

Recurrence and upstaging rates of T1 high-grade urothelial carcinoma of the bladder on repeat resection in a Canadian, resource-limited, healthcare systemAdam Kinnaird¹; Peter Dromparis²; Howard Evans¹¹Division of Urology, Department of Surgery; ²Department of Pathology; University of Alberta, Edmonton, AB, Canada**Cite as:** *Can Urol Assoc J* 2018 April 6; Epub ahead of print.
<http://dx.doi.org/10.5489/cuaj.5039>**Published online April 6, 2018**

Abstract

Introduction: Non-muscle-invasive bladder cancer is the most expensive malignancy to treat. Current Canadian guidelines recommend repeat transurethral resection of bladder tumour (TURBT) within six weeks after initial resection of T1 high-grade (T1HG) urothelial carcinoma, prior to initiation of intravesical bacillus Calmette-Guerin treatment. This is a burden on operating room usage and adds further cost and risk of complications. Internationally, major cancer centres report significant rates of recurrence and upstaging on repeat resection, however minimal Canadian data is available. We aimed to determine the rate of recurrence and upstaging in a resource-limited, Canadian healthcare system.

Methods: A retrospective review of patients receiving TURBT between November 2009 and November 2014 was performed. Patients were included if they had all three of the following: a pathological diagnosis of T1HG, adequate muscularis propria present in the specimen, and a repeat resection.

Results: We reviewed 3166 patients who underwent TURBT and found 173 to meet our inclusion criteria. The overall recurrence and upstaging rates were 57.2% and 9.2%, respectively. Tumour recurrence and upstaging occurred more often in patients who had repeat resection after 12–24 weeks compared to those patients whose repeat resection occurred within 12 weeks.

Conclusions: Although recurrence rates are similar, we have found upstaging rates to be three- to four-fold lower than those previously reported. Despite this, one in 10 patients will be upstaged, justifying use of this resource within our

healthcare system. Finally, timely repeat resection, within 12 weeks, appears to be associated with preventing disease progression.

Introduction

Non-muscle-invasive bladder cancer (NMIBC) is the most expensive malignancy to treat, costing between \$65,000 and \$180,000 US per patient.^{1,2} Pathological stage T1 high grade (T1HG) urothelial cancer of the bladder accounts for 5-20% of NMIBC and is defined as invasion into the lamina propria without invasion into the muscularis propria.³

Current Canadian guidelines recommend repeat transurethral resection of bladder tumour (TURBT) at 4-6 weeks, prior to the initiation of intravesical Bacillus Calmette-Guerin (BCG).⁴ Repeat resection requires further operating room resources and adds further cost and risk of complications to the patient. This recommendation is based on data from major cancer centers in non-universal health care systems, which report rates of recurrence and upstaging on repeat TUR to be 45-76% and 29-40%, respectively.^{3,5,6} However, minimal Canadian data is available and these landmark studies were performed approximately two decades ago. Therefore, we aimed to determine the contemporary rate of recurrence and upstaging in a resource limited system in Canada.

Methods

We received Health Research Ethics Board approval (Study ID: Pro00049775) from the University of Alberta to perform a retrospective chart review of patients receiving TURBT between November 2009 and November 2014 at multiple centers within one health region. Patients were identified in our electronic medical record (EMR) using the three billing codes for TURBT (69.29a, 69.29b, and 69.29c). Fourteen of fifteen adult urologists in this health region use this EMR. All charts were reviewed by two of the authors (AK and PD).

Inclusion criteria

Patients were included if they had all three of the following: (1) a pathological diagnosis of T1 high grade urothelial carcinoma of the bladder on initial TURBT, (2) adequate muscularis propria present in the specimen, and (3) a second, repeat TURBT at one of 3 centers within the health region.

Exclusion criteria

Patients were excluded from our primary outcome if they received intravesical BCG prior to repeat resection, if pathology reports were inadequate or missing, or if the primary pathology was a variant histology (adenocarcinoma, squamous cell carcinoma or small cell carcinoma).

Statistical analysis

Fisher's exact test was used to compare stratification of categorical data. Patient groupings were stratified by: age (older than 65 vs. younger than 65) and time to repeat resection of less than 6 weeks (guideline recommended), or less than 12 weeks compared to 12-24 weeks. GraphPad Software was used for all statistical tests and a two-sided p-value of <0.05 was considered significant.

Results

We identified 3166 patients who underwent at least one TURBT between November 2009 and November 2014. 2321 (73.3%) had both resections during the study period and had adequate pathology reports. 216 of the 2321 (9.3%) were diagnosed with T1HG on initial TURBT. Of these, 173 patients (80.1%) met all inclusion criteria with 43 (19.9%) excluded due to lack of muscularis propria on initial resection (Figure 1).

The average age at time of initial resection was 71 years with the majority (87.9%) male gender. Median time between initial and repeat resection was 8.9 weeks and 76.3% of TURBTs were performed at a community hospital (Table 1).

T1HG was found to recur on repeat resection in 99 of 173 patients (57.2%). 16 of 173 patients (9.2%) were upstaged to muscle invasive disease on repeat resection (Table 2).

We stratified rates of recurrence and upstaging by time interval to repeat resection based on whether they received repeat resection within 6 weeks (i.e. following Canadian guidelines) or greater than 6 weeks. We identified that the recurrence rate is 54.5 vs. 58.1% ($p=0.73$) and the upstaging rate is 6.8 vs. 10.1% ($p=0.76$) for within 6 weeks and greater than 6 weeks repeat resection groups, respectively. Similarly, we performed an exploratory analysis of repeat resection before 12 weeks or 12-24 weeks after initial resection and found tumours to recur in 47.5 vs. 74.2% ($p<0.01$) and be upstaged in 6.8 vs. 22.9% ($p=0.01$), respectively (Figure 2). Stratifying by age, patients older than 65 had higher rates of recurrence (64.8 vs. 35.6%, $p<0.01$), although upstaging did not achieve statistical significance (11.7 vs. 2.2, $p=0.07$).

Discussion

In this study, we examined the rates of cancer recurrence and upstaging after repeat resection in patients with a diagnosis of T1HG disease, from multiple centers within a Canadian health region. We found 57.2% of patients have recurrence and 9.2% have tumour upstaging. While the recurrence rate is similar, the upstaging rate is 3-4 fold lower than those previously published.^{3,5,6} Noting that the impetus for this study was to determine if repeat resection could be

omitted in a Canadian setting (based on financial and resource constraint), we found that repeat TURBT alters patient management in only a minority of cases, while delaying intravesical BCG therapy in ~90%. However, as approximately 1 in 10 patients were upstaged to muscle invasive disease, which requires a completely different care pathway, we believe that this use of resources is justified in our healthcare system. This data, taken in the context that repeat resection may improve response to intravesical BCG in patients with high risk NMIBC further justifies its use.^{7,8}

Our health region has recently employed the use of a tracking program called Adult Coding Access Targets for Surgery (ACATS) in order to measure, manage and report surgical waiting times to improve efficiency and resource use in our system. ACATS does not list a time guideline for repeat resection, however it suggests a target of less than 4 weeks for TURBT. Interestingly, within our data set we had no tumour upstaging in the 9 patients who had repeat resection within 4 weeks, suggesting this may be a good cutoff to use, however this is a small sample size limiting conclusions. Similarly, while there did not appear to be a difference whether repeat resection occurred following the Canadian recommendation of within 6 weeks, there was a significant increase in tumour upstaging in patients who waited 12-24 weeks compared to those who had their repeat resection within 12 weeks (6.8 vs. 22.9%, $p=0.01$), perhaps supporting an upper cutoff of 12 weeks for repeat resection timing. Furthermore, patient stratification by age >65 identified a greater risk of tumour recurrence and a non-statistically significant ($p=0.07$) increase in upstaging. Thus, it appears subpopulations may be at higher risk from development of recurrence and upstaging as has been previously shown using an established risk calculator (based on clinical and pathologic data⁹), perhaps allowing for targeted patient selection to undergo repeat TURBT.

Although our study included more than 3000 patients, it was retrospective in nature and lacked centralized pathological review, limiting definitive conclusions. However, our data provide rationale for larger prospective studies to identify high-risk populations for upstaging with the aim to improve efficiency and reduce cost of NMIBC treatment.

Conclusions

Recurrence of T1HG urothelial cancer after TURBT is roughly 60%, with approximately 10% of patients being upstaged to muscle invasive disease, which was significantly higher with interval TURBT after 3 months. Our data suggest subpopulations are at higher risk of recurrence, providing rationale for the use of established risk calculators and larger prospective studies to identify these populations for targeted management to improve resource utilization in our currently constrained healthcare system.

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Figures and Tables

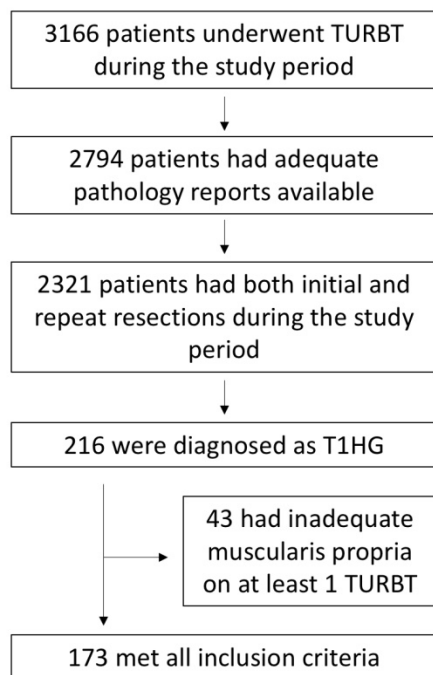
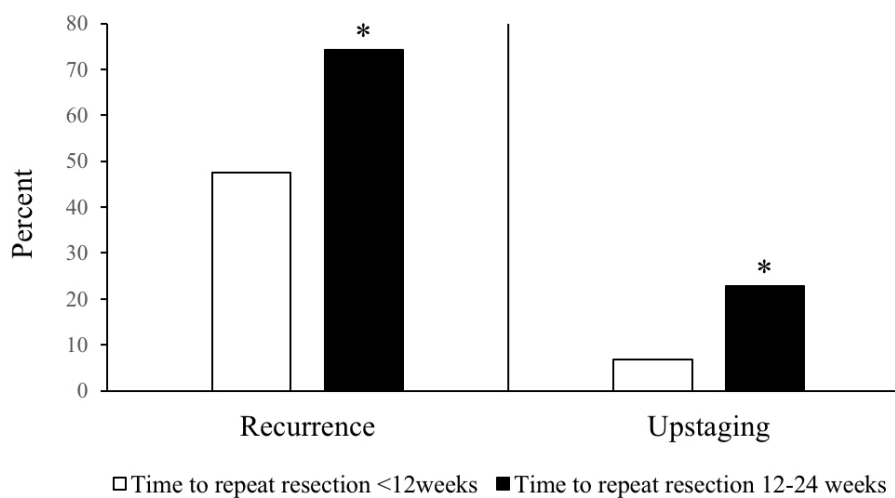
Fig. 1. Identification of patient population.**Fig. 2.** Tumour recurrence and upstaging stratified by time to repeat resection (* $p < 0.05$ vs. time to repeat resection < 12 weeks).

Table 1. Patient demographics	
Demographics	n=173
Average age at initial resection (years)	71.1 (SD 10.1)
Male gender	87.9%
Median time to repeat resection (weeks)	8.9 (IQR 6–14.9)
Hospital type:	76.3%
Community	23.7%
Tertiary care centre	

IQR: interquartile range; SD: standard deviation.

Table 2. Primary outcomes: Rates of tumour recurrence and upstaging	
Primary outcomes	n=173
tumour recurrence	99 (57.2%)
tumour upstaging	16 (9.2%)