Abstract

The optimal treatment of lamina propria invasive bladder cancers remains controversial. Assigning strict treatment guidelines is hampered by the heterogeneous clinical behavior of lamina propria invasive bladder cancers. Although many T1 lesions respond very well to transurethral resection and adjuvant intravesical therapy, others demonstrate a high rate of recurrence and progression. While bladder preservation is desired by most patients, experience has documented that survival is compromised in a substantial percentage of patients if T1 disease is allowed to progress. Radical cystectomy for T1 disease is associated with an excellent survival; however, the optimal timing of radical cystectomy remains one of the more difficult clinical dilemmas in the management of patients with bladder cancer. This article reviews the various features associated with an increased risk of disease progression to provide a framework for optimizing the timing of radical cystectomy. © 2009 Elsevier Inc. All rights reserved.

Keywords: Bladder cancer; Radical cystectomy; Prognostic factors

Introduction

The pathways by which high grade bladder cancers progress have been well documented over many decades through clinical observations and the findings obtained from autopsy studies [1]. The risk of developing either regional or distant metastatic disease is directly associated with the extent of invasion of the bladder wall by the primary tumor. High grade invasive bladder cancers that involve the lamina propria (LP) have historically been thought to possess a lower inherent potential for aggressive behavior and as such were categorized within the grouping designated as superficial bladder cancer. Treatment paradigms were established that managed T1 lesions conservatively using transurethral resection with or without intravesical therapy, offering radical cystectomy only at the time of progression to more invasive disease. However, as the outcomes of conservatively managed T1 patients were presented, it became apparent that poorer than expected outcomes were observed in patients who progressed following conservative therapy [2]. It is clear that invasive tumors that involve the LP comprise a heterogeneous group of lesions that include tumors that respond well to intravesical treatments as well as lesions that progress despite therapy. Significant variations in response to intravesical therapy and risk of progression contribute to the difficult clinical dilemma that arises in assigning treatment to patients with T1 bladder cancer. Several critical questions must be addressed when considering the appropriate management strategy for any given T1 bladder cancer patient including, (1) to whom should early radical cystectomy be offered in an attempt to avoid progressive disease and (2) which patients would be best managed by initial conservative treatment with the understanding that some patients managed with TURBT and intravesical treatment will progress and potentially develop lethal disease.

The heterogeneity in clinical behavior of T1 tumors makes any application of broad treatment recommendations to all patients difficult. The challenge for individualizing treatment centers on the ability to accurately determine which tumor characteristics are associated with a minimal response to conservative therapy and thus should be managed by early radical cystectomy. The decision to offer cystectomy is based on several factors including an overall understanding of the general natural history of T1 bladder cancer, an accurate assessment of the specific factors associated with failure to respond to conservative therapy and future progression, and an assessment of a patient’s overall risk to undergoing radical cystectomy.

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Risk characteristics of T1 bladder cancer

A variety of tumor factors should be considered when assessing a patient’s risk for disease progression. These factors can be broadly categorized as morphologic/physical, pathologic, the clinical response to treatment, and molecular characteristics.

Morphologic features

Morphologic features associated with a higher risk of progression include whether tumors have a papillary vs. solid appearance [3,4]. Solid tumors have a hazard ratio of 2.7 for risk of progression and 2.4 for death from bladder cancer compared with tumors with a papillary configuration. Additional factors such as tumor size and the number of T1 lesions are also prognostically relevant with larger lesions and multifocal T1 disease demonstrating a greater likelihood of progression. Tumor location is an important physical characteristic that should be considered when assigning risk. Lesions located in regions of the bladder that are particularly difficult to access and completely resect with current endoscopic resection equipment (i.e., anterior bladder neck) may contribute to inaccurate staging, incomplete removal of tumor, poor response to intravesical therapy, and early recurrence and progression of disease.

Pathologic characteristics

Pathologic information (i.e., stage, grade) plays a major role in estimating prognosis in patients with T1 disease. Depth of tumor invasion into the lamina propria, associated CIS, lymphovascular invasion, and aberrant growth patterns all have demonstrated importance in predicting progression risk for T1 disease. Pathologic information is preferentially obtained by transurethral biopsy. The goal during transurethral resection is complete macroscopic tumor with and adequate sampling of the bladder wall to provide material for complete local tumor staging. Substantial data supports the role of a restaging transurethral biopsy following an initial diagnosis of T1 disease [5]. Several facts support the role of the restaging TURBT, including the significant understaging of T1 lesions that occurs following a single TURBT. Series have noted up to a 50% understaging rate particularly if no muscularis propria is present in the initial biopsy [6]. Additionally, incomplete tumor resection is commonly encountered after an initial TUR biopsy. Residual T1 or Ta disease is less likely to completely respond to intravesical therapy and therefore will contribute to early local recurrences but may also be the source of cells that progress and disseminate [7]. A restaging TURBT thus has the dual advantage of providing a more accurate assessment of the critical pathologic features used to assess risk and improving the therapeutic efficacy of conservative therapy. Restaging TURBT should be considered as a standard intervention for T1 bladder cancer.

The depth of tumor invasion into the lamina propria has been proven to be associated with outcome [8–11]. T1 lesions vary in the extent and depth of lamina propria involvement and include small tumors with a microscopic region of superficial invasion as well as larger tumors with extensive deep lamina propria involvement down to the region of the muscularis propria. The risk of progression increases with increasing depth of invasion and has led to proposed substaging scheme for T1 tumors. Studies have noted that deep invasion of the lamina propria by tumor below the muscularis mucosae is associated with increased risks of progression and decreased overall survival [8–11]. The pathologic evaluation of the lamina propria for substaging has been a controversial issue amongst pathologists who have noted that the key structures in the lamina propria that are used for substaging (such as the muscularis mucosae) are inconsistently identified, particularly in TURBT specimens [12].

Another important pathologic feature associated with a poor outcome is the finding of concomitant carcinoma in situ. In several studies, associated CIS portends a greater risk of progression and poor overall prognosis [9,13,14]. The European Organisation for Research and Treatment of Cancer (EORTC) risk tables designed to estimate progression risk for T1 lesions, established associated CIS as the most significant feature associated the risk of both recurrence and progression at 5 years after bacillus Calmette-Guerin (BCG) therapy [15]. Other pathologic features associated with a poor outcome following conservative therapy include lymphovascular invasion [3,16,17] and a micropapillary growth pattern [18].

Effect of response to prior treatment

How a tumor responds to previous treatment serves as another powerful indicator of progression risk. Patients with initial T1 disease that recur following BCG therapy, particularly with additional invasive tumors, exhibit a substantial risk of progression, far exceeding that of patients who recur with non-invasive disease [19,20]. Additionally, the results of the restaging TURBT may predict outcome in those patients with no evidence of residual disease on the restaging biopsy to have a much lower risk of progression following BCG therapy compared with patients with residual invasive (T1) disease [21]. These findings may be a surrogate for the extent of disease present and therefore serve as a measure of the tumor’s biologic aggressiveness. These characteristics, especially failure to respond to BCG therapy, should be strongly considered as indicators of a poor outcome with continued conservative therapy.

Role of molecular markers

Several studies have investigated the role of molecular markers as prognostic indicators of progression in T1 bladder cancer. Molecular alterations in tumor cells have been
correlated with outcome in muscle invasive bladder and may reflect a tumor inherent biological aggressiveness [22,23]. The molecular status of many of the key pathways of carcinogenesis has been studied in T1 disease to determine their association with response to conservative treatment and risk of progression. Studies evaluating the prognostic importance of altered p53, Ki67, Cox-2, and NMP-22 have identified an association with an increased progression risk [24–28]; however validation in larger prospective series must be completed if they are to be routinely applied in clinical decision making.

**Conclusion**

T1 bladder cancers comprise a heterogeneous group of lesions with both variable responses to intravesical therapy and risks of progression. While conservative therapy may be safely offered to many patients with T1 disease, early cystectomy should be considered in patients considered at high risk for progression, as survival may be compromised once progression occurs.

**References**


