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Frequency and predictors of recurrence of bladder tumour on first check cystoscopy - a tertiary care hospital experience

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UROLOGY

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Frequency and predictors of recurrence of bladder tumour on first check cystoscopy — a tertiary care hospital experience

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Abstract

Objective: To determine the frequency and predictors of non-muscle invasive bladder tumour recurrence on first-check cystoscopy after transurethral resection of bladder tumour.

Methods: This cross-sectional study was conducted at the Aga Khan University Hospital, Karachi, from April to November 2014, and comprised patients with a suspected newly-diagnosed urothelial cancer. Patients with non-muscle invasive disease with complete resection of all visible lesions along with deep biopsy from the tumour base were included. Patients received standard adjuvant intravesical therapy according to their risk stratification and underwent a white-light check cystoscopy at 3 months to look for tumour recurrence. Association between clinico-pathological variables and recurrence at first cystoscopy was determined. SPSS 20 was used for data analysis.

Results: The mean age of 84 patients at presentation was 63.3±12.5 years (range: 36-89 years). There were 75(89%) men and 9(11%) women. On initial transurethral resection, the size of tumour was less than 3cm in 32(38%) participants and equal to or above 3cm in 52(62%). Single tumour was found in 51(61%) subjects and multiple tumours in 33(39%). None of the resected tumours was primary carcinoma in situ and 35(42%) tumours were of high grade. The overall recurrence rate at first cystoscopy was 28(33.3%). Larger tumour, higher grade and tumour multifocality were factors associated with recurrence at check cystoscopy ($p<0.05$ each). Patients' age, gender, smoking status and tumour stage did not correlate with early recurrence ($p>0.05$ each).

Conclusion: The number, size and grade of the tumour strongly correlated with recurrence at check cystoscopy.

Keywords: Non-muscle invasive bladder cancer, Recurrence, Check cystoscopy, Predictors. (JPMA 66: S-125; 2016)

Introduction

Bladder cancer (BC) is the second most common genitourinary tract malignancy worldwide, with approximately 386,300 new cases and 150,200 deaths annually.[1] Approximately 75% of BCs are non-muscle invasive (NMIBC) at the time of diagnosis with 70% presenting as non-invasive papillary carcinoma (pTa), 20% as tumour invading lamina propria (pT1) and 10% as carcinoma in situ (CIS) lesion.[2] The main problem for pTa NMIBC is recurrence (seen in up to 80% of patients) and for pT1 disease and CIS, the main threat is progression (up to 45%).[3] Transurethral resection of bladder tumour (TURBT) under white-light cystoscopy followed by intravesical instillation of mitomycin C (MMC) is the standard of care for new NMIB tumours. The aim of TUBRT is two-fold, i.e. to clear all macroscopic disease and to establish the type of tumour and accurate pathologic stage.[4]

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Initial check cystoscopy should be done at 3 months after the transurethral resection (TUR) in every patient and subsequently a risk-stratified approach should be adopted for the frequency of follow-up based on risk of recurrence and progression. The overall recurrence rate following TUR is as high as 70%[5] with the greatest risk at the first (check) cystoscopy traditionally done 3 months following TUR.

Due to marked tendency to recur and progress, urothelial cancer (UC) poses significant diagnostic, prognostic and therapeutic challenges. The accurate prediction of which patients are going to recur or progress remains a challenging task. The current study was planned to determine the rate and predictors of recurrence in NMIBC on first check cystoscopy.

Patients and Methods

This cross-sectional study was conducted at the Aga Khan University Hospital (AKUH), Karachi, from April to November 2014, and comprised all patients >16 years of age with a suspected newly-diagnosed UC. Patients with recurrent disease, incomplete resection, absence of

detrusor muscle from the specimen, primary/ concomitant CIS, prior / synchronous UC of upper urinary tract, non-transitional cell tumour or muscle invasive disease were excluded.

Approval for the study was obtained from the institutional ethics review committee. Patient evaluation was done with clinical history and physical examination along with urinalysis and cytology and ultrasound of abdomen and pelvis. Under general or regional anaesthesia a white-light cystoscopy was done using 22 Fr. Karl Storz cystoscopic sheath with 30° lens and TURBT was performed with 26 Fr. continuous flow resectoscope sheaths. Complete resection of all visible lesions of bladder (either en bloc/ in toto for small lesions or piecemeal for larger ones) including a deep biopsy from the tumour base was done. We did not take routine random biopsies from normal looking mucosa. All patients received single intravesical instillation of 40mg of MMC in recovery room within 2 hours. A bladder diagram was drawn, documenting the site of tumour.

Only patients with complete resection by experienced operating surgeon using white-light cystoscopy and standard resection equipment and histologically proven new NMIBC were included. The pathological grade was classified according to 2004 classification of the World Health Organisation (WHO)/International Society of Urologic Pathology (ISUP),[6] and tumour was staged according to the 2009 Tumour node metastasis (TNM) classification system.[7]

Patients received standard intravesical therapy according to risk stratification by European Association of Urology (EAU) guidelines.[8] All patients had their first follow-up white light (check) cystoscopy under general anaesthesia at 3 months. We collected the clinical and pathological data including age, gender, smoking status, tumour characteristics (i.e. size, site, multiplicity, appearance), T category (Ta/ T1), tumour grade, completeness of resection, presence or absence of bladder perforation, post-operative use of intravesical therapy and similar findings at subsequent follow-up (check) cystoscopy.

A recurrence was defined as the presence of a bladder tumour detected on first follow-up cystoscopy after initial TUR, which was confirmed histologically. Data was analysed on SPSS 20. For numerical variables, mean ± standard deviation (SD) were calculated, and for categorical variables, frequency and percentages were recorded. Student's t-test and chi-square test were applied to determine significance. Due to the small sample size, univariate and multivariate logistic regression analyses with forward progression were done to determine the association between clinico-pathological variables and recurrence at first cystoscopy. The Hosmer-Lemeshow goodness-of-fit test was used to assess the multivariate logistic regression model fit. $P<0.05$ was considered statistically significant.

Results

Of the 129 patients, 84(65.1%) met the inclusion criteria and were included. Of the 45(34.9%) excluded, 11(24.4%) had muscle invasive disease, 17(37.8%) had incomplete resection or biopsy only, 1(2.2%) patient had squamous cell carcinoma (SCC) and 1(2.2%) had adenocarcinoma, 3(6.7%) patients missed follow-up at check cystoscopy, and 12(26.7%) patients showed progression in stage (Ta-T1 or T1-T2) or in grade (low-high). Of the participating subjects, 75(89%) were male and 9(11%) were female. The mean age at presentation was 63.3±12.5 years (range: 36-89 years). Besides, 31(37%) subjects were >60 years while 53(63%) were equal to or aged below 60 years. Moreover, 44(52%) participants were smokers. Tumour size on initial resection was less than 3cm in 32(38%) participants and equal to or above 3cm in 52(62%). Multiple tumours were seen in 33(39%) patients. The grade of tumours at initial resection was low in 49(58%) and high in 35(42%) (Table-1).

The overall recurrence at first (check) cystoscopy was seen in 28(33.3%) patients. Uni-variate analysis identified higher tumour grade (p=0.01), size >3 cm (p=0.01) and

Table-1: Patients and tumour characteristics.

Variables	All patients N (%)	Recurrence N (%)
Gender		
Male	75 (89%)	24/75 (32%)
Female	9 (11%)	4/9 (44%)
Age groups		
<60 yrs	31 (37%)	12/31 (39 %)
>60 yrs	53 (63%)	16/53 (30%)
Smoker		
Yes	44 (52%)	18/44 (41%)
No	40 (48%)	10/40 (25%)
Tumour size on initial resection (TUR)		
<3 cms	32 (38%)	4/32 (12.5%)
>3 cms	52 (62%)	24/52 (46%)
Stage at initial resection (TUR)		
pTa	43 (51%)	12/43 (28 %)
pT1	41 (49%)	16/41 (39%)
Number of tumours at initial resection (TUR)		
Single	51 (61%)	10/51 (20%)
>2	33 (39%)	18/33 (54.5%)
Grade of tumours at initial resection (TUR)		
Low grade	49 (58%)	10/49 (20%)
High grade	35 (42%)	18/35 (51%)

TUR: Transurethral resection.

Table-2: Univariate and Multivariate logistic regression analysis of variables' association with recurrence at first (check) cystoscopy.

Variables	Check cystoscopy n	Recurrence frequency n (%)	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)
Age				
<60	31	12 (38.7%)		
≥60	53	16 (30.2%)	0.68 (0.27-1.73)	
p-value		0.42		
Gender				
Male	75	24 (32%)		
Female	9	04 (44.4%)	1.70 (0.42-6.90)	
p-value		0.46		
Smoker				
Yes	44	18 (41%)		
No	40	10 (25%)	2.07 (0.81-5.28)	
p-value		0.12		
Stage				
Ta	43	12 (28%)		
T1	41	16 (39%)	1.65 (0.66-4.13)	
p-value		0.28		
Grade				
Low	49	10 (20.4%)		
High	35	18 (51.4%)	4.13 (1.58-10.78)	3.40 (1.19 - 9.78)
p-value		0.01	0.02	
Number of tumours at TURBT				
Single	51	10 (19.6%)		
≥ 2	33	18 (54.5%)	4.92 (1.86-13.02)	3.42 (1.19 - 9.84)
p-value		0.01	0.02	
Size of tumours at TURBT				
< 3cm	32	4 (12.5%)		
≥ 3cm	52	24 (46.2%)	6.0 (1.84-19.54)	4.5 (1.26-16.0)
p-value		0.01	0.02	

OR: Odds ratio.
CI: Confidence interval.
TURBT: Transurethral resection of bladder tumour.

multi-focality (p=0.01) as predicting factors for recurrence at first cystoscopy. Other factors i.e. age, gender and tumour stage were also evaluated, but none was found to correlate significantly with tumour recurrence (p>0.05). Smoking was not found to be a significant factor for recurrence either (p>0.05). Multivariate analysis showed that larger tumours (>3cm) had 4.5 greater odds of recurrence compared to smaller tumours, and higher grade tumours and multi-focal tumours had 3.4 greater odds each of recurrence compared to low-grade and single tumour at check cystoscopy (Table-2).

Discussion

Bladder carcinoma is the most common malignancy of the urinary tract. In the south Asia, the reported rate of bladder cancer is estimated to be about 2.1 per 100,000 populations.[9] Pakistan has the highest incidence of bladder cancer among the south Asian countries likely attributed to high tobacco use.[10] It is the 4th most common malignant tumour in males, accounting for 5.6 % of all reported cancers in Pakistan with an age-standardised rate (ASR) of 8.9 per 100,000 individuals.[10]

Recurrence in UC is defined as the re-appearance of tumour after complete resection, which could be due to "field effect" or "re-implantation". Literature suggests that 50-70% NMIBC have recurrence within 5 years and 5-20% progress to invasive carcinoma.[11] Tumour recurrence could be due to incomplete resection, persistence, re-growth of residual tumour or new occurrence due to growth of microscopic lesion or implantation and growth of tumour cells at the time of TUR. Due to its prognostic value, after a complete TUR, the first follow-up cystoscopy is of utmost importance in NMIBC. EAU guidelines recommend 3 months as the optimal time for first follow-up cystoscopy. The rate of recurrence on first cystoscopy also depends upon completeness of initial TUR, skills and experience of surgeon and intravesical treatment.[12] The

presence of detrusor muscle is considered a surrogate marker for the quality of resection.[13] The reported frequency of absence of deep muscle biopsy is ranging from 30-50%[14] with higher risk of residual disease especially in pT1 tumour and up to 40% tumour upstaging to pT2.[15]

We excluded all the patients who did not receive any adjuvant treatment due to bleeding or suspected bladder perforation or when the resection was incomplete or in whom deep muscle biopsy was not present in the specimen. Surgeons having more than 15 years of experience performed all the surgeries.

Mariappan et al.[16] have shown that experienced surgeons are more likely to resect detrusor muscle with a lower risk of early recurrence and absence of detrusor muscle on biopsy independently predicts a higher risk of early recurrence. The quality of TUR (which is mostly subjective) can be measured by determining complete resection, presence of detrusor muscle and recurrence at the resection site. Herr et al. in a retrospective study found residual disease in 31.6% of Ta/Tis tumours and 51.7% of T1 tumours.[17]

In a combined analysis of seven European organisations for research and treatment of cancer (EORTC) randomised trials (without re-TUR), the early tumour recurrence was observed in 13.1% (6.7-40%).[18] This wide variability in the recurrence rate at first follow-up (check) cystoscopy shows that there is a significant difference in the quality of treatment between different institutions. A positive recurrence at the time of check cystoscopy significantly affects the recurrence and progression free survival.[19] In newly diagnosed pTa grade-1 and grade-2 patients, Fitzpatrick et al. found that patients free of tumour at 3 months had an 80% chance of having no further recurrences.[20]

Near 50% of our patients had higher stage (pT1) disease and 42% had a high-grade disease thus reflecting a higher chance of recurrence. All the check cystoscopies were done under general anaesthesia with biopsies taken via a larger cold cup biopsy forceps to allow a more accurate diagnosis. A flexible cystoscopy under local anaesthesia might miss small lesions or surface changes.

An inappropriate procedure can lead to early recurrence and inaccurate staging of disease and, therefore, recurrence rate at first follow-up (check) cystoscopy is a strong predictor of subsequent recurrence[21] and possibly progression to higher grade/ stage disease.[22]

In a conventional white-light cystoscopy, which is considered as the gold standard, resections are not "radical" despite complete removal of all lesions and up to 30-50% of cases can have residual tumour. Various strategies have been evaluated to improve the tumour visualisation such as photodynamic diagnosis (PDD)-assisted cystoscopy and narrow band imaging (NBI), both of which have better sensitivity than white-light cystoscopy for detecting bladder cancer, particularly the smaller papillary and flat lesions.

They can be adapted at the time of initial TURBT and subsequent cystoscopy. In a randomised phase-3 trial, Stenzl et al.[23] showed that PDD not only improves the detection of both papillary bladder cancer and CIS, it also significantly prolongs time to recurrence and randomised trials with long-term follow-up have shown that this benefit is also translated in terms of improved bladder preservation. Long-term follow-up studies have shown 6.8 months longer median time to recurrence with PDD compared to white-light cystoscopy with 6% lower recurrence rate.[24] Similarly, NBI-assisted cystoscopy or resection is associated with fewer recurrences and longer recurrence-free survival compared to white-light cystoscopy.[25]

Despite controlling the predictors such as tumour size and number, grade and stage, in a review of seven randomised controlled trials of EORTC, Brausi et al.[18] detected significant variation in recurrence among different institutes on first cystoscopy and concluded that this discrepancy is the result of variability of quality of resections. He attributed most of these recurrences likely to be residual disease rather than the real recurrences.

In a previous study, we determined the recurrence and progression at one year in 92 NMIBC patients who underwent TURBT and compared their results with calculated risk according to EORTC risk table.[26] Forty four per cent of patients had tumours larger than 3cm, 38% had multiple lesions and 8.7% had high-grade disease. At one-year follow-up, the recurrence rate was 37% with significant concordance with EORTC prediction. As compared to that study, a significantly higher proportion of patients had high-grade disease in the current study.

We did not look at the cost analysis in our patients. The cost associated with NMIBC is, however, substantially higher compared to advanced disease due to very high recurrence rate, intensive surveillance strategies and expensive treatment.[27]

EAU guidelines state that the goal of TUR is to make a correct diagnosis and to remove all visual lesions. Different techniques have also been introduced in this regard including modification of resectoscope loop, laser

techniques, water jet-based enucleation and "en-bloc" resection to completely remove the tumour without any incision and scattering hypothesising that this "no touch" technique should improve the resection and recurrence rate.[28]

Holmang et al.[29] studied the relationship of first cystoscopy findings with recurrence and progression rates in large population based series of patients with bladder cancer who were followed up for at least 5 years and found that negative first cystoscopy findings were associated with significantly decreased recurrence and progression for all grades and stage Ta and T1 tumours.

Sylvester et al.[19] in their meta-analysis found overall progression of disease in 25.6% of patients with positive cystoscopy (recurrence) at 3 months compared to only 8.7% progression in patients with negative 3 months cystoscopy. This confers that the findings of check cystoscopy are a significant prognostic factor on time to progression of disease.

Our study is a prospective one, which is the strength as various biases like cystoscopy findings, and pre-operative variables are avoided which could be a problem in a retrospective study. One of the major limitations of our study is the small number of patients and that the resection was deemed complete on a subjective assessment by the operating surgeon on white-light cystoscopy. However, as a quality measure, we excluded all those patients in whom the detrusor muscle was absent in the first specimen and considered it to be a low-quality initial TUR who subsequently underwent a re-TUR in 2-6 weeks' time.

Since none of the cases in our series had any residual or overlooked macroscopic tumour, we assume that the recurrence is mainly due to tumour cell implantation or due to aggressive biology of the disease. In view of excluding the findings, we presume that the factors, which predict the recurrence at first cystoscopy in NMIBC, are tumour grade, multifocality and the size of tumour along with aggressive tumour biology.

Bladder cancer is a significant health problem for Pakistan. There is paucity of data on NMIBC with poor insight regarding the rate of recurrence and progression. In order to establish a better level of evidence, we recommend a collaborative multi-institutional prospective study in the future.

Conclusion

A recurrence rate of 33% was found at first check cystoscopy for NMIBC. The number, size and grade of the tumour strongly correlated with recurrence at check cystoscopy. Patients with these tumour characteristics should be warned of higher probability of recurrence and possibly progression in the surveillance period.

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