



Re-examination of the Natural History of High-grade T1 Bladder Cancer using a Large Contemporary Cohort

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ABSTRACT

Introduction: High-grade T1 (HGT1) bladder cancer represents a clinical challenge in that the urologist must balance the risk of disease progression against the morbidity and potential mortality of early radical cystectomy and urinary diversion. Using two non-muscle invasive bladder cancer (NMIBC) databases, we re-examined the rate of progression of HG T1 bladder cancer in our bladder cancer populations.

Materials and Methods: We queried the NMIBC databases that have been established independently at the Atlanta Veterans Affairs Medical Center (AVAMC) and the University of Pennsylvania to identify patients initially diagnosed with HGT1 bladder cancer. Demographic, clinical, and pathologic variables were examined as well as rates of recurrence and progression.

Results: A total of 222 patients were identified; 198 (89.1%) and 199 (89.6%) of whom were male and non-African American, respectively. Mean patient age was 66.5 years. 191 (86.0%) of the patients presented with isolated HG T1 disease while 31 (14.0%) patients presented with HGT1 disease and CIS. Induction BCG was utilized in 175 (78.8%) patients. Recurrence occurred in 112 (50.5%) patients with progression occurring in only 19 (8.6%) patients. At a mean follow-up of 51 months, overall survival was 76.6%. Fifty two patients died, of whom only 13 (25%) patient deaths were bladder cancer related.

Conclusions: In our large cohort of patients, we found that the risk of progression at approximately four years was only 8.6%. While limited by its retrospective nature, this study could potentially serve as a starting point in re-examining the treatment algorithm for patients with HG T1 bladder cancer.

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INTRODUCTION

High-grade T1 bladder cancer (HGT1) represents a clinical challenge in that the urologist must balance the threat of progression from non-muscle to muscle invasive disease against the

morbidity and mortality of early radical cystectomy (RC) with urinary diversion. Current AUA clinical guidelines for patients with HGT1 disease recommend induction BCG to limit the risk of recurrence and, more importantly, progression after an adequate re-resection (1). Despite high rates of

progression and the associated increase in mortality, the AUA guidelines only state that radical cystectomy as a first-line treatment choice for HGT1 can be considered an option, advising the physician to weigh the likelihood of cure without invasive surgery against the associated morbidity and mortality of radical surgery (1).

Previous studies have reported that HGT1 bladder cancer will progress to muscle invasive disease in a significant number of patients, making early RC a reasonable course of action to consider (2). In one of the earliest series regarding HGT1 bladder cancer, the authors reported a 53% progression rate at 15 years of follow-up with 34% of patients ultimately dying of urothelial carcinoma (3). Other series have demonstrated progression rates ranging from 25 - 56% (4-7).

Understanding the natural history of HGT1 bladder cancer is essential to guiding therapy and creating treatment algorithms that incorporate bladder-sparing protocols along with RC. HGT1 bladder cancer represents a heterogeneous disease with varying phenotypes and outcomes, and currently no test or validated scoring system exists to predict which patients would benefit most from an early RC (8). Thus, this study re-examines the natural history of HGT1 bladder cancer by analyzing the recurrence and progression rates of a large cohort of patients initially diagnosed with HGT1 disease to determine if, in fact, the high incidence of disease progression and death due to bladder cancer is still witnessed in a more contemporary treatment era.

METHODS AND MATERIALS

To identify patients with HGT1 or under the older classification, Grade 3 T1 bladder cancer, two independent databases of non-muscle invasive bladder cancer patients were queried, one at the Atlanta Veteran Affairs Medical Center (AVAMC), the other at the University of Pennsylvania. Institutional Review Board approval was obtained at each institution. Patients identified were diagnosed and treated from 1980 - 2012. Patient demographic, clinical, and pathological variables were examined. Patients were excluded if they had muscle-invasive disease, pure CIS, Ta, or low-gra-

de disease. This produced a total of 222 patients with HGT1 disease to be reviewed, 151 from the University of Pennsylvania database and 71 from the AVAMC.

Biopsies of the bladder distant to the tumor were done at the surgeon's discretion and pathology was uniformly reported. Tumor characteristics such as tumor size, location, and multifocality were not uniformly reported and therefore were not included in our analysis. Patients were followed with endoscopic surveillance every 3 months for 2 years, 6 months until 5 years, and annually thereafter. Primary outcomes measured were recurrence and progression to muscle invasive disease. Recurrence was defined as any tumor present after initial complete resection at any surveillance point. Stage progression was defined as muscle invasive pathology at any surveillance point. However, patients with MIBC on restaging resection were considered to have MIBC at the time of their initial TUR; they were not considered to represent progression of HGT1 disease and were excluded from the analysis. Data was analyzed with Stata® software and statistics were described with Kaplan Meier curves.

All patients with HGT1 disease were reported in the analysis, including those who received definitive surgery with radical cystectomy prior to the occurrence of muscle invasion. This becomes important during the discussion of these patients being a cohort exposed to a more contemporary treatment era.

RESULTS

A total of 222 patients with HGT1 bladder cancer were identified from the two databases. Patient clinical and demographic data are presented in Table-1. One hundred ninety-eight (89.1%) and 199 (89.6%) of the patients were male and Caucasian, respectively. Mean patient age and pack-years smoking were 66.5 years (range = 29-93 years) and 37.3 (0-125). One hundred ninety-one (86.0%) of the patients presented with isolated high-grade T1 disease, and 31 (14.0%) patients had high-grade T1 disease with concomitant CIS. Two hundred and twelve (95.5%) patients presented with pure urothelial histology while 10 (4.5%)

Table 1 - Clinical and Demographic Characteristics at Presentation of Patients with High-Grade T1 Bladder Cancer.

Variable	No. (%)
Gender (Men)	198 (89)
Mean (median) age \pm SD, (range)	66.5 (66.8) \pm 11.28, (29.2-93)
Race	
White	199 (89.6)
Other	23 (10.4)
Mean (median) \pm SD BMI, (range)	27.5 (27.1) \pm 5.3, (16.6 - 48.1)
Mean (median) CCI	2.63 (2)
Mean/median pack-year smoking, \pm SD (range)	37.3 (35.5) \pm 26.9 (0 - 125)
Stage	
T1	191 (86.0)
T1 + CIS	31 (14.0)
Histology	
Urothelial	212 (95.5)
Other	10 (4.5)
Intravesical Therapy	
Peri-operative mitomycin C (1 dose)	41 (18.6)
Induction BCG	175 (78.8)
Induction mitomycin C	1 (1.4)
Mean # BCG Treatments (range)	5.80 (0-28)

patients had histological variants including micropapillary, sarcomatoid, and squamous differentiation. Peri-operative mitomycin C was used for 41 patients (18.6%); induction BCG was utilized in 175 (78.8%) patients and the mean number of BCG treatments was 5.80 (range = 0-28). One patient received induction mitomycin C (Table-2).

At a mean follow-up of 50.8 months (median = 32.5 months, range = 2.2-261.2 months), recurrence occurred in 112 (50.5%) patients. The mean number of recurrences was 1.28 (range = 1-10 recurrences) with a mean and median time to recurrence of 28.8 and 12.9 months, respectively.

Progression to muscle-invasive disease occurred in only 19 (8.6%) patients with a mean and median time to progression of 16.6 and 17.2 months. Kaplan Meier curves for recurrence-free and progression-free survival estimates are displayed in Figures 1 and 2.

At last follow-up, the overall survival of the entire cohort was 76.6%, 170 patients. Only 52 (23.4%) patients had died, 13 (25.0% of deaths, 5.9% of entire cohort) of whose deaths were related to bladder cancer. The remaining 39 deaths (75.0% of deaths, 17.6% of entire cohort) were attributable to patient competing co-morbidities.

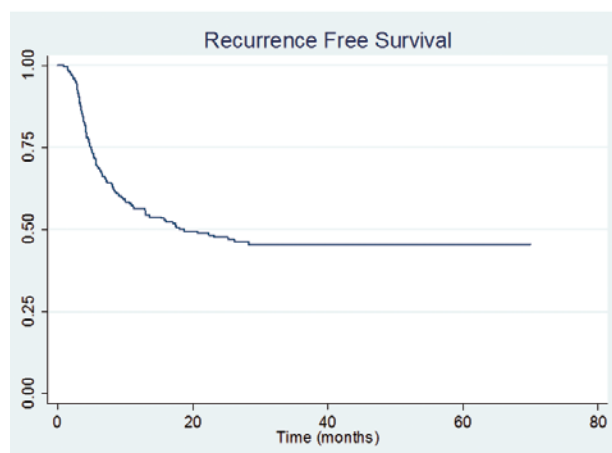
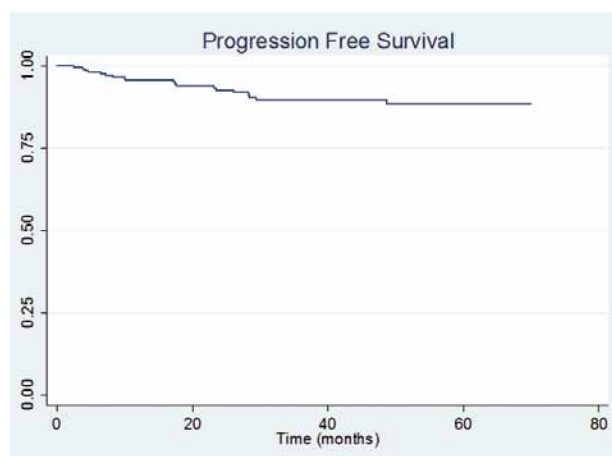
Table 2 - Recurrence, Progression, and Cause of Death.

	No. (%)
Recurrence	112 (50.5%)
Mean No. of Recurrences	1.28 (Range = 1-10)
Mean/median time to recurrence	28.8 (12.9) months
Progression	19 (8.6%)
Mean/median time to progression	16.6 (17.2) months
Alive	170 (76.6%)
Dead	52 (23.4%)
Bladder Cancer-Related Death	13 (25.0%)
Other Cause of Death	39 (75.0%)
Mean Follow-up	50.8 months
Median Follow-up	32.5 months
Follow-up Range	2.2-261.2 months

DISCUSSION

Consistent with earlier reports demonstrating three to five year progression rates below 10% (9,10), our data shows an 8.6% rate of progression to muscle-invasive disease at a mean follow-up of over four years. This data contrasts the largest prospective studies, which report progression rates of 29% at five years, and 53% at 15 years (3,5). Notably, a majority of the patients who progressed in our study presented with variant histology. Additionally, in our large contemporary cohort, 13 patients (5.9%) died due to bladder cancer. This present data may argue for a more conservative approach for patients with HGT1 disease in the absence of high-risk features for progression such as variant histology and CIS.

The high rates of progression and mortality seen in past studies have spurred clinicians to advocate early definitive, radical surgery for patients with HGT1 disease, particularly if they have certain high-risk features (2,8,11,12). Despite no randomized trials, multiple retrospective studies have shown advantages for disease-specific and

Figure 1 - Kaplan-Meier curve of recurrence free survival.**Figure 2 - Kaplan-Meier curve of progression free survival.**

overall survivals in patients treated with RC before muscle invasion occurs (13-16). In these series, reasons to advocate for early RC include residual T1 disease at re-staging resection, extensive multifocal disease, large tumor volume, location making endoscopic management difficult, variant histology, and presence of CIS (2,5,11-13,17,18). Nevertheless, it is important to note that in these prior series, clinical understaging was prevalent in these patients treated with early RC (13,17), indicating, perhaps, that a portion of the survival benefit seen in patients undergoing early cystectomy is really a function of a poor clinical staging of bladder cancer.

To appreciate the lower progression rate seen in our series, the patient cohort must be viewed in the context of contemporary developments in the management of HGT1 bladder cancer. Increasingly, clinicians routinely perform a restaging TUR for patients with HGT1 bladder cancer followed by induction and maintenance BCG (1). High incidences of clinical understaging (34 - 64%) have been cited to support this recommendation (11,19-22). Restaging TUR and identification of patients with clinical T2 disease that should be treated with RC shows a substantial advantage for recurrence and progression free survival (23). Furthermore, restaging TUR before BCG has been shown to improve the response to the intravesical immunotherapy, lowering the observed recurrence and progression rates from 57% and 34% to 29% and 7%, respectively, at 3 year follow-up (9). Thus, the routine use of restaging TUR has two effects on the progression rate of patients with HGT1 disease: first, it selects out patients with clinical T2 disease, removing them from the HGT1 cohort and improving the measured progression rate. Secondly, restaging TUR should resect all remaining visible tumor and thereby improve the response to BCG therapy, further improving the progression rate for patients with HGT1 disease.

Our contemporary cohort also likely benefited from more sophisticated pathologic examinations as histologic variants with more aggressive phenotypes requiring more aggressive treatment have become recognized (24). For example, the presence of micropapillary histology, in particular, has been shown to be a poor prognostic factor for progression and disease free survival, and these patients deserve consideration for RC before muscle invasive disease occurs (25). The high incidence of these variant histologies was established with a recent large series showing variant histology was present in 19.9% of transurethral biopsies (24). It appears that these aggressive variant histologies are being identified more routinely, and patients are now more likely to be offered early RC and less likely to be managed with bladder sparing therapy, potentially improving progression rates.

This study has a number of limitations. It is a retrospective review open to significant selection bias. As previously discussed, restaging TUR,

recognition of histologic variants, and an increased willingness of clinicians to manage worrisome high-risk patients with RC distorts this patient cohort and potentially makes it more an analysis of low-risk HGT1 patients. Importantly, this analysis was done with a relatively short follow up time compared to the prior report that established the natural history of HGT1 bladder cancer (3). At further follow-up, our reported progression rates may increase, nullifying these promising rates of prevention of progression to muscle-invasive disease. Furthermore, there are many tumor factors with important prognostic implications that are not accounted for in this study, making it difficult to characterize and compare the biology of this cohort with previous cohorts. Additionally, as restaging TUR has only recently become routine, our databases poorly captured which patients received this procedure, introducing uncertainty in the analysis of progression versus inadequate primary resection. Moreover, our database poorly captured which patients were treated with radical cystectomy, the time of surgical intervention, and also does not contain the pathologic outcomes of these surgeries.

Nevertheless, it is important to contextualize these results in that many patients diagnosed with HGT1 bladder cancer do not have a 15-year life expectancy. Thus, it is imperative to weigh the expected risk of disease progression against the morbidity and mortality of surgery in the context of a patient's life expectancy, considering one's co-morbidities and goals of care.

CONCLUSIONS

At approximately 4 years of follow-up, the progression rate to muscle-invasive disease in patients initially presenting with high-grade T1 bladder cancer is only 8.6%. Although potentially subject to selection biases, these results from a large, contemporary patient cohort appears promising, arguing against the routine use of early cystectomy. Clearly further follow-up is needed, however when one considers the potential morbidity and mortality of radical cystectomy, the progression rate reported here is acceptable, especially when risk-stratified against an older and co-morbid individual.

ABBREVIATIONS

HGT1 = High-grade T1

NMIBC = Non-muscle invasive bladder cancer

AVAMC = Atlanta Veterans' Administration Medical Center

CIS = Carcinoma in situ

BCG = Bacillus Calmette-Guerin

RC = Radical cystectomy

TUR = Transurethral resection

CONFLICT OF INTEREST

None declared.

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