The best treatment for high-grade T1 bladder cancer is cystectomy

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Abstract

Objectives: To evaluate the role of initial cystectomy in the management of high-grade T1 bladder cancer.

Methods: A selected review of the literature was performed to evaluate outcomes with intravesical therapy vs. initial cystectomy in this patient population, with a focus on identifying risk factors for failure of conservative therapy.

Results: Many studies in the literature fail to include central pathologic review and re-TUR clinical staging, and there are no randomized studies comparing outcomes with these two initial approaches. Retrospective studies of patients with high-grade T1 tumors treated with initial intravesical therapy suggest that approximately 30% of patients will ultimately require cystectomy, and 30% will die of their disease with or without cystectomy. The risk of progression continues for the life of the patient, and late recurrence and progression is common. Initial clinical and pathologic factors can be identified that predict a high risk of progression and are reasonable indicators for initial cystectomy.

Conclusion: Radical cystectomy can provide a very high cure rate for these patients and should be considered early in the treatment plan. © 2007 Elsevier Inc. All rights reserved.

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Introduction

Non-muscle invasive bladder cancer represents a wide spectrum of disease, from a small, solitary, low-grade tumor to multifocal, large, high grade tumors with deep lamina propria invasion. While the majority of patients with these tumors have a high risk of recurrence, only those with the high-grade tumors, especially with lamina propria invasion (G3T1) and carcinoma in-situ (CIS) are at significant risk of progression, metastasis, and death from bladder cancer. Radical cystectomy has a very high cure rate for these tumors and should be considered a viable option for initial treatment.

Problems with the current literature

When one looks to the literature for evidence that 1 treatment approach is superior to another for G3T1 bladder cancer, the available studies fall short. There are a number of randomized studies evaluating intravesical therapies; however, many of them failed to single out patients by grade and stage, mixed various treatments, or had only short term follow-up. Fortunately, there are several studies that focus specifically on G3T1 disease treated initially with intravesical BCG [1–3].

In most of the published studies, the pathologic evaluation of the tumor has not been centrally reviewed. While assignment of grade is relatively straightforward, interpretation of lamina propria invasion may be very difficult in TUR specimens, especially when there is a high degree of cautery artifact. A patient with a small grade 2–3 tumor with minimal (or questionable) lamina propria invasion may have a very different prognosis than one with a large, very high-grade tumor with deep submucosal invasion up to the edge of the muscularis propria [4]. When central review was undertaken within the EORTC study group for over 500 G3T1 patients enrolled in their clinical trials, over half of all T1 tumors were reclassified as Ta, and almost 5% as T2 [5]. Similar inaccuracies are likely to affect other reported series. As discussed below, it is also critically important to know if there was adequate muscle in the specimen of the initial TUR, and whether a repeat TUR was routinely performed.

Perhaps most importantly, there are no prospective randomized trials comparing intravesical BCG with radical cystectomy as primary treatment of patients with high grade
T1 tumors. All cystectomy series in the literature that focus on non-muscle invasive disease include many patients who have already failed previous courses of intravesical therapy [6–8]. Patients who have been treated with initial cystectomy tend to be those with more adverse prognostic factors. Therefore, it is difficult to compare retrospectively the outcome for these selected patients with the outcome of those who were initially treated with intravesical therapy.

**Importance of repeat TUR**

Several authors have emphasized the importance of repeat TUR in patients with T1 disease [9,10]. It is clear from cystectomy series that up to 40% of patients with high grade clinical T1 or Tis disease are upstaged on the final pathology at the time of cystectomy [6,11]. Herr [9] and Dutta et al. [10] have both shown that the probability of upstaging increases 50% to 60% if there was no muscle in the initial TUR specimen. Even in the presence of muscle in the initial specimen, repeat TUR will uncover muscle invasion in up to 14% of patients. These patients are destined to fail any attempt at management with intravesical therapy. Thus, repeat TUR is strongly recommended for patients with high-grade T1 disease in whom conservative management is being considered, and particularly if no muscularis propria was present in the initial resection specimen, if inadequate sampling of muscle was obtained subjacent to the presenting lesion, or if extensive and deep lamina propria invasion was present.

**Long-term outcomes with intravesical therapy**

Surprisingly few series have documented the long-term outcome for patients with G3T1 disease treated with initial intravesical therapy. Cookson and colleagues reported 15-year results in 86 high-risk patients randomized to BCG vs. TUR alone prior to 1981. Three fourths of the patients ultimately received BCG in a crossover design. Over half of the patients suffered progression, 36% required cystectomy, and 34% died of metastatic bladder cancer [12]. Shahin and colleagues showed very similar results in a retrospective, nonrandomized study of 153 patients treated with TUR alone or TUR plus BCG [1]. In both of these studies, disease-specific survival continued to fall well beyond 5 and even 10 years of follow-up. This is in contrast to cystectomy series, where disease-specific death is rare after 5 years [11]. Neither group could demonstrate a significant impact of the BCG therapy on these long-term outcomes.

**Results with radical cystectomy**

Nearly all cystectomy series describing patients with clinically non-muscle invasive disease include a large percentage of patients who have failed previous intravesical therapy. Attempts to single out patients treated with initial cystectomy have been severely hampered by selection bias—initial cystectomy is generally only recommended for patients with features that imply high risk for progression such as large, multifocal tumors, associated CIS, or those in whom understaging is suspected. Therefore, it is probably not appropriate to retrospectively compare these patients with those who were treated with initial BCG, as has been done by some authors [13].

However, even taking into account these factors, the ultimate outcome with cystectomy is excellent. If cystectomy is performed when the tumor is still confined to the lamina propria, over 80% of those patients will be cured [8,11]. If one waits until muscle invasion is clinically evident, cure rates may drop significantly [11].

**Advantages of initial cystectomy**

There are 3 primary advantages of initial cystectomy for patients with clinical G3T1 tumors. First, one obtains pathologic staging and lymph node status—the strongest known predictors of ultimate cancer outcome. This can allow selective application of adjuvant therapies (such as systemic chemotherapy) to those with the highest risk of harboring occult metastatic disease. Second, in this early stage of disease it may be possible to perform a nerve-sparing cystectomy with continent ileal neobladder reconstruction—affording the patient the highest likelihood of recovering preoperative sexual and urinary functions. This surgical approach is more problematic in the patient with a large T2 tumor or gross extravesical disease. Finally, cystectomy greatly reduces the risk of late recurrence in these patients. Follow-up is therefore simplified, being reduced after 3 years to an annual radiological and laboratory evaluation to watch for stones, ureteral strictures, or upper tract or urethral recurrence—all relatively uncommon events. At that point patients can be considered cured of their invasive cancer and will unlikely die of their disease.

**Balance and indications for early cystectomy**

Obviously, cystectomy is a major surgical undertaking, with significant perioperative morbidity and mortality. Though not to be taken lightly, especially in elderly patients, it should be applied to those cases where the risk of tumor progression and metastasis is significant and the probability of cure with this treatment is high.

Long-term follow-up studies of patients with G3T1 tumors suggest that approximately one third of those patients treated with intravesical BCG never suffer a recurrence of their disease [1,14]. If we could accurately identify those patients clinically, radical cystectomy would be unnecessary in these cases. Although several features of the tumor
diathesis in these patients have been characterized as presenting lesser risk of progression (e.g., minimal lamina propria invasion, absence of concomitant carcinoma in situ, prompt and definitive response to intravesical BCG with negative biopsy and urinary cytology that is maintained with maintenance or booster treatments), we do not have sufficiently accurate markers to clearly identify such patients at the onset of their treatment course.

In the absence of such predictive biologic markers, I would suggest the following algorithm for all patients with a diagnosis of G3T1 TCC of the bladder:

1. Patients who are considered for possible intravesical therapy should undergo repeat TUR at 2 to 6 weeks following the initial resection.
2. Consider a single dose of postoperative intravesical chemotherapy with mitomycin C or Adriamycin after each TUR [15].
3. Patients with any one of the following features either on initial presentation or in follow-up should be counseled to strongly consider cystectomy: (a) associated CIS; (b) deep lamina propria invasion; (c) significant irritative voiding symptoms; (d) lymphovascular invasion; (e) involvement of the prostatic ducts or stroma; (f) large or multifocal lesions; (g) persistent G3T1 disease on repeat TUR.
4. In a patient initially treated with resection and BCG, persistent or recurrent disease (G3T1 and/or carcinoma in situ) at the 3-month follow-up should be a strong impetus to proceed with cystectomy [16]. Patients with late recurrences, more than 1 year after initial treatment, may also be at high risk of progression and are therefore also appropriate candidates for prompt cystectomy.

**Conclusion**

Radical cystectomy is a curative treatment for patients with non-muscle invasive bladder cancer who are at high risk of progression and death, and should be considered early in the treatment plan for these patients.

**References**