Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2017; 5(4C):1380-1384 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublishers.com DOI: 10.36347/sjams.2017.v05i04.032

Original Research Article

Predictive factors of muscle invasiveness in patients undergoing TURBT

Dilip Kumar Pal[1], Dipak Kumar Bera[2], Debarshi Jana[3]
[1]Professor & Head, Dept. of Urology, Institute of Post Graduate Medical Education & Research, Kolkata, West Bengal
[2]Post-Doctoral Trainee, Dept. of Urology, Institute of Post Graduate Medical Education & Research, Kolkata, West Bengal
[3]Young Scientist, Dept. of Urology, Institute of Post Graduate Medical Education & Research, Kolkata, West Bengal

***Corresponding author**
Prof. Dilip Kumar Pal
Email: drdkpal@yahoo.co.in

Abstract: Preoperative diagnosis of muscle invasiveness in bladder tumor patients can reduce the time interval between diagnosis of invasive tumor and definitive management, which may translate into improve quality of life. This study was aimed at identifying whether there is any factor that can predict muscle invasiveness preoperatively so that a deep muscle biopsy can be taken definitely during initial operation without the need for a restage TURBT. From August 2014 to July 2016, the preoperative and intra-operative details of tumor characteristics of all patients undergoing TURBT were collected and post operatively, the biopsy reports were also collected. Of the 74 patients whose biopsy reports came to be muscle invasive along with another 74 patients with non-muscle invasive tumor taken randomly, all records were taken for the study. For statistical analysis data were entered into a Microsoft excel spreadsheet and then calculated by SPSS 20.0.1 and Student's independent sample's t-test was applied to compare normally distributed numerical variables between groups. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. Under univariate analysis significant risk of Muscle Invasive groups was found 4.3636[OR-4.3636 (3.0235, 6.2977); p<0.0001] times more for positive hydroureteronephrosis,2.0571 [OR-2.0571 (1.7391, 2.4333); p=0.0426] times more for positive calcification, 4.0833 [OR-4.0833 (2.8842, 5.7810); p<0.0001] times more for positive sessile tumors, 2.2333 [OR-2.2333 (1.8505, 2.6954); p<0.0001] times more for positive multiple tumors and 2.6818 [OR-2.6818 (2.1223, 3.3888); p<0.0001] times more for large size (>9.5 cm) tumors. According to Linear Regression analysis significant risk was found in sessile tumor, positive hydroureternephrosis, and multiple number and muscle invasive groups. The presence of hydroureternephrosis, large size tumor, multiple tumors, sessile tumors were significantly associated with muscle invasive disease. This may help in predicting muscle invasiveness in bladder tumor patients.
Keywords: Bladder cancer, muscle invasive, predictive factors

INTRODUCTION:

Bladder cancer has the fifth highest incidence of all malignancies in the United States [1]. In India, according to the recent reports of the National Cancer Registry Program, the overall incidence rate is 2.25%; 3.67% among males and 0.83% for females [2]. Broadly, bladder cancers are divided into two groups, non-muscle invasive and muscle-invasive, based on the treatment approach [3]. About 20% to 30% of neoplasms are muscle-invasive (≥T2) and/or metastatic at the time of initial presentation. Clinical under-staging is not uncommon at the time of initial diagnosis with muscle-invasive tumor. Muscle-invasive bladder cancer is a highly lethal entity and if left untreated will result in mortality within 2 years of diagnosis in 85% of cases [4]. Also in some studies it was shown that patients who progress from non-muscle-invasive disease, they fare worse; and this is likely related to under staging of invasive tumor [5].

When cystectomy is delayed more than 12 weeks from initial diagnosis of muscle invasion to cystectomy, there is increase chance of extra vesical tumors, nodal metastasis, and worse survival [6, 7]. Therefore if patients with an invasive tumor can be recognized in an early stage, aggressive therapy can be initiated before it is too late and it may improve the prognosis of the patient. This in turn can improve the patient's quality of life. The relation between depth of bladder wall invasion and impaired prognosis and

development of metastasis is reported in many studies. Although hydroureternephrosis is a marker of muscle invasiveness, it is not always the case [8, 9]. So we need to find whether there is any other factor that can predict muscle invasiveness preoperatively.

The aim of this study is to find any predictive factor for muscle invasive bladder tumor preoperatively, so that treatment can be guided by it to achieve a better outcome in bladder cancer patient management. Patients who are having muscle invasive tumor can be identified on first time TURBT without the need for restage TURBT, thereby shortening the time interval to initiate definitive management i.e. radical cystectomy with adjuvant therapy where needed.

MATERIALS AND METHODS:

Between August 2014 to July 2016, data collection was done for 215 patients after obtaining ethical clearance from institutional ethics committee (No-Inst/EC/2016/341 dated 25.04.2016) who underwent trans-urethral resection of bladder tumor. Preoperatively data collection included presence of hydroureteronephrosis, size of the tumor on imaging study, location of the tumor, whether the tumor was sessile or pedunculated, calcification on tumor present or not, number of the tumor, whether the tumor was primary or recurrent.

During cystoscopy the findings regarding the tumor's characters were noted and corroborated with preoperative findings. After taking ethical clearance from the institute and consent from every patients, we included 148 (74 case and another 74 control) patients in the study. All the resected tumour samples and muscle biopsies were sent in separate container to institute's pathology department for histo-pathological analysis. After receiving the histo-pathological reports 74 patients whose reports were muscle invasive, were taken as case and another 74 patients from non-muscle invasive group were taken as control for analysis.

Data Analysis:

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analysed by SPSS 20.0.1 and Graph Pad Prism version 5. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. Student's independent sample's t-test was applied to compare normally distributed numerical variables between groups. P-value ≤ 0.05 was considered as statistically significant.

RESULTS:

In muscle invasive group, the mean age (mean± S.D.) of patients was 61.1351 ±8.3393 years with range 48.00-78.00 years and the median age was 61.00 years. In non-muscle invasive group, the mean age (mean± S.D.) of patients was 61.5270 ±7.4009 years with range 48.00 - 73.00 years and the median age was 61.50 years. Difference of mean age in two groups was not statistically significant (p=0.7628); [t-test]. Thus age matched patients were selected in two groups.

In muscle invasive group, the mean tumor size (mean± S.D.) of patients was 9.9427 ±5.3112 cm with range 4.60- 24.60cm and the median size was 7.9500 cm. In non-muscle invasive group, the mean tumor size (mean± S.D.) of patients was 6.6216 ±1.1666 cm with range 4.9000 - 8.6000 cm and the median size was 6.3500 cm. Difference of mean size in two groups was statistically significant (p<0.0001); [table-1].

Table-1: Distribution of mean size of the tumor in two groups

	Group	Number	Mean	SD	Minimum	Maximum	Median	p-value
Size	**Muscle Invasive**	74	9.9427	5.3112	4.6000	24.6000	7.9500	<0.0001*
	Non Muscle Invasive	74	6.6216	1.1666	4.9000	8.6000	6.3500	

*Statistically significant

As per table-2, in muscle invasive group 5 (6.8%) patients were female but in non-muscle invasive group 9 (12.2%) patients were female. Muscle invasive group 69 (93.2%) patients were male but in non-muscle invasive group 65 (87.8%) patients were male.

Table-2: Distribution of gender, hydroureteronephrosis, character of tumor, calcification, number and recurrence in two groups

		Muscle Invasive		Non Muscle Invasive		p-value
		Number	Percentage	Number	Percentage	
Gender	Female	5	6.8	9	12.2	0.2612
	Male	69	93.2	65	87.8	
Hydrouretero -nephrosis	No	21	28.4	74	100.0	<0.0001*
	Yes	53	71.6	0	0.0	
Character of tumor	Pedunculated	24	32.4	74	100.0	<0.0001*
	Sessile	50	67.6	0	0.0	
Calcification	No	70	94.6	74	100.0	0.0426
	Yes	4	5.4	0	0.0	
Number	Multiple	14	18.9	0	0.0	<0.0001*
	Single	60	81.1	74	100.0	
Recurrence	No	71	95.9	69	93.2	0.4672
	Yes	3	4.1	5	6.8	

*Statistically significant

Association between gender in two groups was not statistically significant (p=0.2612). In present study, sex was matched in two groups. In muscle invasive group 53 (71.6%) patients had hydroureternephrosis but in non-muscle invasive group no patients had hydroureternephrosis .This difference was statistically significant (<0.001). In muscle invasive group 21 (28.4%) patients had no hydroureternephrosis but in non-muscle invasive group, 74 (100.0%) patients had no hydroureternephrosis .This difference was statistically significant (<0.001).In muscle invasive group, 24 (32.4%) patients and in non-muscle invasive group, 74 (100.0%) patients were pedunculated tumor. This percentage difference was statistically significant (<0.001).In muscle invasive group, 50 (67.6%) patients were sessile tumor but there was no sessile tumors found in non-muscle invasive group. This difference was statistically significant (<0.001).In muscle invasive group, 4 (5.4%) patients had calcification but in non-muscle invasive group, no patients had calcification. This difference was statistically significant (p=0.005).In muscle invasive group, 70 (94.6%) patients had no calcification and in non-muscle invasive group 74 (100.0%) patients had no calcification. This difference was not statistically significant p=0.638).In muscle invasive group, 14 (18.9%) patients were multiple tumors and in non-muscle invasive group, no patients were multiple tumors. This percentage difference was statistically significant (<0.001).In muscle invasive group, 60 (81.1%) patients were single tumors but in non-muscle invasive group 74 (100.0%) patients were single tumors. This difference was not statistically significant (p=0.087).In muscle invasive groups, 71 (95.9%) patients had no recurrence and in non-muscle invasive group, 69(93.2%) patients had no recurrence. This difference was not statistically significant (p=0.810).In muscle invasive group, 3 (4.1%) patients had recurrence and in non-muscle invasive group, 5(6.8%) patients had recurrence. This difference was not statistically significant (p=0.317).

Table-3: Risk of Muscle Invasive groups according to Hydrouretero Nephrosis, Character of tumor, Calcification, Number and size

		Risk Ratio	Upper	Lower	% of CI	p-value
Hydrouretero Nephrosis	Yes vs No	4.3636	3.0235	6.2977	95%	<0.0001*
Calcification	Yes vs No	2.0571	1.7391	2.4333	95%	0.0426*
Character of tumor	Sessilvs Pedunculated	4.0833	2.8842	5.7810	95%	<0.0001*
Number	Multiple vs Single	2.2333	1.8505	2.6954	95%	<0.0001*
Size	>9.5 vs ≤9.5	2.6818	2.1223	3.3888	95%	<0.0001*

*Statistically significant

In table-3, Under univariate analysis significant risk of muscle invasive groups was found 4.3636[OR-4.3636 (3.0235, 6.2977); p<0.0001] times more for positive hydroureternephrosis, 2.0571 [OR-2.0571 (1.7391, 2.4333); p=0.0426] times more for positive calcification, 4.0833 [OR-4.0833 (2.8842, 5.7810); p<0.0001] times more for positive sessile tumors, 2.2333 [OR-2.2333 (1.8505, 2.6954); p<0.0001] times more for positive multiple tumors and 2.6818 [OR-2.6818 (2.1223, 3.3888); p<0.0001] times

more for large size (>9.5 cm) tumors. As per table-4, According to Linear Regression analysis significant risk was found in sessile tumor, positive hydroureternephrosis, and multiple number and muscle invasive groups.

Table-4: Linear Regression analysis of Muscle Invasive groups according to Hydrouretero Nephrosis, Character of tumor, Calcification, Number and size

Variable		Coefficient	Std Error	F-test	P-Value
Calcification	Yes vs No	0.282	0.159	3.135	0.0787
Character of tumor	Sessile vs Pedunculated	0.559	0.104	29.008	<0.0001*
Hydrouretero Nephrosis	Yes vs No	0.284	0.090	9.933	0.0019*
Number	Multiple vs Single	0.529	0.100	27.872	<0.0001*
Size	>9.5 vs ≤9.5	0.042	0.080	0.273	0.6016
Group (Constant)	Muscle Invasive vs Non Muscle Invasive	0.145	0.030	24.167	0.0000*

*Statistically significant

DISCUSSION:

Accurate staging of any tumor is a prerequisite to ensure that the proper treatment is instituted in appropriate time. Given that the muscle invasive bladder cancer is highly lethal and it poses severe impact on patient's quality of life, early and correct diagnosis of muscle invasion is very much important in the management of this disease. Association between increasing depth of bladder wall penetration by tumor with impaired prognosis and development of metastases was noted by Geraghty in 1922 [10]. It was not until 1946, that depth of tumor invasion was used by Jewett and Strong for clinical staging [11]. One of the most important prognostic factors is the extent of the tumor. The relation between depth of bladder wall invasion and impaired prognosis and development of metastases is reported in many studies.

It is seen that, in case of high-grade non-muscle-invasive tumor, residual disease is found in up to 33-53% of patients [12-18]. And to reduce the risk of under-staging, a second transurethral resection is often done to plan the future treatment strategy [13, 14]. To do this one has to wait for at least one or two weeks for the biopsy report to be available. Also this poses financial, physical as well as mental agony to the patient. If we can have the accurate biopsy report of the tumor as either muscle invasive or non-muscle invasive from the initial TURBT, the further appropriate treatment can be instituted without much time lag. This may improve the overall survival as well as the quality of life of the patients.

It is evident from our study that, certain characteristics of the tumor like associated hydroureternephrosis large size, sessile and also multiplicity have statistically significant chance of being muscle invasive. So whenever one would encounter bladder tumor having any one or more of the above characteristics, should made every effort to take the muscle biopsy at initial resection bearing in mind that this tumor has high probability of being muscle invasive. Although the results of our study are encouraging, these preliminary findings need to be corroborated with more investigation to substantiate the conclusions. A larger, multi-institutional study would be needed to determine the validity and reliability of our findings. Pending further studies and validations, we suggest that the above mentioned tumor characteristics may be used for predicting muscle invasiveness for clinical practice. This may represent an early step to better decision making regarding treatment strategy and, eventually, improvement in survival and quality of life in bladder cancer patients.

COCLUSION:

Although there is several new sophisticated imaging techniques available including multipara metric MRI, the clinical staging for bladder cancer continues to be inaccurate. We investigated whether the presence of one or more factors could accurately predict muscle invasive disease preoperatively. And as it is evident from the study, the presence of hydroureternephrosis, large size, sessile or multiplicity is statistically significant markers of muscle invasive bladder cancer.

REFFERENCES:

1. Kratz JR, He J, Van Den Eeden SK, Zhu ZH, Gao W, Pham PT, Mulvihill MS, Ziaei F, Zhang H, Su B, Zhi X. A practical molecular assay to predict survival in resected non-squamous, non-small-cell lung cancer: development and international validation studies. The Lancet. 2012 Mar 9;379(9818):823-32.

2. Naik DS, Sharma S, Ray A, Hedau S. Epidermal growth factor receptor expression in urinary bladder cancer. Indian Journal of Urology. 2011 Apr 1; 27(2):208.
3. 3. Messing EM. Urothelial tumors of the bladder. In: Campbell-Walsh Urology. 9th ed. Chapter 75. Philadelphia: Saunders Elsevier; 2007: 2407-46.
4. Prout GR, Marshall VF. The prognosis with untreated bladder tumors. Cancer. 1956 May 1; 9(3):551-8.
5. Guzzo TJ, Magheli A, Bivalacqua TJ, Nielsen ME, Attenello FJ, Schoenberg MP, Gonzalgo ML. Pathological upstaging during radical cystectomy is associated with worse recurrence-free survival in patients with bacillus Calmette-Guerin-refractory bladder cancer. Urology. 2009 Dec 31; 74(6):1276-80.
6. Chang SS, Hassan JM, Cookson MS, Wells N, Smith JA. Delaying radical cystectomy for muscle invasive bladder cancer results in worse pathological stage. The Journal of urology. 2003 Oct 31; 170(4):1085-7.
7. Gore JL, Lai J, Setodji CM, Litwin MS, Saigal CS. Mortality increases when radical cystectomy is delayed more than 12 weeks. Cancer. 2009 Mar 1; 115(5):988-96.
8. Bartsch GC, Kuefer R, Gschwend JE, De Petriconi R, Hautmann RE, Volkmer BG. Hydronephrosis as a prognostic marker in bladder cancer in a cystectomy-only series. European urology. 2007 Mar 31; 51(3):690-8.
9. Canter D, Guzzo TJ, Resnick MJ, Brucker B, Vira M, Chen Z, Tomaszewski J, VanArsdalen K, Wein AJ, Malkowicz SB. Hydronephrosis is an independent predictor of poor clinical outcome in patients treated for muscle-invasive transitional cell carcinoma with radical cystectomy. Urology. 2008 Aug 31; 72(2):379-83.
10. Geraghty JT. Treatment of malignant disease of the prostate and bladder. J Urol. 1922 Jan; 7:33-65.
11. Jewett HJ, Strong GH. Infiltrating carcinoma of the bladder; relation of depth of penetration of the bladder wall to incidence of local extension and metastases. The Journal of urology. 1946 Apr; 55:366.
12. Miladi M, Peyromaure M, Zerbib M, Saïghi D, Debré B. The value of a second transurethral resection in evaluating patients with bladder tumours. European urology. 2003 Mar 31; 43(3):241-5.
13. Jakse G, Algaba F, Malmström PU, Oosterlinck W. A second-look TUR in T1 transitional cell carcinoma: why?. European urology. 2004 May 31; 45(5):539-46.
14. Brauers A, Buettner R, Jakse G. Second resection and prognosis of primary high risk superficial bladder cancer: is cystectomy often too early? The Journal of urology. 2001 Mar 31; 165(3):808-10.
15. Schips L, Augustin H, Zigeuner RE, Gallé G, Habermann H, Trummer H, Pummer K, Hubmer G. Is repeated transurethral resection justified in patients with newly diagnosed superficial bladder cancer?. Urology. 2002 Feb 28; 59(2):220-3.
16. Grimm MO, Steinhoff C, Simon X, Spiegelhalder P, Ackermann R, VÖgeli TA. Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. The Journal of urology. 2003 Aug 31; 170(2):433-7.
17. Divrik RT, Yildirim Ü, Zorlu F, Özen H. The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesical mitomycin: a prospective, randomized clinical trial. The Journal of urology. 2006 May 31; 175(5):1641-4.
18. Jahnson S, Wiklund F, Duchek M, Mestad O, Rintala E, Hellsten S, Malmström PU. Results of second-look resection after primary resection of T1 tumour of the urinary bladder. Scandinavian journal of urology and nephrology. 2005 May 1; 39(3):206-10.