases (61,62). CIS has also been associated with nodal metastases in 4-6% of patients, along with risk of development of nodal metastases in up to 12% of patients when followed out to 3 years after cystectomy (63,64). Considering the high risk of both understaging and progression, the outcomes for radical cystectomy in patients with CIS-only disease are promising, with 3-year disease-free survival reported as high as 88% (63). Furthermore, Masood et al. (58) found 5-year cancer-specific survival to be 82% for CIS with concomitant T1 NMIBC. However, these results have been challenged in the era of neoadjuvant chemotherapy with Amini et al. (65) reporting no difference in oncologic outcomes for patients with CIS versus those without CIS, when adjusted for stage.

Variant histologies of NMIBC represent pathologic subsets that fall into the high-risk category in the AUA risk stratification table, accounting for 7-10% of new bladder cancer diagnoses (4,66). These include micropapillary, nested, plasmacytoid, neuroendocrine and sarcomatoid variants, each of which is thought to have its own tumor biology (67). One of the major concerns regarding variant histology is the relative rarity with which they are encountered as compared to pure urothelial carcinoma, and thus the lack of consistency regarding their identification and staging. Variant histologies go unrecognized in up to 44% of cases in one study of community pathologists

(68). This may also play a factor in the 30-60% rate of understaging in variant histology, which represents up to triple the rate of pure urothelial carcinoma understaging (69,70). Irrespective of difficulties with identification, variant histologies are considered more aggressive than pure urothelial carcinoma. Variant histologies present as muscle-invasive disease in up to three quarters of cases, as opposed to urothelial carcinoma that presents as non-muscle invasive in 70% of cases (71). Furthermore, variant histologies are associated with higher rates of locally advanced disease (72). The presence of a histologic variant has also been shown to be an independent predictor of nodal metastatic disease and decreased survival (73). Nested variant urothelial carcinoma has a propensity to progress to muscle-invasive disease more quickly than pure urothelial carcinoma, with a 54% rate of upstaging to muscle-invasive or metastatic disease after early cystectomy, even after thorough restaging TURBT showing cT1 disease (74). Regardless of the increased aggressiveness of variant histologies, it is important to note that intravesical therapy shows reduced effectiveness when compared to pure urothelial carcinoma, although this should be considered on a variant by variant basis. Kamat et al. (69) reported that up to 89% of patients with variant histology do not respond to intravesical therapy, with 67% actually progressing on BCG. This same cohort was then updated, showing that in patients with micropapillary variant, 5-year disease specific survival was 100% following upfront radical cystectomy versus 60% with BCG (75). A larger review of almost 900 patients with cT1 micropapillary bladder cancer showed no significant survival benefit for early cystectomy over bladder preserving therapy (76). It should be noted as well that the benefit of neoadjuvant chemotherapy is not quite clear, with a Vetterlein et al. (77) demonstrating improved rates of non-organ confined disease for many common histologic variants, but a survival benefit for only neuroendocrine variant.

As mentioned previously, in this age of personalized medicine, molecular and genomic classifications of bladder cancer are becoming critical in the considerations of potential patient management, although they have not yet been included in current risk stratifications. Biomarkers including p53, pRB and Ki-67 have all been associated with both increased recurrence and decreased survival for MIBC after radical cystectomy (78,79). For NMIBC, while early trials had conflicting results, newer evidence is emerging that suggests that recurrence may be predicted, and prognostic models improved, by molecular marker data (53,80,81,82,83,84).

Epigenetics, including oncogene activation, chromosomal alterations, tumor suppressor loss and cell-cycle regulation, has been associated with non-invasive tumor progression, which may serve as an indicator of patients who would benefit from timely, initial cystectomy (85,86,87). Mutation of the tumor suppresser gene p53 has been shown in many studies to be associated with tumor progression, although there is some conflicting evidence (88,89). Fibroblast growth factor receptor 3 (FGFR3) mutations, found to be present in up to 88% of low-grade papillary lesions but only 16% of high-grade T1 tumors, have been associated with a lower rate of progression, recurrence and disease-specific survival (90). RNA sequencing has also be implicated as a possible classifier of NMIBC, showing the ability to predict progression and recurrence (91). Furthermore, combining panels of molecular markers has further improved risk stratification for NMIBC. Combinations of FGFR3 mutation status with Ki-67 expression have been associated with progression, as well as shown significant improvement in the accuracy of the EORTC risk calculator (92,93). Tissue microarrays using a large number of genetic markers including p53, pRB, p21 and p27, as well as one using cyclin D1, MCM7, TRIM29 and UBE2C, have not only shown an association with tumor progression, but have also provided a continuum on which the number of marker alterations correlates with the probability of progression (86,94). While these various biomarkers have been shown to improve prognostication, they are not yet widely available in clinical practice.

The highest yield application of the increasing genetic and epigenetic knowledge base of bladder cancer may be the identification of two distinct molecular subtypes of NMIBC, namely the basal and luminal subtypes (11,12,95). The luminal subtype tends to have more papillary features, rich in FGFR3, whereas the basal subtype are often associated with squamous and sarcomatoid features and are often found to be metastatic at diagnosis (11,95). These new classifications may provide not only a more robust risk stratification model, but also a framework for increasingly targeted therapeutic algorithms (96).

Furthermore, bladder-sparing therapy is also likely to expand beyond the current intravesical options based on the increasingly deepening understanding of the basal and luminal subtypes (97,98). Basal type tumors, for example, respond well to immunotherapy given their concentration of programmed death ligand-1 T-cells as well as EGFR inhibitors (12,99,100). The potential for both improved risk stratification, as well as individualized patient care, could signal a paradigm shift in the approach to both MIBC and NMIBC. This is most clearly evidenced by the 25 ongoing clinical trials in the US for NMIBC (101).

Conclusion

The evidence for the oncologic benefit of cystectomy in the NMIBC setting is quite clear. However, the morbidity of cystectomy, both in the short-term perioperative period and in the long-term follow-up period, must be considered. Unfortunately, the data suggests that radical cystectomy for NMIBC is not as effective following ineffective, prolonged intravesical therapy. When choosing appropriate candidates, decisions about their treatment plans should follow repeat transurethral resections, when indicated, and their surgical fitness should be considered. Patients with non-invasive tumors not amenable to transurethral resection, regardless of risk stratification, should be considered for initial cystectomy. Those with tumors amenable to complete visual transurethral resection in patients fit for surgery, with tumor pathology reflecting pure urothelial carcinoma with high-risk characteristics like lamina propria invasion on repeat resection, deeper or more extensive lamina propria invasion, LVI, CIS or patients with histologic variants should all strongly be considered for a timely, initial cystectomy. As patients accumulate more of these risk factors, they should be considered increasingly stronger candidates

for timely, initial cystectomy. Genetic, epigenetic and genomic risk factors are paramount to the future of bladder cancer risk stratification and treatment, for both NMIBC and MIBC, and will likely add more variables to consider in the decision for bladder-sparing therapy versus timely, initial cystectomy for NMIBC.

Acknowledgements

Publication: The results of the study were not published in full or in part in form of abstracts.

Contribution: There is not any contributors who may not be listed as authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.S.C., Design: G.E.K., Data Collection and Processing: G.E.K., Analysis and Interpretation: G.E.K., Literature Search: G.E.K., Writing: G.E.K.

Short Quiz

1- Which of the statements below <u>is not</u> correct.

A) Contemporary series have reported the 90-day morbidly of radical cystectomy to be between 27-60%

B) More than 20% of patients initially diagnosed with T1 NMIBC have been found to be incorrectly staged on repeat TURBT.

C) Both genitourinary and sexual outcomes are equally impacted by radical cystectomy and bladder-sparing therapy.

D) Muscularis mucosa is often scattered and discontinuous, and its reported detection rate ranges from 6 to 76%.

E) For NMIBC, large, multicenter cohorts have also shown independent associations with recurrence-free survival, progression-free survival and cancer-specific survival

Answer: C

2- Which of the genetic factors below <u>has not</u> a study showing its effect on NMIBC

A) p53

B) pRB

C) p21

D) p27

E) p99

Answer: E

3- Which of the factors below <u>does not</u> contribute to the AUA risk stratification

A) Lymphovascular invasion (LVI),

B) Concomitant carcinoma in situ (CIS),

C) Tumor size

D) Cystoscopic appearance of the tumor

E) Tumor location

Answer: D

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