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ARTICLE

Repeat transurethral resection is still an essential tool in treating non-muscle invasive bladder cancer: the Western Australian experience

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Abbreviations used: CIS, carcinoma *in situ*; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle invasive bladder cancer; TaHG, stage Ta and high-grade; TCC, transitional cell carcinoma; TUR, transurethral resection; TURBT, transurethral resection of bladder tumors; T1HG, stage T1 and high-grade; T1LG, stage T1 and low-grade

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ABSTRACT

OBJECTIVES: To determine the rate of residual disease and under-staging after primary transurethral resection (TUR) of bladder tumors (TURBT) in tertiary hospitals in Western Australia.

METHODS: A retrospective study was performed evaluating all patients with TaHG (stage Ta, high-grade), T1LG (stage T1, low-grade) or T1HG (stage T1, high-grade) bladder cancer on primary TURBT conducted between January 1, 2012 and December 31, 2017 at the four largest metropolitan public hospitals in Western Australia. Only patients who underwent repeat resection within 3 months from initial resection were included. Those with previous history of bladder cancer, incomplete follow-up data and visibly incomplete initial resection were excluded. Baseline patient demographics, macroscopic clearance at initial resection, and disease data at initial and repeat resections were recorded.

RESULTS: Sixty-seven patients with a median age of 71 years were included in this study. At initial resection, T1HG was the most common disease stage (64.2%) and detrusor muscle was present in 82.1% of initial resections. At repeat resection, 41.8% of cases had residual disease. The rate of upstaging to muscle-invasive bladder cancer was 3.0%. Patients treated by operators with five or less years of formal training did not have a significantly different rate of residual disease from patients treated by operators with more than five years of experience.

CONCLUSIONS: Repeat TUR should remain an essential practice due to high rates of residual disease and a small risk of tumor under-staging. The presence of detrusor muscle and macroscopic clearance should not be used as surrogates for adequacy of resection or consideration of avoiding a repeat TUR, even for TaHG disease.

Keywords: bladder detrusor muscle; cancer staging; residual cancer; TNM staging; urinary bladder neoplasms

INTRODUCTION

Bladder cancer is one of the top ten most common cancers and the second most common urological cancer in Australia. The estimated age-standardized incidence rate of bladder cancer in Australian men and women in 2017 were 16.7 and 4.5 per 100000 persons, respectively [1]. Globally, the age-standardized incidence rate for bladder cancer was 6.69 per 100000 persons in 2016 [2]. Bladder cancer is one of only two cancers in Australia with a decrease in the 5-year relative survival rate in the period of 2009 to 2013 (53%) as compared to 1984 to 1988 (67%) [1]. Accurate staging is essential to direct effective treatment in bladder transitional cell carcinoma (TCC) as muscle-invasive bladder cancer (MIBC) and non-muscle invasive bladder cancer (NMIBC) have significantly different treatment regimens and outcomes. Transurethral resection (TUR) of bladder tumor (TURBT) remains the gold standard for this purpose although significant reports of tumor under-staging have been described. In a systematic review of 24 studies encompassing 2417 patients, upstaging of stage T1 disease at initial TUR to T2 disease at repeat TUR ranged from 0% to 32% in individual studies, with a pooled prevalence rate of 8% [3]. In patients with extensive high-grade stage T1 disease, the rate of under-staging can be as high as 67.9% [4].

The primary objective of this study was to determine the rates of

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under-staging and residual disease following initial TURBT in tertiary hospitals in Western Australia. Correlations between detrusor sampling and operator experience were also assessed.

METHODS

A multi-institutional retrospective study was performed over six years at the four largest metropolitan public hospitals in Western Australia (Fiona Stanley Hospital, Royal Perth Hospital, Sir Charles Gairdner Hospital and Fremantle Hospital). The inclusion criteria were: (1) newly diagnosed pathological TaHG (stage Ta, high-grade), T1LG (stage T1, low-grade) or T1HG (stage T1, high-grade) (with or without carcinoma *in situ* [CIS]) bladder TCC; (2) initial TUR performed between January 1, 2012 and December 31, 2017; and (3) repeat TUR performed within 3 months from the initial resection. Patients were excluded if: (1) they had any history of urothelial cancer or intravesical therapy, (2) incomplete follow-up data (such as patients who passed away or migrated out-of-state after the initial TUR) or (3) visibly incomplete initial TUR. Baseline patient demographics, operator experience, surgery dates and disease data at initial and repeat resections were recorded. The Research Ethics and Governance committee of the relevant health services considered this study to be a low-risk project as it only involved data collection with no intervention and thus deemed that approval was not required.

For the purpose of this study, operator experience was defined according to a hierarchy of increasing experience in urology training in Australia, starting with service registrar (doctors in registrar-level positions but not in formal training), SET (Surgical Education and Training) years 1 to 6 (doctors in formal urology training), fellow (fellows of the Urology college in Australia or internationally but not working in a Consultant position) and finally, consultant (fellows of the Urological Society of Australia and New Zealand working in Consultant Urologist positions). If a case was performed by two operators (*e.g.*, started by a junior then taken over by a senior operator), the case was entered as performed by the more senior operators. Descriptive statistics were used to analyze the data.

RESULTS

There were 67 patients who met the criteria for inclusion in this study. The median age at the time of initial resection was 71 years. The median time between the initial and repeat TUR was 48 d. At initial resection, T1HG was the most common stage (64.2%), followed by TaHG (34.3%) and T1LG (1.5%). Concurrent CIS was present in 73.1% (49/67) of cases. Detrusor muscle was present at initial resection in 82.1% (55/67) of cases, and in 29.9% (20/67) of cases, the deep/muscle specimen was sent separately from the resected tumor for histological analysis. Of 67 patients, 26 (38.8%) had their repeat TUR within 6 weeks (median 34.5 d) with 41 patients (61.2%) having it beyond 6 weeks but within 3 months (median 59 d).

At repeat resection, residual disease was found in 41.8% (28/67) of cases. Of these, CIS was the most common disease stage found, followed by TaHG, TaLG, T1HG, TaHG plus CIS, and T2HG (MIBC) in descending order of frequencies (**Fig. 1**). Only two cases had upstaging to MIBC at repeat TUR, both of which had T1HG with detrusor muscle present at the initial resection. The rate of residual disease for cases with TaHG on initial TURBT was 39.1% (9/23). The rate of residual disease for cases where stage T1 (including low and high-grade TCC) disease was detected at initial TUR was 43.2% (19/44). When detrusor muscle was absent or present at initial TUR, the rate of residual disease was 41.7% (5/12) and 41.8% (23/55), respectively. Among patients with TaHG at initial TUR, the rate of residual disease when muscle was present was 35.3% (6/17) compared to 50% (3/6) when muscle was absent. When stage T1 disease and detrusor muscle were detected at initial TUR the rate of residual disease was 44.7% (17/38). In patients who had repeat TUR within 6 weeks *vs*. beyond 6 weeks, the rate of residual disease was 50.0% (13/26) and 36.6% (15/41), respectively. Low grade disease (TaLG) accounted for 7.7% (1/13) and 26.7% (4/15) of residual disease at repeat TUR within 6 weeks and beyond, respectively. Patients treated by fellows (33.3%, 3/9) and SET4 registrars (33.3%, 2/6) had the lowest rate of residual disease, followed by SET5 (35.0%, 7/20), SET3 (46.7%, 7/15), consultants (50.0%, 8/16), and service registrars (100.0%, 1/1) (**Fig. 2**).

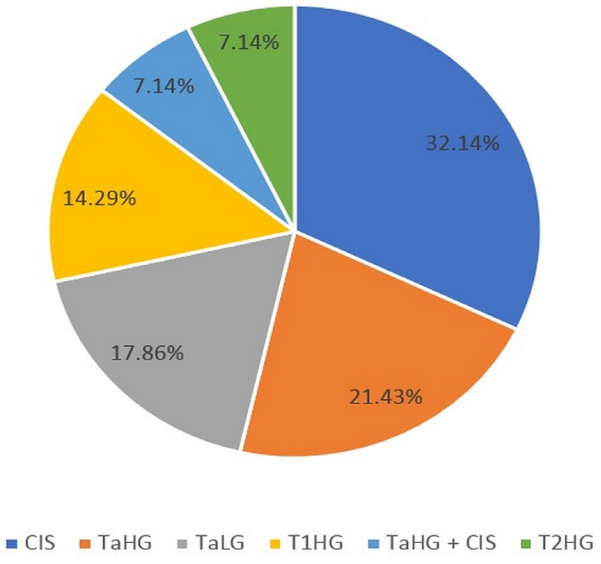

Figure 1. Stage and grade of residual disease at repeat resection (*n* = 28).

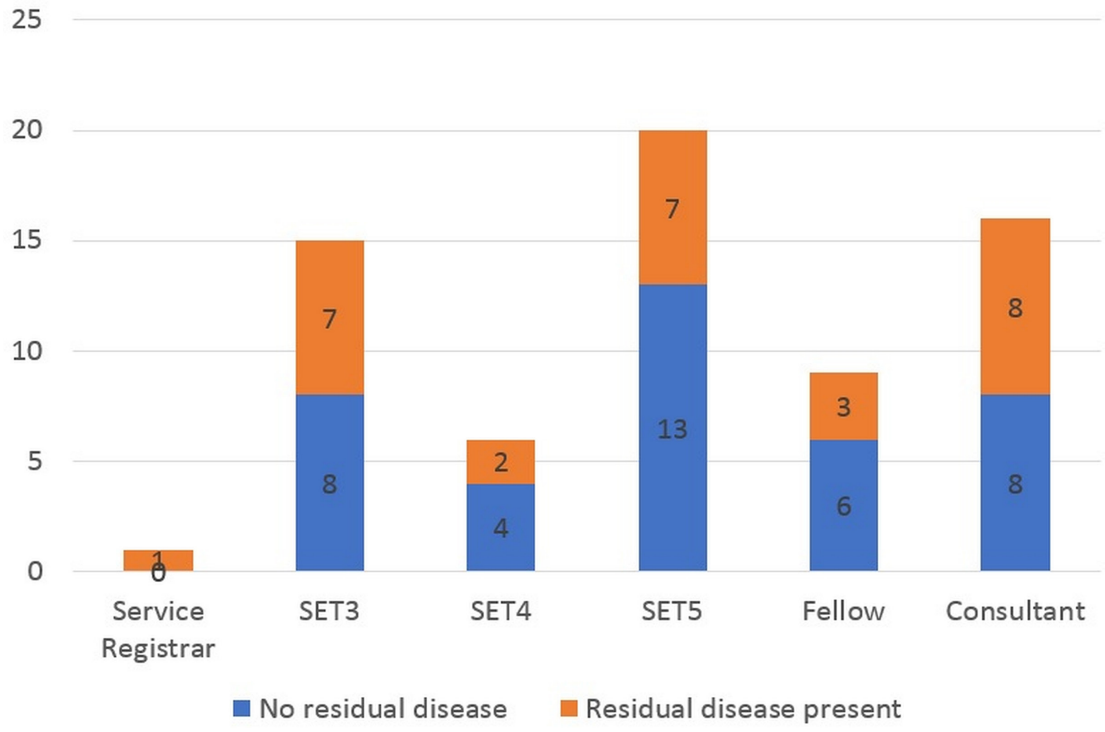

Figure 2. Incidence of residual disease by operators of different experience levels.

DISCUSSION

The role for a repeat resection after TURBT was based on studies demonstrating that upstaging from stage T1 to stage T2 disease ranged from 0% to 32% of patients, with a pooled prevalence rate of 8% [3]. In prospective studies, the rate of upstaging to stage T2 disease at second TUR ranged from 3.8% to 17.6% [5-7], but if stage T1 disease was detected at initial TUR, the rate of upstaging to stage T2 disease at repeat TUR ranged from 26.2% to 30% [7,8]. In patients with extensive high-grade stage T1 disease, the rate of under-staging can be as high as 67.9% [4]. In a recent meta-analysis, the pooled prevalence rate of upstaging to stage T2 disease at repeat TUR was 11% (95% CI 0.06–0.18) [9]. In the subgroup with muscle detected at initial TUR, the pooled prevalence rate of upstaging to stage T2 disease at repeat TUR was 10% (95% CI 0.06–0.14) [9]. In comparison, our study demonstrated a low rate of upstaging to stage T2 disease (3.0%) at repeat TUR but a significant rate of residual disease (41.8%). Our study found that the rate of residual disease was only slightly higher if stage T1 disease (including low and high-grade TCC) was detected at initial TUR as compared with TaHG TCC (43.2% *vs*. 39.1%). This finding was similar to that found on a recent systematic review where the pooled prevalence rates of residual tumor at repeat TUR for stage Ta and T1 tumors were 55% (range 17% to 67%) and 51% (range 20% to 71%), respectively [3]. In the subgroup where detrusor muscle was detected at initial TUR for all patients, those with stage T1 disease again had higher rate of residual disease than those with TaHG TCC detected (44.7% *vs*. 35.3%).

In our study, detecting detrusor muscle in the initial TUR did not lead to statistically significant difference in risk of residual disease on repeat resection (41.7% *vs*. 41.8%). In TaHG disease, the rate of residual disease was lower (35.3%) when detrusor muscle was present than in cases where it was absent (50.0%), but it still affected more than one in three cases. In a multi-center study of more than 2000 patients, the absence of detrusor muscle at initial TUR led to a higher rate of residual disease at repeat TUR than if detrusor muscle was initially present (85.9% *vs*. 65.2%) [10]. This study and our results reflected that the presence of detrusor muscle was not an indicator of resection completeness due to high residual disease rates and repeat TUR should still be performed.

Our study also did not demonstrate a significant association between years of experience and the quality of initial TUR as the rates of residual disease did not necessarily trend downwards with increased experience. If a junior subgroup consisted of operators with five or less years of training each, the rate of residual disease was 40.5% (17/42) for junior operators and 44.0% (11/25) for senior operators in our study. This may possibly reflect the complexity of cases.

An interesting finding in this study was that more than 60% of patients had the repeat TUR performed after six weeks. It is local practice to aim for repeat TUR within 6 weeks but due to the limitation of resources in reality it leaned towards a timeframe of within 2–3 months. In our cohort, the rate of residual disease was higher if repeat TUR was performed within 6 weeks than after (50.0% *vs*. 36.6%). A possible explanation is that cases with visibly higher stage or grade disease may have prompted the primary operators to push for early repeat TUR within 6 weeks. This is supported by our other finding that nearly all (92.3%) residual disease detected at repeat TUR within 6 weeks were high grade disease, whereas low grade disease was detected in 26.7% of repeat TUR beyond 6 weeks. This increase in low grade disease at repeat TUR performed beyond 6 weeks could also represent early recurrence as opposed to true residual disease.

Our study reinforces the importance of a repeat resection after any

high-grade disease or stage T1 urothelial cancer. Upstaging is very low (and significantly lower than historical reports) with a good TUR but residual disease is present in higher than anticipated rates despite macroscopic clearance. While our study did not have the numbers to look at long term outcomes, others have shown that repeat TUR led to lower disease recurrence rates at 3 months (9.6% *vs*. 43.3%) [11], 12 months (28.3% *vs*. 58.2%) [11] and 5 years (39.8% *vs*. 71.4%) [6]. Repeating TUR also led to longer recurrence-free survival periods (47 months *vs*. 12 months) [6] and lower rates of disease progression (7% *vs*. 34%) within 3 years [12] than not repeating TUR.

In conclusion, repeat TUR should remain an essential practice due to high rates of residual disease and a small risk of tumor under-staging. The presence of detrusor muscle and macroscopic clearance should not be used as surrogates for adequacy of resection or consideration of avoiding a repeat TUR, even for TaHG disease.

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