



Original article

A cyto-histo pathological correlation of bladder tumors in relation to smoking as a risk factor

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Abstract

Urinary bladder serve as an excretory dustbin, is exposed to all toxic and non toxic substances excreted by the body, thus it is a host to many metaplastic and neoplastic conditions apart from inflammatory changes. Urinary cytodiagnosis and biopsy studies are sufficient for confirmation in most cases. In this study also an attempt has been made to correlate smoking as a high risk factor. To correlate cytology and histology of different bladder tumors with smoking as a predisposing factor. This study was conducted on 74 patients who were admitted to the department of urology, Hi-Tech Medical College, Bhubaneswar between June 2012 and October 2014. Routine urinary cytology was done and stained by both diff quick and papanicoloke stain and biopsy specimen were stained by hematoxylin and eosin stains. By standard questionnaire the history of smoking was documented with consent from the patients who were included in the study. Out of 74 cases, 17 cases did not turn up for follow up. Samples were inadequate in 5 cases. 52 cases were analyzed in the study. Strong correlation between cytodiagnosis and histology was observed with over all sensitivity 92.5% and specificity 80.0%. Out of 52 cases 21 were having history of smoking upto 10 cigarettes a day for a period of more than 20 years and 17 of them had high grade urothelial carcinoma 40.3% and 31 non smokers had 21.1% risk of developing bladder tumors. The present study concluded that urinary cytodiagnosis is well correlated with histopathology of bladder tumors. This can be performed in centres where molecular marker study is not available. This is fairly cheap and accurate for early diagnosis and treatment. History of smoking habit is equally important to correlate with bladder tumors as a risk factor.

Key words: Bladder tumor, CECT, Cytodiagnosis, Fluorescence in-situ hybridization, Histopathology, Immune histochemistry, Smoking

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The urothelial neoplasms are known for their recurrence and morbidity than mortality. All types of neoplasms can be seen in bladder, but more than 95% of bladder tumors are of

epithelial in origin and the rest are mesenchymal. Variants like squamous cell carcinoma and adenocarcinoma of urinary bladder carry worst prognosis where as prognosis of even high grade urothelial

carcinoma stands better survival rate¹. The challenge is that, early detection and treatment of new or recurrent cases are required to optimize bladder preservation, reduced patient morbidity and increase survival rate. Urinary cytodiagnosis and histopathological study are cost effective and have fairly accurate morphological assessment for early detection of bladder tumors as such patients present with history of painless hematuria².

The first report in 1955 by Holsti and Ermalan suggested a relationship between bladder cancer and smoking. Since then few available literature established a strong association of bladder tumor with smoking as a risk factor³. Though different investigation modalities are available in cases of suspected bladder tumor such as (a) ultrasonography, (b) cystoscopy (c) Computed tomography (CE-CT) scan (d) Magnetic resonance imaging (MRI) and (e) Molecular markers, yet urinary cytodiagnosis and morphological correlation with histopathology are cost effective and fairly accurate⁴.

Most of the published literature and data on urinary cytodiagnosis and histopathological correlation of bladder tumors specifically in relation to smoking as a risk factor are from research works outside the state and country, with occasional reference from our state. So this study was taken up.

Materials and methods

This study was approved by the ethical committee of Utkal University. All patients with complain of painless hematuria and suspicion of bladder tumor were included in the study. Those patients unwilling to co-operate were excluded from the study.

A. Urine cytology was performed by standard procedure and slides fixed with 95% isopropyl alcohol were stained by Diff-quick stain, hemotoxylene and eosin stain and also by papanicolaou stain separately. Cytology findings include hazy or turbid urine specimen, presence of numerous polymorphs, histiocytes, occasionally eosinophils, Inflammatory changes in epithelial cells, presence of pathogenic microorganisms and evidence of associated pathology may be seen. Histological grading of Invasive carcinomas of the bladder composed of orderly sheets of cells resembling normal urothelium (grade I tumors) are very rare. Essentially all invasive tumors are grade II, III, or IV, depending on the level of architectural and cytologic abnormality. Grade II tumors mimic papillary tumors of high grades and are composed of sheets of relatively uniform cancer cells separated from each other by bands of connective tissue. Grade III tumors are usually

solid and are characterized by variability in the size of cancer cells and marked nuclear abnormalities. Grade IV tumors are either composed of large cancer cells, spindle and giant cells, or of small cancer cells.

- B. Biopsy samples as received from transurethral resection of bladder tumors (TURBT) specimen were subjected to standard tissue processing, cutting and stained with hemotoxylene and eosin stain.
- C. History of addiction to smoking of cigarette, bidi and pica (as used by males and females in tribal belts of Odisha) 10 numbers a day for period of beyond 20 years were included in this study.

Statistical analysis

Data were statistically analyzed using SPSS software version 20.0. Frequency and percentages were calculated for categorical and ordinal variables. Chi-square test was carried out and p value ≤ 0.05 were considered statistically significant.

Results

Total 74 patients with suspected bladder tumors presented with history of painless hematuria were subjected for urinary cytology. 17 cases were lost to follow up, 5 samples were inadequate and 52 cases were included. Total urinary cytosmears reported were listed in table 1. From the table 2, it was found that, out of 52 cases subjected to urinary cytodiagnosis, we received 51 TURBT biopsy specimens which were subjected for histopathological study. 46 cases were neoplastic, 30 malignant and 7 benign tumours. 5 cases were non-neoplastic. Of the 46 neoplastic cases, 37 were males (80%) and 9 were female patients (20%). In female, we had 1 benign and 8 were having malignant tumors (ratio 1:8) where as in males 6 were benign and 31 were malignant tumors (ratio 1:5). Other than the routine transitional cell carcinomas we had one case of adenocarcinoma in a 70 year old male and only one case of squamous cell carcinoma in a 60 year old female. The 39 malignant tumors included 26 were high grade tumors, 8 cases of low grade and 5 cases were tumors with low malignant potential. Of the 7 benign tumors we had 1 squamous papilloma, 1 Cavernous hemangioma and 5 cases were inverted papilloma. Amongst 26 malignant tumors, LVI found in 8 cases (31%), muscle invasion in 21 cases (81%) of low and intermediate grade malignant tumors 2 out of 13 (15%) showed LVI and 4 out of 13 (30%) showed muscle invasion (Fig 1a-d), (Fig 2 a-d). In our study incidence of bladder tumor is more amongst smokers (40.3%) in comparison to non smokers (21.1%) (Table 3).

Urinary cytosemears		N
Inadequate		05
Negative	Inflammatory-14	17
	Catheter injury-3	
Suspicious		05
Low intermediate grade tumor		06
High grade tumor		19
Total cases		52

Histology	Tumor Present	Tumor Absent	Total	
Cytology	Positive	25 (a)	05 (b)	30 (a+b)
	Negative	02 (c)	20 (d)	22 (c+d)
		27 (a+c)	25 (b+d)	52

Sensitivity of cytology = $a/a+c = 25/27 = 92.5\%$
 Specificity of cytology = $d/b+d = 20/25 = 80\%$
 Positive predictive value = $a/a+b = 25/30 = 83.3\%$
 Chi-square = 25.13, df 1 and $p < 0.0001$, which is significant

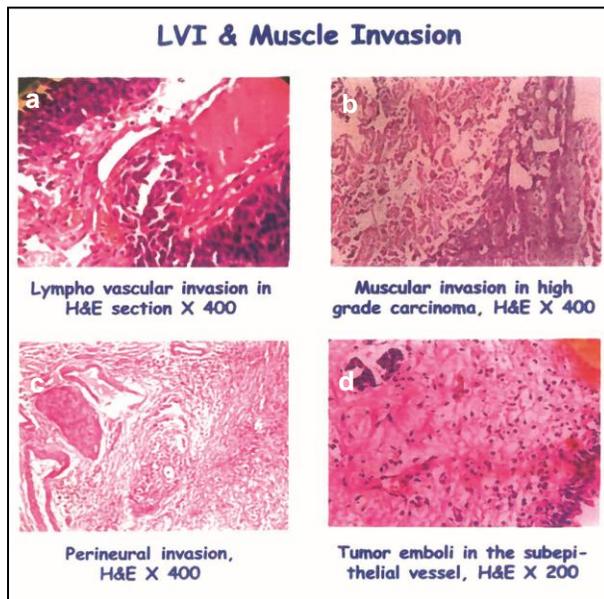


Fig 1. Lymphovascular invasion and muscle invasion

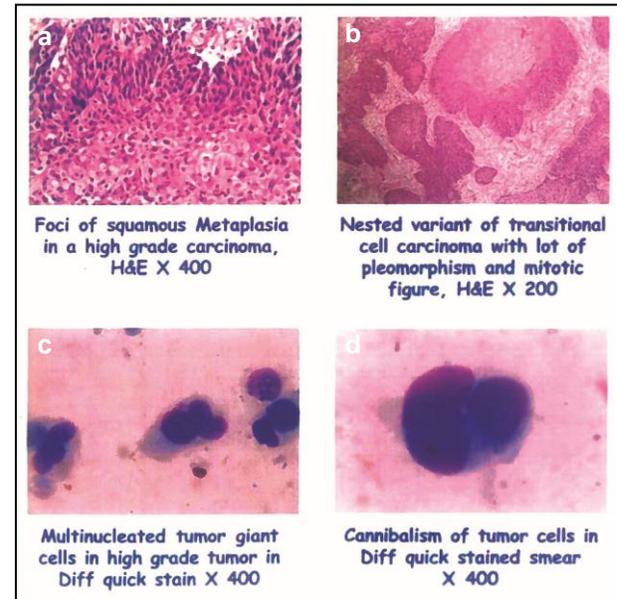


Fig 2. Metaplasia and malignant cells

Histology	Smokers (n=21)				Non Smokers (n=31)			
	Benign	Gr I	Gr II	Gr III	Benign	Gr I	Gr II	Gr III
Positive (n=25)	-	-	1	17	-	-	2	5
Cytology Suspicious (n=5)	-	-	1	1	-	2	1	-
Negative (n=22)	-	1	-	-	-	-	1	-
52	-	1	2	18	-	2	4	5

Discussion

Total number of patients admitted to urology department in two years was 2254, out of which bladder tumor was found in 46 cases, constitutes 2% of total patients which matches with study by shenoy et al⁵. About 95% of bladder tumors are of

epithelial origin, the remainder being mesenchymal tumors. Most epithelial tumors are composed of urothelial (transitional) type cells and are thus interchangeably called urothelial or transitional tumors, but squamous and glandular carcinomas also occur. Urothelial carcinoma (UC) is two to three times more common in men than women.

Bladder neoplasm was mostly seen in elderly age group 83% of the patients which correlates with the finding of Nabi et al⁶. In our study male to female ratio is 4.2 : 1. In the study of Canter et al⁷ it was 4 :1 and the study by Nabi et al⁶. It was 3.5:1. Most common clinical presentation was gross haematuria, 71% of patients which almost matches with study Nabi et al⁶ i.e. 72%. Our study shows recurrence of bladder tumor in 8 patients within 1-3 years of treatment. Tumor recurrence or progression could be due to clinical under diagnosis as found by Chenko D⁸. It could also be due to the synchronous and metachronous multifocality of transitional cell carcinoma⁹. So the patients are to be followed up by urinary cytology. Mitra et al¹⁰ in their study pointed out that it is unlikely for a single marker to be sufficient for conclusion to improve the prognosis for patients with bladder tumors, but a combination of multiple markers are required for prognostication. This will be very expensive. Therefore urinary cytodiagnosis and correlation with histopathological study becomes the cheap as well as fairly accurate diagnosis criteria as mentioned by Steiner et al¹¹ and Nabi et al⁶. Lymphovascular invasion (LVI) which is an important determinant of metastasis was seen in 31% high grade and 15% low grade tumors which almost matches with the study of Bolenz et al¹². Incidences of muscular invasion in our study was found in 81% of high grade tumors and 31% in low grade tumors which shows our figures are higher than the study by Karakiewicz et al¹³. Tobacco smoking is the best established factor for bladder carcinoma in both men and women. As the composition of cigarettes has changed over the past 50 years, leading to reduction of levels of tar and nicotine concentrations in cigarette smoke and at the same time the concentration of some carcinogens like beta-naphthylamine, a bladder carcinogen and tobacco-specific nitrosamines. Population attributable risks for tobacco smoking have been estimated to be 50-60% in men and 20-30% in women. The risk of bladder cancer is generally more in smokers than non-smokers. We found the history of tobacco addiction for smoking in 53.8% and 21.1% in non smokers. Pietzak et al¹⁴ suggested that smokers have three fold increased risk of developing bladder cancer than non smokers. Our study matches with study by Grotehivs et al¹⁵ showed (50.9% / 18.8%) and Rink et al¹⁶ (46.0% / 28.0%). Alberg et al¹⁷ showed the rate of bladder cancer was 22% in smokers and 52% in non-smokers whereas Tripathi et al¹⁸ reported 23% in smokers and 39% in non-smokers. Sturgeon et al¹⁹ found that risks of each stage of bladder cancer increased with number of cigarettes smoked per day, but the more

advanced the stage the higher the relative risk. Similarly, in this study we found that smokers were proportionally more likely than nonsmokers to be diagnosed with invasive disease and this difference was statistically significant.

Conclusion

Early detection and treatment of new / recurrent cases is required to optimize bladder preservation, reduce patient morbidity and increase quality of life. We have evaluated in our study that urinary cytodiagnosis and subsequent histopathological correlation has high sensitivity and specificity 92.5% and 80% in our study. Even though many other modalities such as Immune Histochemistry (IHC), Fluorescence-in-situ Hybridization (FISH), are available, these are expensive and requires specialised centres where these studies are available. While taking history, persons addicted to prolonged tobacco smoking 10 cigarettes / Picca / Bidi per day for a period of more than 20 years should be correlated with bladder tumor. Though smoking is not the only causative factor yet stands as a major risk factor for urinary bladder cancer.

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Competing interest: Authors have declared that no competing interests exist.

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