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Original Research Article

Role of Prognostic Factors in Non-Muscle Invasive Transitional Cell Carcinoma of Bladder

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Abstract

Background: Bladder cancer is the 9th most common cancer worldwide & accounts for 7% of all cancers inmale and 2% of all cancers in female. Bladder cancer is a heterogeneous disease, with 70% of patients presenting with superficial tumours and 30% presenting as muscle-invasive disease associated with a high risk of death from distant metastases. Bladder cancer is less common in developing areas, with 0.6% of men and 0.2% of women diagnosed before the age of 75 years.

Materials and Methods: A Cross sectional study conducted from January 2019 to June 2021 at K.R Hospital, Mysore. Study included 40 patients of all age group with NMIBC, who were diagnosed by ultrasonography/CT-KUB and underwent TURBT, The progress of the study and data collection reviewed every two months and at the end of study period, data was analysed with SPSS software in reference to prognostic factors in NMIBC.

Results: These patients were within the age of 45 and 86 years with a mean age of 63.22 years. 82.5% were male and 17.5% were female. 77.5% patients had Hematuria as the main symptom. 17.5% and 5% patients had dysuria and increased frequency of micturition along with Hematuria respectively. Out of the 40 patients 13 had T1 disease and 26 had Ta disease. One patient had Tis component. Out of 10 patients, who had received BCG, 3 patients had recurrence andunderwent check cystoscopy and Re-TURBT. Among those 3 patients, 2 (5%) patients progressed to T2 (MIBC). And the patients who progressed to MIBC were found to be of T1G3and Tis group of tumours.

Conclusion: Our results suggest that intravesical BCG therapy with lower dose than recommended after transurethral bladder resection for stage T1 grade 3 bladder cancer may delay the time to recurrence and cystectomy. Further large-scale randomized study is required to assess the outcome after short course BCG with lower dose in high grade NMIBC.

Keywords: Non muscle invasive bladder carcinoma, Transitional cell carcinoma, Cytology, Histopathology, TURBT (Transurethral resection of bladder tumor).

Introduction

Carcinoma of the bladder is the fifth most common cancer [1]. In the United State and the eleventh most common cancer in the world [2]. Carcinogens and inherited factorsthat inhibit the ability to detoxify the carcinogens effectively play a role in causing bladder cancer. Urinary stones and parasitic infection also predispose to malignancyby causing chronic irritation.

The age standardized mortality rate for the European population was 8.5 per 1 lakh and in the US population was 7.3 per 1 lakh [2]. In countries of the European sub-continent there has been a considerable decline in the incidence and mortality of bladder malignancies [3]. This is likely due to better understanding of the disease pathology, good surgical practice and strict follow up. Amongst the population with bladder tumors non muscle invasive tumors comprise of about 75% [(4)] and as expected theyhave a better mortality and morbidity rate as compared to the muscle invasive tumors.

The management of non-muscle invasive bladder tumors has been Trans urethral resection of the tumor followed by three monthly follow up with cystoscopy. But in the recent past, even in the absence of macroscopic disease, Re-TURBT has been carried out to prevent under-staging of the tumour. This study aims in the review of diagnosis and management of non-muscle invasive transitional carcinoma of bladder.

Aims and Objectives

- To study the various prognostic factors in non-muscle invasive bladder cancer (NMIBC).
- To study the better understanding of prognostic factors affecting therapy response.
- To review the diagnosis and management of non-muscle invasive bladdercarcinoma

Methodology

This study was done at K.R. Hospital attached to Mysore Medical College and Research Institute, Mysore for a period of January 2019 to June 2021.

All newly diagnosed NMIBC, Recurrent NMIBC and follow up patients were included in the study. 40 patients were recruited and analyzed the role of various prognostic factors affecting the therapy response. The patient was explained in detail about the present study, the disease (Bladder cancer and T1G3 disease), and the management needed in the language best understood by the patient. Informed consent was taken. Patient details, along with the clinical history and physical and systemic examinations were noted. Relevant blood and urine investigations and the radiological assessment were performed.

We treated all with transurethral bladder resection and additional BCG was considered for all high grade and some intermediate grade after check cystoscopy under anesthesia,urine cytology & USG at 3months after TURBT. ReTURBT was done for patients for residual disease at the resected area on check cystoscopy at 3rd month.

Induction therapy: BCG was administered intravesically as 80mg each time -dissolved in 100 ml saline, retained for up to 2 hours; weekly for 6 weeks for patients without tumor at 3rd month after TURBT.

Maintenance therapy: 80mg every week for 3 weeks at 6months, 9 months and at 12 months in first year. Later at 18 months and 24 months.

The progress of the study and data collection reviewed every two months and at the end of study period, data was analysed with SPSS software in reference to prognostic factors in NMIBC.

Most of the patients had low grade tumour (75%) and the rest were grade2 and 3 in ourstudy. In our study group out of 40, 10 (25%) of the patients had received complete course of BCG, rest had

not received for various reasons, like low grade tumors. These patients were contacted and the most common reason for this default was the distance. The other reasons being financial constraint and lack of awareness of the disease.

Out of 10 patients, who had received BCG, 3 patients had recurrence and underwent check cystoscopy at 3rd month and Re-TURBT. Among those 3 patients, 2 (5%) patients progressed to T2 (MIBC). And the patients who progressed to MIBC were found to be of T1G3 and Tis group of tumours. Among the patients who had come for follow up 85% of the patients had come on time. The remaining 15% were late for follow up and had comefor follow up between 6 months to 1 year.

A second TUR was routinely performed in all the pT1G3 bladder tumors within 10-12 weeks. Resection was performed at the previous resection scar sites as documented by the earlier surgery records. and also, at the doubtful areas. Presence of any new residual or recurrent disease is specifically looked for and the doubtful areas resected and sent for histopathological examination. The resected specimen was assessed for any residual tumor, its stage, grade and upstaging of the disease if any.

In our study group there were only 3 recurrences. The various factors with regards to the tumour and its histopathology were assessed to look for association with increased incidence of recurrence. 2 out of 40 patients progressed to MIBC and required radical cystectomy. Both of them did not take BCG in 2rd year and irregular follow ups.

Recurrence patterns were defined as early (less than 12 months) or late (12 or more months). All patients were followed for determination of vital status. Outcome measure of overall survival was assessed using Kaplan-Meier analysis and adjustment for covariates was done with proportional hazards models.

Even with lower BCG dose, we got comparable results to other studies in terms of recurrence and progression rates.

Observation & Results

Descriptive data:

Based on the inclusion and exclusion criteria 40 patients were recruited. These patients werewithin the age of 45 and 86 years with a mean age of 63.22 years. Out of these 40 patients 82.5% were male and 17.5% were female.

Table 1: Age distribution

Age (years)	Frequency	Percent
45	2	5.0
50	3	7.5
52	2	5.0
54	1	2.5
55	3	7.5
58	1	2.5
60	4	10.0
64	2	5.0
65	9	22.5
67	1	2.5
68	2	5.0
70	3	7.5
74	1	2.5
75	2	5.0
76	2	5.0
80	1	2.5
86	1	2.5
Total	40	100.0

Table 2: Sex distribution

Sex	Frequency	Percent
F	7	17.5
M	33	82.5
Total	40	100.0

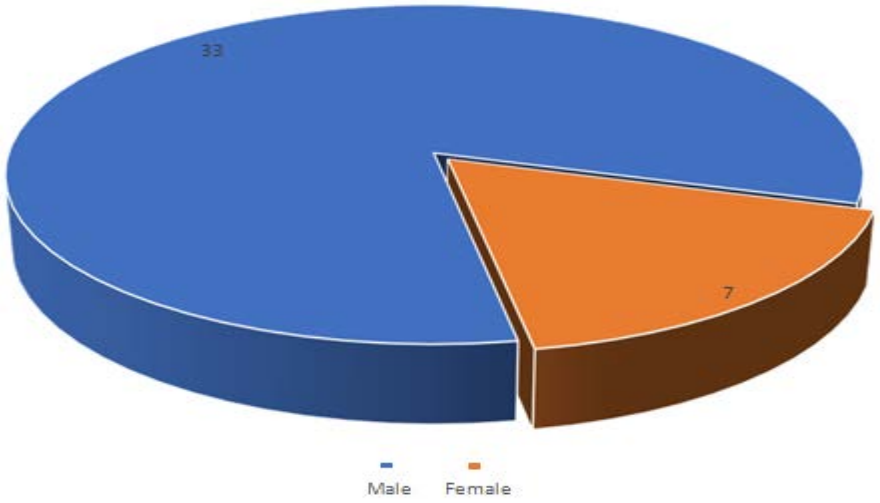

Figure 1: Sex distribution

Table 3: Symptoms [7]

Symptoms	Frequency	Percent
DYSURIA, HEMATURIA	7	17.5
FREQUENCY,HEMATURIA	2	5.0
HEMATURIA	31	77.5
Total	40	100.0

77.5% patients had Hematuria has the main symptom. 17.5% and 5% patients had dysuriaand increased frequency of micturition along with Hematuria respectively.

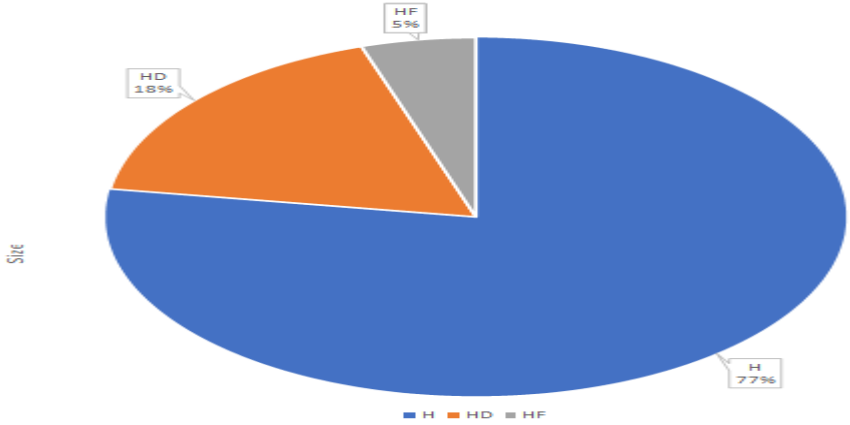

Figure 2: Symptoms

H- Hematuria
HD- Hematuria, Dysuria
HF- Hematuria, Increased frequency of micturition.

Table 4: Size of the tumor

Size (cm)	Frequency	Percent
<3	30	75.0
>3	10	25.0
Total	40	100.0

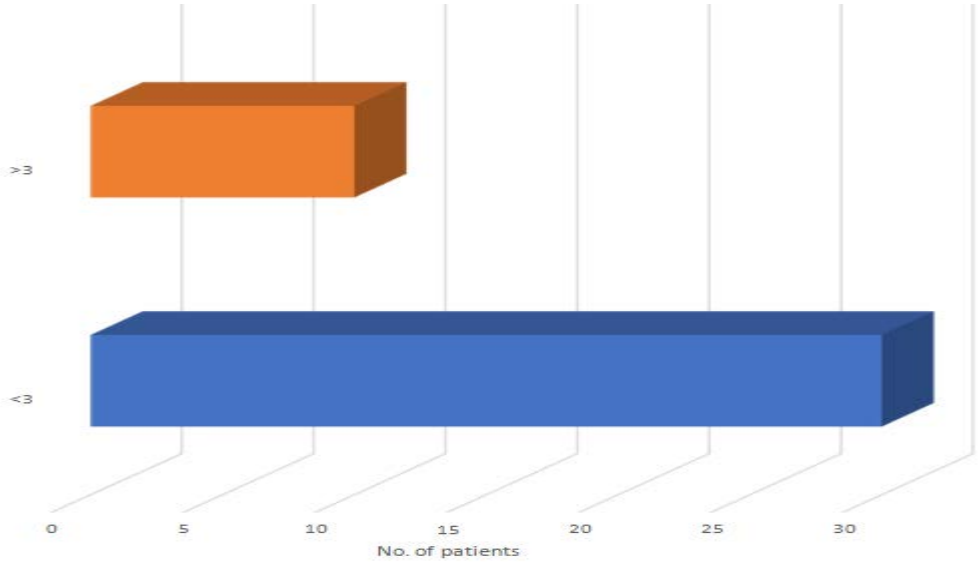

Figure 3: Size of the tumor

Table 5: Type of lesion

Type of lesion	Frequency	Percent
SES (sessile)	7	17.5
PED (pedunculated)	33	82.5
Total	40	100.0

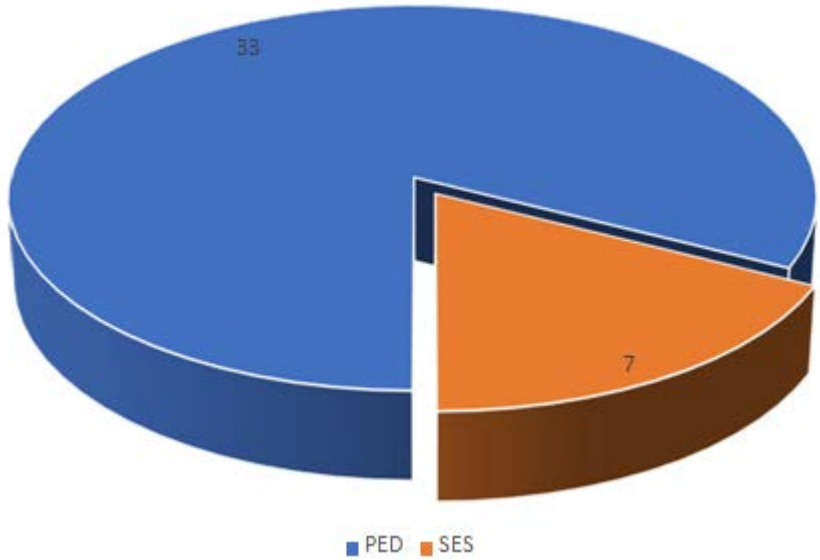

Figure 4: Type of lesion

Majority of the patients had papillary/pedunculated growth – 82.5% .while the next major group was sessile. About 17.5% had sessile growths. None of our patients had both a combination of sessile and papillary growths.

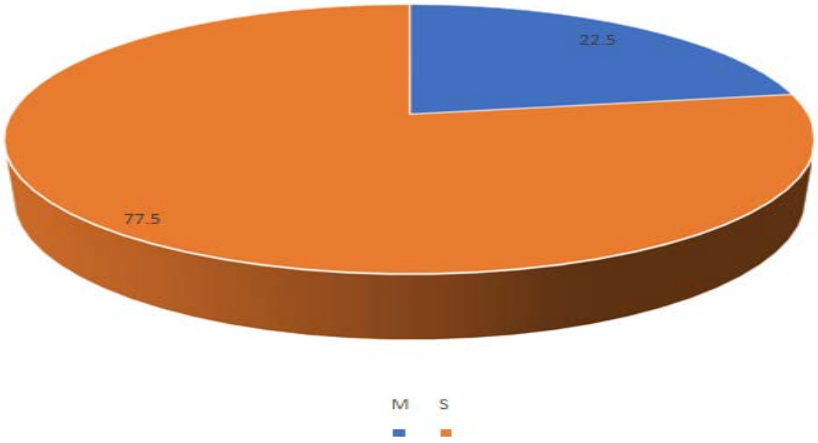

Figure 5: Number of tumor
(M- Multiple, S- single)

Table 6: Number of tumor

Number	Frequency	Percent
M	9	22.5
S	31	77.5
Total	40	100.0

The patients included were those with non-muscle invasive bladder tumour. Out of the40 patients included 13 had T1 disease and 26 had Ta disease. One patient had Tis component

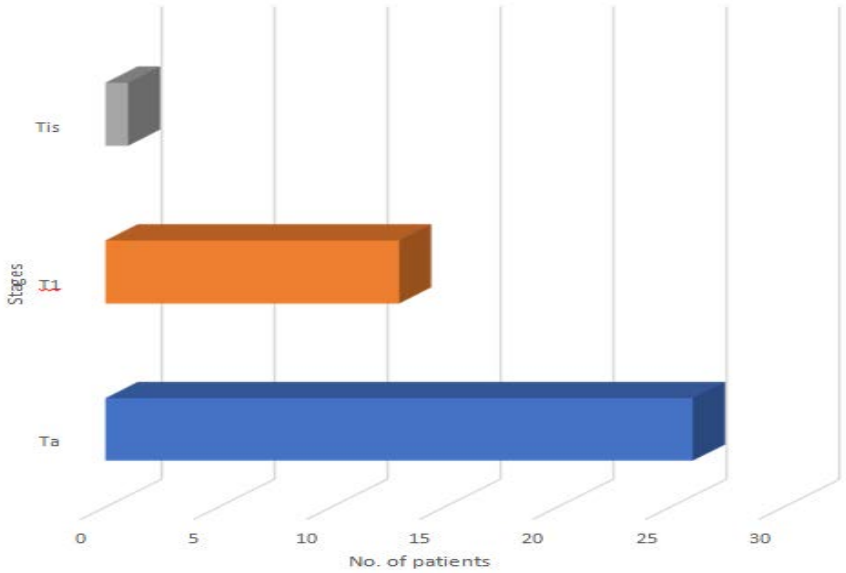

Figure 6: HPE

Table 7: HPE at initial presentation [6]

	Frequency	Percent
T1	13	32.5
Ta	26	65.0
Tis	1	2.5
Total	40	100.0

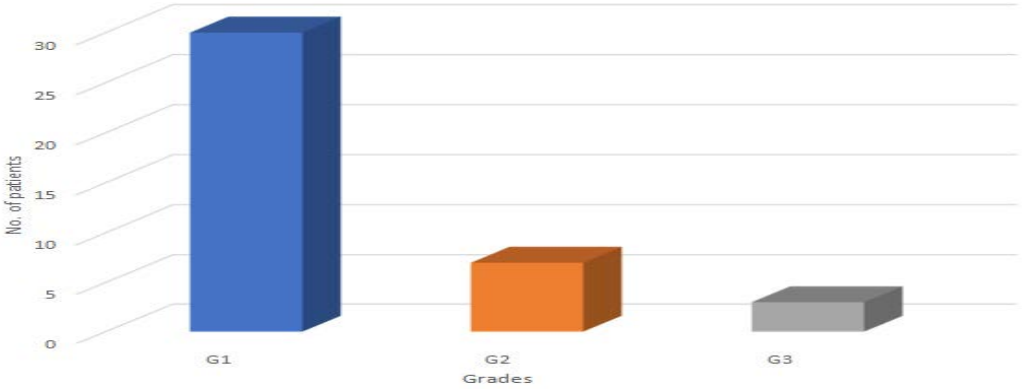

Figure 7: Grade of the tumor

Out of 40 patients 30 had low grade tumour. 7 and 3 patients had grade 2 and grade 3 tumour respectively.

Table 8: Grade of the tumor

Grade	Frequency	Percent
1	30	75.0
2	7	17.5
3	3	7.5
Total	40	100.0

Table 9: Intravesical BCG therapy

BCG	Frequency	Percent
no	30	75.0
yes	10	25.0
Total	40	100.0

In our study group out of 40, 10 (25%) of the patients had received complete course of BCG, Rest had not received for various reasons, like low grade tumours.

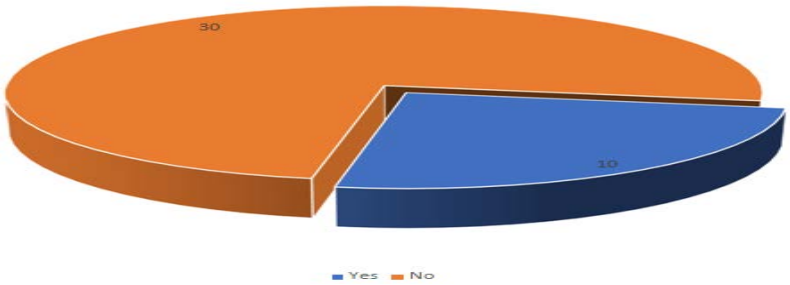

Figure 8: BCG therapy

Table 10: Recurrence following BCG therapy

Recurrence	Frequency	Percent
Valid	30	75.0
No	7	17.5
Yes	3	7.5
Total	40	100.0

RECURENCE * BCG

Crosstab

Table 11: BCG v/s recurrence

			BCG		Total
				yes	
RECURENCE		Count	30	0	30
		% within BCG	100.0%	.0%	75.0%
	no	Count	0	7	7
		% within BCG	.0%	70.0%	17.5%
	yes	Count	0	3	3
		% within BCG	.0%	30.0%	7.5%
Total		Count	30	10	40
		% within BCG	100.0%	100.0%	100.0%

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	40.000[a]	2	.000
Likelihood Ratio	44.987	2	.000
N of Valid Cases	40		
Chi-Square Tests			

3 cells (50.0%) have expected countless than 5. The minimum expected count is .75.

RECURENCE * GRADE

Crosstab

Table 12: Recurrence v/s grade

			GRADE			Total
			1	2	3	
RECURENCE		Count	30	0	0	30
		% within GRADE	100.0%	.0%	.0%	75.0%
	no	Count	0	7	0	7
		% within GRADE	.0%	100.0%	.0%	17.5%
	yes	Count	0	0	3	3
		% within GRADE	.0%	.0%	100.0%	7.5%
Total		Count	30	7	3	40
		% within GRADE	100.0%	100.0%	100.0%	100.0%

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	80.000[a]	4	.000
Likelihood Ratio	57.204	4	.000
N of Valid Cases	40		
Chi-Square Tests			

a. 6 cells (66.7%) have expected count less than 5. The minimumexpected count is .23.

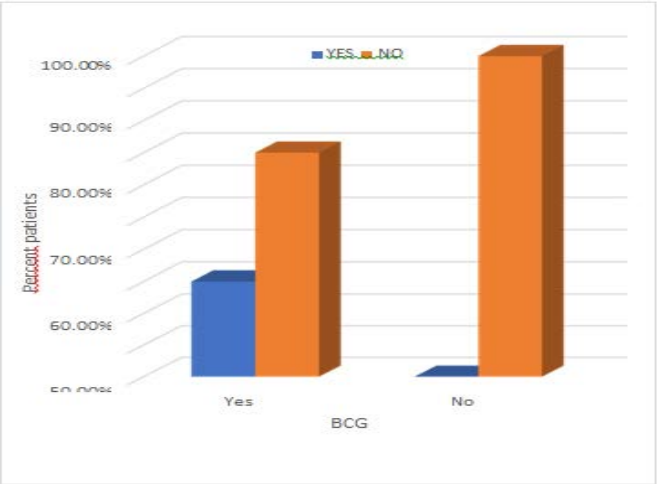

Figure 9: BCG v/s Recurrence

RECURENCE * STAGE

Crosstab

Table 13: Stage of the tumor v/s recurrence

			STAGE			Total
			T1	Ta	Tis	
Recurrence		Count	9	21	0	30
		% within STAGE	69.2%	80.8%	.0%	75.0%
	no	Count	3	4	0	7
		% within STAGE	23.1%	15.4%	.0%	17.5%
	yes	Count	1	1	1	3
		% within STAGE	7.7%	3.8%	100.0%	7.5%
Total		Count	13	26	1	40
		% within STAGE	100.0%	100.0%	100.0%	100.0%

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	13.267[a]	4	.010
Likelihood Ratio	6.196	4	.185
N of Valid Cases	40		
Chi-Square Tests			

a. 7 cells (77.8%) have expected count less than 5. The minimum expected count is .08.

RE-TURBT * BCG

Crosstab

Table 14: RE-TURBT

			BCG		Total
				yes	
RE-TURBT		Count	30	7	37
		% within BCG	100.0%	70.0%	92.5%
	yes	Count	0	3	3
		% within BCG	.0%	30.0%	7.5%
Total		Count	30	10	40
		% within BCG	100.0%	100.0%	100.0%

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	40.000[a]	2	.000
Likelihood Ratio	21.311	2	.000
N of Valid Cases	40		

Chi-Square Tests

	Value	df	Asymp. Sig.(2 sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	9.730[a]	1	.002		
Continuity Correction[b]	5.886	1	.015		
Likelihood Ratio	9.093	1	.003		
Fisher's Exact Test				.012	.012
N of Valid Cases	40				

Chi-Square Tests

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .75.
b. Computed only for a 2x2 table

RE-TURBT * GRADE

Crosstab

Table 15: RE-TURBT v/s grade of the tumor

			GRADE			Total
			1	2	3	
RE-TURBT		Count	30	7	0	37
		% within GRADE	100.0%	100.0%	.0%	92.5%
	yes	Count	0	0	3	3
		% within GRADE	.0%	.0%	100.0%	7.5%
Total		Count	30	7	3	40
		% within GRADE	100.0%	100.0%	100.0%	100.0%

a. 4 cells (66.7%) have expected count less than 5. The minimum expected count is .23.

RE-TURBT * STAGE

Crosstab

Table 16: RE-TURBT v/s stage of the tumor

			STAGE			Total
			T1	Ta	Tis	
RE-TURBT		Count	12	25	0	37
		% within STAGE	92.3%	96.2%	.0%	92.5%
	yes	Count	1	1	1	3
		% within STAGE	7.7%	3.8%	100.0%	7.5%
Total		Count	13	26	1	40
		% within STAGE	100.0%	100.0%	100.0%	100.0%

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	12.834[a]	2	.002
Likelihood Ratio	5.783	2	.056
N of Valid Cases	40		
Chi-Square Tests			

a. 4 cells (66.7%) have expected count less than 5.
The minimumexpected count is .08.

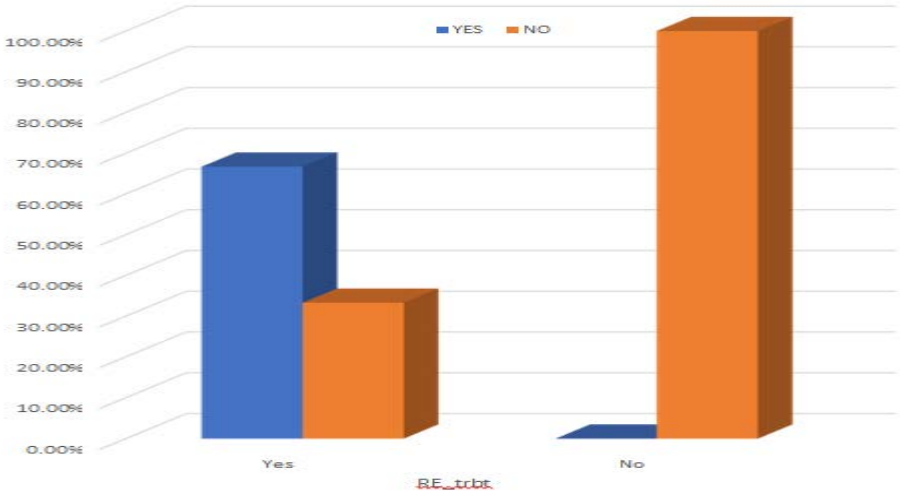

Figure 10: Percentage of patients who underwent RE-TURBT

Progression * BCG

Table 17: Tumor progression

Crosstab					
			BCG		Total
				yes	
Progression		Count	30	7	37
		% within BCG	100.0%	70.0%	92.5%
	no	Count	0	1	1
		% within BCG	.0%	10.0%	2.5%
	yes (T2)	Count	0	2	2
		% within BCG	.0%	20.0%	5.0%
Total		Count	30	10	40
		% within BCG	100.0%	100.0%	100.0%

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	9.730[a]	2	.008
Likelihood Ratio	9.093	2	.011
N of Valid Cases	40		
Chi-Square Tests			

a. 4 cells (66.7%) have expected count less than 5.
The minimumexpected count is .25.

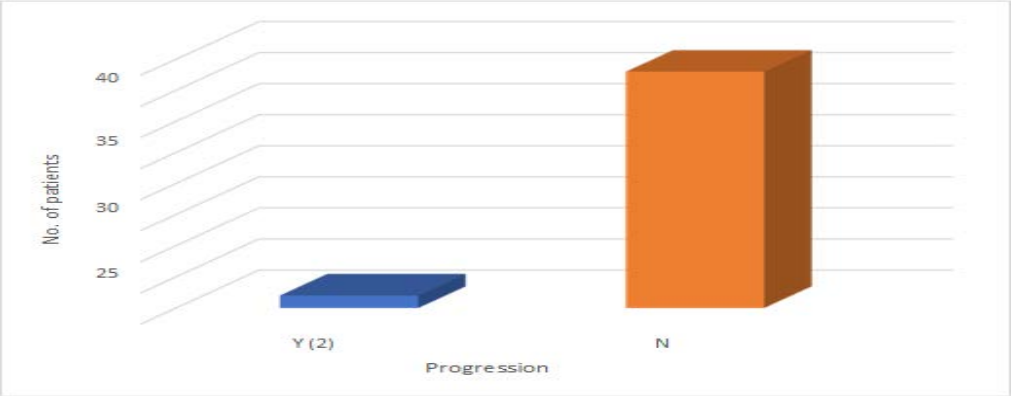

Figure 11: Progression of tumor

Progression * Grade

Crosstab

Table 18: Progression v/s grade of the tumor

			GRADE			Total
			1	2	3	
Progression		Count	30	7	0	37
		% within GRADE	100.0%	100.0%	.0%	92.5%
	No	Count	0	0	1	1
		% within GRADE	.0%	.0%	33.3%	2.5%
	yes (T2)	Count	0	0	2	2
		% within GRADE	.0%	.0%	66.7%	5.0%
Total		Count	30	7	3	40
		% within GRADE	100.0%	100.0%	100.0%	100.0%

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	40.000[a]	4	.000
Likelihood Ratio	21.311	4	.000
N of Valid Cases	40		
Chi-Square Tests			

a. 7 cells (77.8%) have expected count less than 5. The minimumexpected count is .08.

Progression * Stage
Crosstab

Table 19: Progression v/s stage of the tumor

			STAGE			Total
			T1	Ta	Tis	
Progression		Count	12	25	0	37
		% within STAGE	92.3%	96.2%	.0%	92.5%
	No	Count	0	1	0	1
		% within STAGE	.0%	3.8%	.0%	2.5%
	yes (T2)	Count	1	0	1	2
		% within STAGE	7.7%	.0%	100.0%	5.0%
Total		Count	13	26	1	40
		% within STAGE	100.0%	100.0%	100.0%	100.0%

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	21.040[a]	4	.000
Likelihood Ratio	9.602	4	.048
N of Valid Cases	40		
Chi-Square Tests			

a. 7 cells (77.8%) have expected count less than 5. The minimumexpected count is .03.

Discussion

In our study 40 patients were recruited. Out of this only 17.5% were females. 82.5% were males. As shown in the earlier studies, bladder malignancy has been a disease of the elderly men and our study has followed the same pattern. Most of the patients in our study group werewithin 45-86 years of age [8]. The mean age was 63.22 years. The initial stage of the bladder tumors was almost equal with 65% in the Ta group and 32.5% in the T1 and 2.5% in Tis group.

Most of the patients had low grade tumour (75%) and the rest were grade2 and 3 in our study. In our study group out of 40, 10 (25%) of the patients had received Complete BCG. Rest had not received for various reasons, like low grade tumours. These patients were contacted and the most common reason for this default was the distance. The other reasons being financial constraint and lack of awareness of the disease.

Out of 10 patients, who had received BCG, 3 patients had recurrence and underwent check cystoscopy at 3rd month and Re-TURBT. Among those 3 patients, 2 (5%) patients progressed to T2 (MIBC). And the patients who progressed to MIBC were found to be of T1G3 and Tis group of tumours [9]. Among the patients who had come for follow up 85% of the patients had come on time. The remaining 15% were late for follow up and had come for follow up between6 months to 1 year.

In our study group there were only 3 recurrences. The various factors with regards to the tumourand its histopathology were assessed to look for association with increased incidence of recurrence. There was no difference in the incidence of recurrence with regards to size or site.But there was a statistically significant increase in the recurrence of multifocality, high grade and presence of carcinoma in situ.

On the other hand, patients with risk factors of recurrence should be educated on the high chance of recurrence of the disease and the importance of the check cystoscopy at 3 months must be emphasized. They should be kept on strict follow up with a low threshold for further management. Radical cystectomy upfront is an option that should be discussed with the patient and his relatives [10]. They should be explained regarding the conventional method of treatment, the need for regular follow up, and in patients who are not willing for such a strict follow up, radical cystectomy should be strongly advocated.

Limitations

- The use of intravesical chemotherapy and their role in post resection was not studied inthis study.
- BCG failure cannot be accurately predicted on an individual basis with clinical andhistologic parameters.

Conclusion

- Our results suggest that intravesical BCG therapy with lower dose than recommended after transurethral bladder resection for stage T1 grade 3 bladder cancer may delay the time to recurrence and cystectomy.
- Further large-scale randomized study is required to assess the outcome after short course BCG with lower dose in

high grade NMIBC.

- In BCG-intolerant patients, especially those who never completed an induction course, intravesical therapy combined with another drug at time of recurrence could bebeneficial.
- Also, further studies are needed whether probability of recurrence would have reduced further if patients continued BCG into 3rd yr.

Summary

Transitional cell carcinoma of the bladder is a common malignant neoplasm affecting both menand women. Non-muscle invasive TCC (about 70% of the affected population) is a chronic illness with no definite curative measures. However, patients with these tumors have excellent survival rate. Therefore, the main goal in their management is to diagnose the primary and recurrent tumors as early as possible and treat them. Follow up cystoscopy is the gold standard for surveillance of this tumor.

Tumor architecture, papillary or sessile, and multifocality of these lesions, and the size of the lesion are important prognostic factors for recurrence and progression of the disease. A solitary papillary lesion is considered to be a good prognostic factor as against multiple papillary and sessile lesions [5].

References

1. Cancer of the Urinary Bladder - SEER Stat Fact Sheets [Internet]. [cited 2015 Apr 27]. Available from: http://seer.cancer.gov/statfacts/html/urinb.html
2. Fact Sheets by Population [Internet]. [cited 2015 Nov 6]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx
3. Trends in Mortality From Urologic Cancers in Europe, 1970–2008 - European Urology [Internet].[cited2015 Nov 6]. Available from: http://www.europeanurology.com/article/S0302-2838(11)00319-8/fulltext/trends- inmortality-from-urologic-cancers-in-europe-1970-x02013-2008
4. Gupta P, Jain M, Kapoor R, Muruganandham K, Srivastava A, Mandhani A. Impact ofage and gender on the clinicopathological characteristics of bladder cancer. Indian J Urol IJU J Urol Soc India. 2009;25(2):207–10.
5. Molina Escudero R, Alvarez Ardura M, Ripalda Ferretti E, Crespo Martínez L, González Avila N, Dorado Valentín M, *et al*. Predicting factors for recurrence in low grade Ta primary bladder tumours. Arch Esp Urol. 2014 Jul;67(6):541–8.
6. Scosyrev E, Noyes K, Feng C, Messing E. Sex and racial differences in bladder cancerpresentation and mortality in the US. Cancer. 2009 Jan 1;115(1):68–74.
7. Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. J Urol. 2000 Feb;163(2):524–7.
8. Burger M, Catto JWF, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, *et al*. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013Feb;63(2):234–41.
9. Modification of Occupational Exposures on Bladder Cancer Risk by Common Genetic Polymorphisms. [Internet]. [cited 2015 Nov 6]. Available from: http://www.pubfacts.com/detail/26374428/Modification-of-Occupational-Exposureson-Bladder-Cancer-Risk-by-Common-Genetic-Polymorphisms
10. Koutros S, Silverman DT, Baris D, Zahm SH, Morton LM, Colt JS, *et al*. Hair dye use and risk of bladder cancer in the New England bladder cancer study. Int J Cancer JInt Cancer. 2011 Dec 15;129(12):2894–904.