Original Research Article

CLINICOPATHOLOGIC PROGNOSTIC FACTORS IN NMIBC FOR RECURRENCE & PROGRESSION

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 about 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 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.

Results

On multivariate analysis, patients with size >3cm and multiple tumors were found to have 1.7 times and 3 times greater odd of recurrence respectively as compared to patients with 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. Quantitative factors, none of them were significantly associated for prediction for recurrence and progression.

Conclusion

Multiple tumors had increased risk for both recurrence and disease progression. Size >3cm is a risk factor for recurrence and T1 stage for progression of disease.

Keywords : Bladder, Cancer, Recurrence, Progression,Smoking

Abbreviations: NMIBC- non muscle invasive bladder cancer ,NLR- Neutrophil lymphocyte ratio, PLR- Platelet lymphocyte ratio

INTRODUCTION

Bladder cancer is the second most common malignancy aof the genitourinary tract[1]. In India, according to the recent reports of the National Cancer Registry Programme, the overall incidence rate of the 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 belong to non muscle invasive bladder cancer (NMIBC) which is confined to either the mucosa [pTa, carcinoma *in situ* (CIS)] or the submucosa (pT1)[5]. The tumors of NMIBC are routinely treated by transurethral resection (TUR) and/or intravesical instillation. However, the prognosis of NMIBC is not satisfying, as the 5-year recurrence rate for NMIBC was reported ranging from 31% to 78% and the progression rate from NMIBC to muscle invasive bladder cancer (MIBC) 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 significantly associated with recurrence and progression 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 are controversial its significance is yet to be proved.

MATERIALS AND METHOD

Aim of the study was to analyze the predictive factors of recurrence and progression of NMIBC. A retrospective study was done on 322 patients initially confirmed as NMIBC after transurethral resection(TURBT) between January 2012 and June 2016 at Department of Urology,Government Medical College, Trivandrum . Complete transurethral resection of bladder tumour of all visible tumours was carried out in all patients, and the stage and grade were

determined. All these patients were regularly followed until June 2017.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 tumour, HB, S.albumin, NLR,PLR. 63 patients were excluded from the study including patients diagnosed T2(muscle invasive) on second turbt(n=11),without a minimum of 6 months of follow-up (n = 22),who lost to follow-up (n = 24),without complete blood parameters (NLR,PLR,ESR,S.Albumin) (n = 6) were excluded.

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

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. Procedure were performed under spinal anesthesia. Resection 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 UC (LGUC) and 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 6 monthly. Annual abdomen imaging were performed in high risk groups.

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

RESULTS

The mean age of the patients was 63.41±9.81 (26-88). During follow-up 259 patients 43.6% were outcome negative (neither recurred nor progressed) at the time of last follow-up, 97(37.45%) had a recurrence and 49(18.92%) had progressed to muscle-invasive disease. Other patients and tumour characteristics are presented in Table 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 >3cm. On Multivariate analysis with forward regression(Table 6),patients with size >3cm were found to have 1.7 times greater odd of recurrence as compared to patients with size < 3cm.Patients with multiple tumors had 3 times greater odds of recurrence as compared to single lesion.

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 tumour 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.

DISCUSSION

TCC is the most common histological variety, seen in 90% of patients with BC[9]. Various variants of TCC such as squamoid, sarcomatoid, and glandular differentiation are reported, which are very rarely seen. Most of the TCCs are NMIBC and are treated by transurethral resection. More than half of these patients experience recurrence with time[10].The treatment of Non muscle invasive bladder cancer is challenging due to the risk of recurrence and progression. Majority of recurrence occur within 3 years and close followup 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 , male female ratio was 7:1 and 60% of patients were smokers.

In NMIBC there have been several studies investigating the prognostic role of various clinicopathological factors in association with recurrence and progession. Allard etal.[2] defined a Predictive index based on the number of primary adverse tumour characteristics, namely stage T1,number of primary tumours, grade 2 or 3 and tumour diameter of >3cm.Parmar etal.[3] used the two variables of the result of cystoscopy at 3 months and multiplicity of the tumours to construct a PI. Herr etal.[4] reported on four risk factors based on two variables,i.e.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. Tumour stage is one of the most important prognosticators in most studies [5,6,7] ,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 27/99(27%) G3 patients received adjuvant therapy in form of intravesical, chemotherapy or radiotherapy which may alter the biological behaviour of tumor and minimise the effect on disease character. Tumour multiplicity was a significant factor in relation to recurrence and progression free survival in previous studies [3,7,8] and in the present one. Number of tumour is the predictors 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 tumours can be contributed by incomplete resection of tumour at diagnosis or aggressiveness of the disease[13]. Furthermore, the size of the tumour was a significant prognostic variable in the present study as well as in others [4].

Limitations of the study

Retrospective review of database was the most important limitation of the study. Biases in cystoscopic evaluation and preoperative parameters were not able to eliminate. Quantitative variable of prior recurrence rate 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.

CONCLUSION

In our study, Multiple tumors had increased risk for both recurrence and disease progression .Size > 3cm was 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 multiinstitutional prospective study to develop better level of evidence in the understanding of NMIBC.

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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	
< 3cm	142(54.8%)
>3cm	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

Table 1: Description of patient and tumor characteristics and response to therapy

Table 2: Bivariable analysis of factors predicting recurrence
Qualitative factors

Variable	Recurrence Yes	Recurrence No	Chi Square Test P value (Sig<0.05)	Odds Ratio Hazard ratio(95%CI)

Sex **Male** **Female**	82(84.5%) 15(15.5%)	145(89.5%) 17(10.5%)	.239	1.560(.741-3.28)
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** **papillary**	79(81.4%) 18(18.6%)	135(83.3%) 27(16.7%)	.698	1.139(.590-2.199)
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: Quantitative factors

Variable	**Recurrence** **Yes**	**Recurrence** **No**	**MannWhitney U Test** **P value** **{Sig <0.05}**

Hb	11.94±2.01	12.25±2.15	.147
Albumin	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 factors predicting progression

Qualitative factors

Variable	Progression Yes	Progression No	Chi Square Test	Odds Ratio Hazard

			P value (Sig<0.05)	**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: Quantitative factors

Variable	**Progression Yes**	**Progression No**	**MannWhitney U Test P value {Sig <0.05}**

Hb	12 ±2.35	12± 2.04	.575
Albumin	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