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Clinicopathologic Prognostic Factors in NMIBC for Recurrence & Progression

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Authors' contributions

This work was carried out in collaboration among all authors. Authors PG and VSP designed the study. Authors PG and SD wrote the protocol. Author PG performed the statistical analysis, and wrote the first draft of the manuscript. Authors RS and RSK managed the analyses of the study. Authors SD and RSK managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Transitional cell carcinoma (TCC) accounts for more than 90% of all the bladder cancers out of which 70% are non-muscle invasive bladder cancer (NMIBC) at diagnosis. The high rate of recurrence and progression following transurethral bladder resection of tumor makes the follow up essential as well as crucial in detecting early recurrence of tumor. In our study, we investigated the predictive value of various factors for recurrence and disease progression which could help in identifying patients for early definitive treatment.
Objectives: To determine the predictive factors of recurrence and progression of NMIBC managed in a single centre.
Methods: Retrospective study of 256 patients of NMIBC after TURBT was done to review the factors related with recurrence and progression. Bivariable analysis (Chi square test &Mann U Whitney test) and multivariable binary logistic regression were used to identify predictors of recurrence and progression.

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Results: On multivariate analysis, patients with tumor-size >3 cm and multiple tumors were found to have 1.7 times and 3 times greater odd of recurrence respectively as compared to patients with tumor size < 3cm and single tumor. Patients diagnosed with T1 stage and multiple lesions were found to have 1.9 times and 1.8 times greater odds of progression respectively as compared to patients with Ta stage and single lesion. With regard to quantitative factors, none of them were significantly associated for prediction for recurrence and progression.
Conclusion: Multiple tumors had increased risk for the development of both recurrence and disease progression. Size of tumor >3 cm is a risk factor for the development of recurrence and T1 stage was found to be a risk-factor for progression of the disease.

Keywords: Bladder; cancer; recurrence; progression; smoking.

ABBREVIATIONS

NMIBC : Non muscle invasive bladder cancer;
Hb : Hemoglobin;
NLR : Neutrophil lymphocyte ratio;
PLR : Platelet lymphocyte ratio.

1. INTRODUCTION

"Bladder cancer is the second most common malignancy of the genitourinary tract" [1]. "In India, according to the recent reports of the National Cancer Registry Programme, the overall incidence rate of urinary bladder cancer is 2.25 per 100,000 annually; 3.67% among males and 0.83% for females". [2]. "The incidence of bladder cancer rises with age, peaking between age 50 and 70 years, and is three times more common in men than in women" [3]. "Commonly accepted risk factors for bladder cancer include cigarette smoking, occupational exposure to aniline dyes, benzidene compounds, analgesic abuse (phenacetin) and chronic irritation, such as indwelling catheters" [4].

"Approximately 75% of patients with bladder cancer have non muscle invasive bladder cancer (NMIBC) which is confined to either the mucosa [pTa, carcinoma insitu (CIS)] or the submucosa (pT1)" [5]. "The tumors of NMIBC are routinely treated by transurethral resection (TUR) and/or intravesical instillation of mitomycin or Bacillus Calmette Guerin (BCG). However, the prognosis of NMIBC is not satisfactory, as the 5-year recurrence rate for NMIBC was reported to have ranged from 31% to 78% and the progression rate from NMIBC to muscle invasive bladder cancer (MIBC) had ranged from 0.8% to 45%" [6].

The recognition of prognostic factors associated with the recurrence and progression of NMIBC is crucial for patient counseling and clinical decision making related to adjuvant therapy. In this study, we aimed to confirm the prognostic factors which are significantly associated with recurrence and progression of the tumor4 after TURBT in a Tertiary care center patients with NMIBC. We included inflammatory markers to assess the prognostic significance along with pathological markers. Even though in previous studies the results of inflammatory markers were controversial, its significance is yet to be proven.

1.1 Aim

The aim of the study was to analyze the predictive factors of recurrence and progression of NMIBC.

2. MATERIALS AND METHODS

A retrospective study was undertaken on 322 patients who were initially diagnosed as NMIBC after they had undergone transurethral resection of bladder tumor (TURBT) between January 2012 and June 2016 at the Department of Urology, Government Medical College, Trivandrum. Complete transurethral resection of bladder tumor of all visible tumors were carried out in all patients, and the stage and grade of the tumors were determined. All the patients were evaluated on entry and at follow-up intervals. The list of patients were collected from the medical records database which is maintained prospectively by a Urology resident. Study predictors included were Age, Sex, Smoking & alcohol history, T1 grade, size, multiplicity, macroscopic appearance of the tumor, Hemoglobin (HB), Serum albumin, NLR, PLR. Total of 259 patients were included after excluding 63 patients from the study. We excluded patients diagnosed as having T2 (muscle invasive tumor) on second TURBT (n=11), without a minimum period of 6 months of follow-up (n = 22), those patients who were lost to follow-up (n = 24), patients without complete blood parameters (NLR, PLR, ESR, Serum Albumin) (n = 6).

Study end points that were determined were Recurrence and Progression of tumor. Recurrence was defined as first pathologically confirmed tumor relapse in the bladder regardless of the tumor stage and progression was defined as increase in T stage from Ta to T1, development of T2 or greater than T2, increase from low grade to high grade. (IBCG2016) [1].

2.1 Procedure

After confirmation of a bladder tumor either by ultrasonography or office cystoscopy, all patients were initially treated with TURBT. Pre-operatively, blood parameters &urine culture of all patients were checked and they were treated accordingly in order to prevent septic complications. The procedures were performed under spinal anesthesia. Resections were done using 26 Fr resectoscope. Tumors were resected entirely and sent for pathological examination along with another separate specimen obtained from deeper tissue. The pathological specimens were evaluated by a single genitourinary pathologist. Tumors were graded as G1, G2 or G3 according to the 1973 WHO system and as low-grade Urothelial cancer (LGUC) and high grade HGUC according to the 2004 WHO system and staged to the 2009 TNM classification of urinary bladder cancer. Primary PUNLMP were excluded from this study. A second TURBT was performed after incomplete or insufficient initial TURBT and in patients with T1 tumor. Patients were categorized according to EORTC risk tables and adjuvant treatment were administered according to indications. Patients were followed with regular cystoscopy at 3 months in first 2 years and then subsequently at 6 monthly intervals. Annual radiology abdomen imaging was performed in high-risk groups.

2.2 Statistical Analysis

Study analysis were done with Univariate analysis and multivariate Cox regression to identify predictors of recurrence and progression. Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version 19. Descriptive analysis of patient, tumor characteristics were done. Chi-square test and Mann Whitney U test was used to determine significance of prognostic markers. A p-value of less than 0.05 was considered as significant. Multivariable logistic regression analysis with forward progression was done to determine the association of prognostic factors with recurrence and progression.

3. RESULTS

The mean age of the patients was 63.41±9.81 (26-88). During follow-up of 259 patients, 43.6% (113) outcome were negative (neither recurred nor progressed) at the time of last follow-up. 97(37.45%) had a recurrence and 49(18.92%) progressed to muscle-invasive disease. Other patients and tumor characteristics are presented in Table 1.

Table 1. Patient and tumor characteristics

Patient characteristics	
Age , mean, range	63.41±9.81 (26-88)
Gender	
Male	227(87.6%)
Female	32 (12.4%)
Smoker n%	154(59.5%)
Alcoholic n%	68(26.3%)
Tumor characteristics	
Size	
< 3 cm	142(54.8%)
>3 cm	117(45.2%)
Number	
Single	177(68.3%)
multiple	82(31.7%)
Type	
Papillary	214(82.6%)
Solid	45(17.4%)
Response to therapy	
Recurrence %	97(37.45%)
Progression %	49(18.92%)
Time to recurrence, months	23.49±12.31

3.1 Factors Predicting Recurrence

Tables 2 and 3 show univariate and multivariate regression analysis of factors predicting recurrence in the 97 patients. The factors significantly affecting recurrence on univariate analysis were T1 stage, multiplicity, size >3 cm. On Multivariate analysis with forward regression (Table 6), patients with size >3 cm were found to have 1.7 times greater odd of recurrence as compared to patients with size < 3 cm.Patients with multiple tumors had 3 times greater odds of recurrence as compared to single lesion.

3.2 Factors Predicting Progression

Tables 4 and 5 show univariate and multivariate regression analysis of factors predicting progression to muscle invasion in the 49 patients. On univariate analysis, stage and multiple tumor lesions were significant in affecting progression. On multivariate analysis with forward regression (Table 6), patients diagnosed with T1 stage were found to have 1.9 times greater odds of progression as compared to patients with Ta stage. Patients with multiple lesions had 1.8 times greater odds of progression compared to single lesion.

4. DISCUSSION

"TCC is the most common histological variety, seen in 90% of patients with BC" [7]. "Various rare variants of TCC reported are squamoid, sarcomatoid, and glandular differentiation. Most of the TCCs are NMIBC and are treated by transurethral resection. More than half of these patients experience recurrence with time" [8]. The treatment of Non muscle invasive bladder cancer is challenging due to the risk of recurrence and progression. Majority of the recurrence occur within 3 years and close follow-up is warranted. Development of predictive model for recurrence and progression is much needed and EORTC risk scoring system has been in use including clinicopathologic factors.

High male preponderance may be due to high exposure to cigarette smoking and industrial carcinogens. The higher sex ratio in Asia is probably due to higher tendency of males to smoke cigarettes and females tend to present to hospital less frequently due to social reason. In our study, we found that the male female ratio was 7:1 and 60% of patients were smokers.

Table 2. Bivariable analysis of qualitative factors predicting recurrence

Variable	Recurrence Yes	Recurrence No	Chi Square Test P value (Sig<0.05)	Odds Ratio Hazard ratio(95%CI)
Sex				
Male	82(84.5%)	145(89.5%)	.239	1.560(.741-3.28)
Female	15(15.5%)	17(10.5%)		
Smoker	56 (57.7%)	98(60.5%)	.661	.892 (.535-1.487)
Alcoholic	24 (24.7%)	44(27.2%)	.669	.882 (.495-1.569)
Type				
soild	79(81.4%)	135(83.3%)	.698	1.139(.590-2.199)
papillary	18(18.6%)	27(16.7%)		
Size >3cm	52 (53.6%)	65(40.1%)	**.035**	1.724(1.038-2.866)
T1	38(39.2%)	43(26.5%)	.034	1.782(1.042-3.048)
G3	42(43.3%)	57(35.2%)	.193	1.407(.840- 2.354)
Multiplicity	46(47.4%)	36(22.2%)	**.000**	3.157(1.832-5.439)

Table 3. Bivariable analysis of quantitative predictors of recurrence

Variable	Recurrence Yes	Recurrence No	MannWhitney U Test P value {Sig <0.05}
Hb (gm/dl)	11.94±2.01	12.25±2.15	.147
Albumin(gm/dl)	3.89±0.36	3.82±0.42	.362
NLR	2.34±1.10	2.29±1.18	.603
PLR	120.22±58.99	112.87±57.12	.150

Table 4. Bivariable analysis of qualitative predictors for progression

Variable	Progression Yes	Progression No	Chi Square Test P value (Sig=0.05)	Odds Ratio Hazard ratio(95%CI)
Sex Male Female	42(89.4%) 5(10.6%)	185(87.3%) 27(12.7%)	.693	.816(.297-2.24)
Smoker	30(63.8%)	124(58.5%)	.661	.892(.535-1.48)
Alcoholic	11(24.7%)	57 (26.9%)	.623	.831 (.396-1.74)
Type Soild Papillary	 7(14.9%) 40(85.1%)	 38 (17.9%) 174 (82.1%)	 .623	 1.13(.59 -2.19)
Size >3cm	23(48.9%)	94 (44.3%)	.567	1.20(.63-2.26)
T1	21(39.2%)	60 (28.3%)	**.028**	1.78(1.04-3.04)
G3	23(48.9%)	76 (35.8%)	.095	1.71(.90-3.24)
Multiplicity	21(44.7%)	61 (28.8%)	**.034**	1.99(1.04-3.82)

Table 5. Bivariable analysis of quantitative predictors for progression

Variable	Progression Yes	Progression No	MannWhitney U Test P value {Sig <0.05}
Hb(g/dl)	12 ±2.35	12± 2.04	.575
Albumin(g/dl)	3.8 ± .402	4± .403	.825
NLR	2.20 ± .88	2.13± 1.20	.524
PLR	107.75 ± 58.13	100 ± 57.79	.169

Table 6. Multivariate logistic regression with forward progression analysis to evaluate variable association with recurrence and progression

RECURRENCE		
Variable	Odd Ratio	p value
Size >3cm	1.72(.922-3.23)	.044
Multiplicity	3.13(1.63-5.98)	.001
PROGRESSION		
T1	1.93(1.00-3.73)	.048
Multiplicity	1.89(.982-3.63)	.057

In NMIBC there have been several studies investigating the prognostic role of various clinicopathological factors in association with recurrence and progression of tumor. Allard et al. [2] defined “a Predictive index (PI) based on the number of primary adverse tumor characteristics, namely stage T1, number of primary tumors, grade 2 or 3 and tumor diameter of >3 cm”. Parmar et al. [3] used the two variables of the result of cystoscopy at 3 months and multiplicity of the tumors to construct a PI. Herr et al. [4] reported on “four risk factors based on two variables, the presence or absence of T1 disease and whether cytology was positive or negative”. In the present study, on univariate and multivariate analysis, three prognostic factors had significant and independent associations with recurrence and progression. Tumor stage is one of the most important prognosticators in most studies [5,6,9], as well as in the present one. In our study, a failure to show the correlation between high grade and disease recurrence & progression was noted.

We identified that 27 out of 99 (27%) G3 patients received adjuvant therapy in the form of intravesical, chemotherapy or radiotherapy which may alter the biological behavior of tumor and minimize the effect on disease character. Tumor multiplicity was a significant factor in relation to recurrence and progression free survival in previous studies [3,9,10] and in the present one. Number of tumors, is the predictor of recurrence in patients with superficial TCC of bladder [11]. “Multifocality is associated with high rate of recurrence in high grade superficial lesions” [12].

In our analysis, “multifocality was related to recurrence. This high recurrence rate in multiple tumors can be contributed by incomplete resection of tumor at diagnosis or aggressiveness of the disease” [13-18]. Furthermore, the size of the tumor was a significant prognostic variable in the present study as well as in others [4].

5. CONCLUSION

In our study, Multiple tumors had increased risk for both recurrence and disease progression, Size > 3cm was a risk factor for recurrence but not progression. T1 stage factor had increased risk for progression of disease rather than recurrence. In recognition of the fact that bladder cancer is a significant disease burden in our population we need to develop multi-institutional prospective study to develop better level of evidence in the understanding of NMIBC.

6. LIMITATIONS OF THE STUDY

Retrospective review of database was the most important limitation of the study. Cystoscopic evaluation and preoperative parameters biases were not able to eliminate. Quantitative variables of prior recurrence rates were not included in our study. Data regarding adjuvant therapy in non recurrence arm group was not included due to unavailability of relevant data. Implementations of these parameters could have improved the assessment of the current risk calculations.

CONSENT

The authors declared that the written informed consent was obtained from all patients for participation in the study.

ETHICAL APPROVAL

The study protocol was reviewed and ethical clearance was obtained from the Institutional Review Board of Government Medical College Trivandrum.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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