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Research Article

The Value of Repeat TURBT in High Grade T1 Bladder Cancer

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Abstract

Purpose: To evaluate the incidence and predictors of pathologic upstaging at time of repeat transurethral resection of bladder tumor for high grade T1 bladder cancer in a contemporary cohort.

Methods: A retrospective review was performed in patients diagnosed with high grade T1 bladder cancer between June 2013 to March 2019. All patients underwent repeat TURBT at our institution. Age, gender, time interval between TURBTs, institution of initial resection (outside hospital vs. our institution), history of bladder cancer, history of intravesical therapy, and presence of muscle in initial specimens were assessed as potential predictors of upstaging.

Results: 104 patients were evaluated. Median age was 72 years (IQR: 64-77) with male predominance, 70% (73/104). 39% (40/103) of patients had detrusor muscle present in their initial resections. On repeat resection, T0 disease was noted in 35% (36/104) of patients and 17% (18/104) where upstaged to T2 or greater disease. On multivariable analysis, the institution of initial TURBT (OR 4.04, 95% CI 1.13–14.5) and presence of muscularis propria in the initial specimen (0.23, 95% CI 0.06–0.91) were independent predictors of upstaging to muscle invasive disease at time of repeat TURBT. Gender was identified as an independent predictor of having muscularis propria in the initial TURBT specimen (OR 3.76. 95% CI 1.31–10.8).

Conclusions: Upstaging to muscle invasive disease during repeat TURBT for high grade T1 bladder cancer remains prevalent in contemporary series. Predictors of upstaging may reflect quality of initial resection and disparity in bladder cancer care based upon gender.

Keywords: Bladder Cancer; High Grade; Repeat TURBT; Stage 1; Urothelial carcinoma

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Background

High Grade T1 bladder cancer (HG T1) accounts for as many as 5-20% of new bladder cancer diagnoses [1]. Given known risks of upstaging and early tumor recurrence/progression, repeat transurethral resection of bladder tumor (TURBT) is recommended within 6 weeks of the initial resection. This recommendation is reflected by multiple society's guidelines, including the AUA, EUA, and NCCN [2-4]. The recommendation for repeat TURBT is primarily based upon the rates of upstaging to muscle invasive disease. AUA guidelines note the rate of upstaging in this population is between 15-20% when muscularis propria is present and as high as 40-50% when muscularis propria is absent in initial TURBTs [2]. However, repeat TURBT provides additional benefits including, opportunity to resect additional tumor [5-7] and prognostic value [8], increased responsiveness to BCG [9-10], and independent recurrence, progression, and survival benefit [11]. However, contemporary series have suggested that upstaging rates are significantly lower than previously reported. For example, Gendy et al reported that of those initially diagnosed with T1 disease only 14.6% were upstaged on repeat TURBT, 4.5% when muscularis propria is present in the initial specimen and 25% when muscularis propria is absent in initial TURBT [12]. While there is randomized controlled evidence in one study to suggest decrease rates of recurrence and progressions free survival at 1, 3, and 5 years in this population, contradicting evidence exists suggesting that the repeat TURBT does not improve recurrence, progression, cancer specific survival, or overall survival after adjusting for age, number of tumors, tumor size, the presence of CIS, and the use of maintenance BCG in one retrospective series [11-13]. In another series, researchers found a benefit in the patient population with HG T1 who received an early repeat TURBT by way of detecting upstaging events, reduced recurrence rate at 3 months and reduced rate of progression in the 1st year. However, on long term follow up no differences were identified in recurrence, progression, or cancer specific death when compared to a cohort who did not receive early repeat TURBT [14].

While repeat TURBT in patients with HG T1 disease remains the standard of care, in the setting of declining rates of upstaging and the presence of conflicting data in regard to efficacy of repeat TURBT, we set out to look at our institutional experience with this patient. Specifically, with the goal to evaluate rates of upstaging and presence of muscularis propria in initial specimens. In doing so, we also sought to identify potential effects of the quality of initial resections by means of comparing a patient population initially resected at outside practices to those patients initially resected at our institution.

Materials and Methods

After institutional review board approval, we performed a retrospective review of patients with HG T1 who underwent a repeat TURBT between June 2013 and March 2019**.** Patients with prior history of bladder cancer with or without intravesical therapy were eligible. The initial TURBT was performed at our institution or by referring providers. All repeat resections were performed at our

institution. The following variables were collected on each study subject: age, gender, interval between initial and repeat TURBT (days), history of bladder cancer, history or intravesical BCG, initial presence of muscularis propria, institution of initial resection (outside hospital vs. our institution), and pathologic stage at the time of repeat TURBT. In every case, pathologic specimens from the initial resection were reviewed by our institution's pathologists. In cases of discrepant pathologic staging between the referring center and our center, the pathologic stage of our review was considered correct and is presented. Comparisons were made to evaluate predictors of having muscularis propria in the initial TURBT and pathologic upstaging at repeat TURBT. Baseline demographics and clinical characteristics were examined using t-test and Wilcoxon rank-sum test for normally and non-normally distributed continuous variables respectively, chi-square test for categorical variables. The associations between the independent variables of interest and outcome (i.e. having muscularis propria in the initial TURBT and pathologic upstaging at 2nd TURBT) were assessed using univariate and multivariable logistic regression models. All significance tests were two-sided, with a p-value < 0.05 considered statistically significant. Statistical analyses were performed using Statistical Analysis Software (SAS) version 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

104 patients who underwent a repeat TURBT for HG T1 bladder cancer at our institution were identified. Patient demographics stratified based on the institution of initial TURBT, specifically to differentiate those patients who underwent initial TURBT at our institution verse the referred population who underwent TURBT in community practices or other institutions is presented in (Table 1). Significant differences were noted in gender and upstaging at repeat TURBT when comparing patients initially resected at our institution to the referred population. In the referred population 81% of the patients were male vs. 58% (p = 0.009) at our institution. The rate of upstaging to muscle invasive disease at 2nd TURBT was also significantly increased in the referred population, 26% versus 8% (0.016).

	All patients	Our Institution	Referred population	P value
Gender (% male)	70.19% (73/104)	58%	81%	0.009
Age (years)	69.5	69	70	0.64
Time between TURBTs Median, IQR, days)	Median 44 IQR 34-64	40.5 IQR 66-78	53.5 IQR 36-71	0.01
Muscularis Propria present in in initial resection (% yes)	38.83% (40/103)	36%	41.51%	0.57
History of Bladder cancer (% yes)	39.42% (41/104)	46%	33%	0.19
Upstaging at re TURBT (% yes)	17.31% (18/104)	8%	26%	0.016
History of BCG (% yes)	25% (36/104)	26%	24%	0.82
Residual Cancer on re TURBT (% no)	65.38% (68/104)	58%	72%	0.13

Table 1: Patient Demographics.

Multivariable analysis of predictors for presence of muscularis propria on initial TURBT identified gender as the only independent predictor of muscularis propria in the initial specimen, OR 3.76 (95% CI 1.31 – 10.8), in favor of muscle propria being present in males. Multivariable analysis of predictors of upstaging to muscle invasive disease identified independent predictors of pathologic upstaging were the institution of initial resection with increased rates of upstaging occurring in the referred patient population (OR 4.04, 95% CI 1.13 - 14.5) and decreased rates of upstaging when the initial specimen contained muscularis propria for pathologic review (OR 0.23, 95% CI 0.06 – 0.91). Down staging to T0 disease was noted in 35% (36/104) of patients overall, 41% (21/51) at our institution vs 28% (15/53) from outside practices (p = 0.17). Multivariable analysis of predictors of T0 disease failed to identify any significant associations with respect to patient, age, gender, time interval between initial and repeat resection, institution of initial resection, history of bladder cancer, history of BCG, or presence of muscularis propria in the initial resection. Multivariable analysis of all data presented in (Table 2).

	Odds Ratio (95% CI)		
	Muscularis Propria in Initial TURBT	**Upstaging to Muscle Invasive Disease**	**T0 Disease at Repeat TURBT**
Age	1.016 (0.974 – 1.060)	1.011 (0.956 – 1.069)	0.999 (0.959-1.040)
Gender	**3.763 (1.307 – 10.834)**	1.707 (0.443 - 6.582)	0.960 (0.371-2.482)
Time between TURBTs	1.009 (0.997 – 1.021)	1.001 (0.984 – 1.018)	1.001 (0.989-1.013)
Institution of initial TURBT	0.819 (0.339 – 1.975)	**4.041 (1.126 – 14.506)**	0.529 (0.222-1.262)
History of Bladder Cancer	0.430 (0.133 – 1.392)	1.620 (0.372 – 7.068)	0.741 (0.235-2.333)
History of BCG	1.241 (0.340 – 4.524)	0.989 (0.200 – 4.890)	0.998 (0.286-3.479)
Presence of Muscularis Propria in initial TURBT	N/A	**0.225 (0.056 – 0.913)**	0.842 (0.344-2.060)

Table 2: Multivariable Analysis of Predictors for Having Muscularis Propria in Initial TURBT, Upstaging to Muscle Invasive Disease and T0 disease on repeat TURBT

Discussion

The greatest benefit of repeat TURBT for HG T1 urothelial carcinoma of the bladder is identifying patients who were under staged at initial resection. Therefore, there is great value in identifying those variables which impact upstaging rates in this population. Given that our institution receives referrals from multiple outside providers, our dataset is unique in that 52% of the patients included in this study had their initial TURBT at an institution/community practice other than our own. Interestingly, when comparing those patients initially resected at our institution to the referred population, we found that those in the referred group were at increased risk of upstaging relative to those initially resected at our institution. Specifically, 26% of our referred patient population was upstaged to muscle invasive disease versus only 8% of those resected at our institution initially (p=0.02). On multivariate analysis this was associated with an OR of 4.04 (95% CI 1.13-14.5). However, this is not the first time such a difference has been suggested. A retrospective study at the Seoul National University Hospital found that patients with Ta and T1 bladder tumors being referred from other institutions had higher rates of residual tumor, overall upstaging, and upstaging to muscle invasive disease compared to patients undergoing initial TURBT at their center. Specifically, upstaging to muscle invasive disease in this study was noted in 20.4%

(11/69) of referred patients versus 3.2% (6/187) [15]. However, while these rates appeared to indicate a difference, on multivariate analysis they failed to find statistically significant differences between these two groups. Nevertheless, the study suggested that these differences were due to difference in the operator's experience and the initial stage of the two groups. We believe that while such an association may be accounted for by provider technique, there are several confounding variables that may influence this finding. First, in at least one case, a referred individual in our cohort who was upstaged to muscle invasive disease was in fact initially diagnosed with muscle invasive cancer by an outside pathologist. Only on reread of the slides sent to our institution's pathologist where they read as T1 thus allowing for inclusion in our study. Second, without procedural documentation of the initial TURBT for many of the referred patients in our cohort, it is difficult to know if they all received a complete resection initially. Finally, based upon the referral pattern to our institution, patients referred to us from the community may be inherently more complex than our local patients, thus presenting additional underlying unmeasured confounding variables. Given these limitations it is difficult to solely attribute this finding to operator technique, though it cannot be excluded as a potential factor. While the institution of initial resection may be a surrogate marker for operator experience/quality and thus have an independent and measurable impact on rates of upstaging, the presence of muscularis propria in the initial resection specimen was the strongest predictor of upstaging and perhaps also the most obvious. In our single institution retrospective cohort of 104 individuals, we found that patients initially diagnosed with HG T1 bladder cancer 17% were upstaged to muscle invasive disease. When stratified by presence of muscularis propria in the initial specimen, upstaging occurred in 8% (3/39) of patients who had muscularis propria in the initial specimen were upstaged compared to 23% (15/65) who did not (p=0.02). Furthermore, the presence of muscularis propria in the initial specimen predicted upstaging to muscle invasive disease on repeat resection. While this finding was not unsurprising and has been demonstrated in multiple prior studies, it is important to note that the overall rates of upstaging in the population are significantly lower than what has previously been reported. AUA guidelines note the rate of upstaging in this population is between 15-20% when muscularis propria is present and as high as 40-50% when muscularis propria is absent in initial TURBTs.[2] Further, it is important to note that while our observed rates of upstaging are much lower than what is traditionally reported, these findings are not in isolations. In 2015, a retrospective series out of Australia similarly reported rates of upstaging as low as 14.6% overall, with only 4.5% of patients upstaged when muscularis propria is present in the initial specimen and 25% when muscularis propria is absent in initial TURBT [12]. Given that contemporary rates of upstaging in this population seem to be on the decline, especially in those who have muscularis propria in their initial resection, the importance of capturing muscularis propria in the initial specimen is further underscored. Therefore, it was important for us to identify our own rates of muscularis propria capture in initial resection specimens and to identify those variables that impact this rate. We found that 39% of patients in our series had muscularis propria in their initial resection, with no significant difference when stratified by the institution of the initial resection (36% vs. 41.5% at our institution vs referred population, p = 0.56). The only independent predictor of presence of muscularis propria in our series was gender. Specially, we found males were significantly more likely to have muscle in their initial specimen (OR 3.76. 95% CI 1.31 – 10.8). Although, gender was not associated with pathologic upstaging or presence of residual cancer at the time of 2nd TURBT, perhaps due to collinearity on multivariable analysis. The finding that female gender was an independent predictor of absence of muscularis propria may be explained by virtue of the fact that that female bladder walls are generally thinner than those of males resulting in an unconscious bias to resect more conservatively. This is mainly driven by known increased rates of bladder perforation in women as a complication of TURBT. Specifically, these rates have been documented to be being 1.05-2.6% in males vs 2.7-7.2% in females [16-17]. Therefore, our findings of female gender predicting absence of muscularis propria are perhaps more indictive of operative bias for conservative resection in the female population. However, it is important to note that conflicting evidence exists to suggest that gender does not influence rates of muscularis propria capture in TURBTs, at least at some centers. There is limited data available investigating gender disparities in muscularis propria capture in TURBTs specifically. Of two series evaluating the impact of gender on the presence of muscularis propria in the resection specimen, both found no significant association with gender. One, which found rates of muscularis propria presence in their TURBTs over the course of 1 year and 332 resections to be 80% in both males and females [18]. Another, with 921 patients that had pTa , pT1, and pTis found on multivariate analysis that predictors for the presence of muscularis propria were age ≥65 years, pT1 tumors, grade 3 tumors, tumors ≥ 3cm in size, multifocality, and concomitant CIS but specifically not gender. Although in this study, their overall rates of muscularis propria capture across all their resections is 79% [19]. In these studies with high rates of muscularis propria capture overall, their lack of gender influence on rates of muscularis propria is perhaps due to more aggressive resections in general. Additionally, neither study reported their rates of bladder perforation. Finally, it is also important to note that in our study, while only 36% of participants initially resected at our institution had muscularis propria in their initial resections, a disproportionately high percent of our patients were female 42% when compared to the national incidence bladder cancer among women being 24% [20]. While our study offers good insight into potential variables that impact rates of upstaging in this population, our multivariate analysis of predictors of T0 disease failed to identify any significant associations with respect to patient, age, gender, time interval between initial and repeat resection, institution of initial resection, history of bladder cancer, history of BCG, or presence of muscularis propria in the initial resection. We recognize that our study has several limitations. Frist of which being it is retrospective in nature. Additionally, given the limited and variable information on those patients referred to us for their repeat TURBT, the circumstances surrounding their initial resection cannot be entirely known – including whether their initial resections were complete. Further, as a teaching institution, the resections were performed by a variety different faculty and residents which inevitably caused variability in depth and extent of resections.

Conclusion

Our contemporary series demonstrates the continued role of repeat TURBT for HG T1 bladder cancer. Upstaging to muscle invasive disease during repeat TURBT for high grade T1 bladder cancer may be less than previously reported but nevertheless remains prevalent. Specifically in those without muscularis propria in their initial resections, there is unquestionable value in the repeat TURBT. Further, the quality of the initial resection may also play a role in predicting rates of upstaging. These findings support the need for future efforts to improve

on the quality of initial TURBTs and to decrease gender disparities in bladder cancer care.

Author's Contribution

Massari M: Protocol/project development, data collection/management, data analysis, manuscript writing/editing.

O'Malley P: Data collection/management, manuscript writing/editing.

Bozorgmehri S: Data analysis.

Dennis M: Data collection/management.

Crispen PL: Protocol/project development, data collection/management, data analysis, manuscript writing/editing.

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Declaration

There were no funding sources for the research submitted in the manuscript. None of the authors have a conflict of interest with the submitted research. Raw, deidentified data is available on request by contacting corresponding author and has been submitted to the publishing journal. Statistical analyses were performed using Statistical Analysis Software (SAS) version 9.4. Author contributions are listed below. The University of Florida – Health Science Center Institutional Review Board approval was obtained prior to initiating the research and the research was completed in a manner complaint with our institutions regulations for research involving human subjects. The need informed consent was waived by our Institution Review Board for the current study based upon the nature of the research. All listed authors have reviewed the reviewed and read the submitted manuscript and are agreement with submission.

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