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Pathology

Histopathologic Pattern of Bladder Cancer with Pathological Staging and Grading: An experience at a Tertiary Care Center in Bangladesh

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Abstract **Original Research Article**

Aims and objectives: To determine the histopathologic pattern of bladder cancer with pathological staging and grading. ***Methods:*** A retrospective study were undertaken from the records of the diagnosed bladder cancer at the Department of Histopathology, National Institute of Kidney Diseases and Urology, Dhaka, during the period from January 2019 to June 2020. ***Results:*** A total of 250 histopathologically diagnosed cases of bladder neoplasm were studied. Of the 250 cases, 224 cases (89.6%, n=250) showed malignant bladder neoplasm and 26 (10.4%) benign bladder neoplasm. Male patients were 201 and female 49. Male: female ratio was 4.1:1. The age ranged from 1yaer to 90 years and average 55 years. A total of 151 cases (67.41%) were non-invasive, 41 (18.30%) invasive and rest 32 (14.28%) advanced bladder cancer. Most frequent non-invasive cancer were pTa stage group 121 (54.01%) followed by pT1 stage group 18(8.03%). Most frequent muscle invasive bladder cancer were in pT2a stage group (8.03%) followed by pT_2b stage group (4.91%). Most frequent advanced bladder cancer were pT4a 21 (9.37%) followed by 11 (4.91%). TCC was the most frequent 135 (89.40%) followed by SCC 08 (5.30%). TCC with different grades of differentiation were 61 (83.57%, n=73) followed by invasive TCC with squamous differentiation 08 (10.97%, n=73). ***Conclusion:*** Histopathologic pattern of bladder cancer, its pathological staging and grading are of great clinical as well as diagnostic and prognostic importance.

Keywords: Bladder cancer, squamous cell carcinoma (SCC), transitional cell carcinoma (TCC). Transurethral resection of bladder tumor (TURBT), pT= primary tumor.

INTRODUCTION

Over 90% of urothelial tumors are malignant and rest 8-10% benign which are also called non-invasive urothelial neoplasm. Urothelial carcinoma (UC) is a common malignancy of the genitourinary system, typically affecting the bladder, renal pelvis, and the ureter. Bladder cancer is the 9th most common cancer worldwide and the 13th most common cause of death, accounting for 145,000 deaths worldwide[1]. It accounts for 6% of all cancers in men and 2% of all cancers in women globally.[2,3] In North America and Europe, 95% to 97% of cases of bladder cancer are of urothelial variety. In Africa, 60% to 90% are urothelial and 10% to 40% are squamous cell carcinoma[1]. Overwhelmingly, it is a male predominant disease with males more frequently impacted than females in an approximate ratio of 4:1. The most frequent histologic type of bladder cancer is urothelial carcinoma, not otherwise specified (NOS) which recapitulates the usual urothelial lining of the bladder, urethra and upper urinary tracts. This represents ~80–90% of all bladder cancers worldwide[3]. Lower tract urothelial carcinoma: bladder and urethra represent 90 - 95%. Upper tract urothelial carcinoma: ureter and renal pelvis represent 5 - 10%[6].

An important part of assessing bladder cancer is grading the cancer according to how aggressive the cancer cells appear under a microscope, and pathological staging which is assessing the extent of the cancer within the bladder and, more rarely, elsewhere in the body.

Histologically, 90% of bladder cancers are of urothelial origin, 5% are squamous cell carcinoma and less than 2% are adenocarcinoma or other variants.[5]

Bladder cancer is a heterogeneous disease with a variable natural history. Approximately 70–75% of patients present with noninvasive (pTa or pTis) or superficially invasive (pT_1) at the time of diagnosis, 20% present with muscle-invasive tumors (pT2–3) and rest 5-10% of the bladder cancers present with advanced bladder cancer [7]. Surgical and medical treatment of noninvasive and invasive bladder cancer is of totally different. Therefore it is mandatory to histopathological stage categorization of the bladder cancer as noninvasive or superficial bladder cancer and invasive or advanced bladder cancer for proper treatment and follow up. Urothelial carcinoma that has penetrated the basement membrane and invaded into the lamina propria or deeper is called invasive urothelial carcinoma. Histologic characterization and depth of invasion are the most important factors for determining prognosis.

Urothelial carcinoma is morphologically heterogenous with many variants and subtypes.
Subtype (variant) histology and divergent differentiation of invasive urothelial carcinoma are used inter-changeably by some authors. However, they are two different processes. Subtype of urothelial carcinoma (SUC), defined here as urothelial carcinoma with any histologic subtype or divergent differentiation, is a clinically aggressive disease. SUC accounted for approximately 31% of muscle-invasive bladder cancers, 12% of upper tract urinary cancers, and 34% of metastatic diseases [4,5].

Invasive urothelial carcinoma can have variants in both morphology and differentiation. Morphologic variants of invasive urothelial carcinoma may be sarcomatoid, plasmacytoid, nested, micropapillary, microcystic, giant cells, clear cells, small cell and lymphoepithelioma-like. Invasive urothelial carcinoma are of two main histologic types which are mainly urothelial (90%) and non-urothelial (10%) origin[11]. Variants of invasive urothelial carcinoma are usually of squamous, glandular and trophoblastic differentiation. Some variants urothelial carcinoma are associated with a poor prognosis. These variants have different therapeutic implications, such as different surgery criteria and chemotherapy regimens. It is recognized that certain subtypes impact patient prognosis and outcome hence the need to correctly recognize and document their presence. In these way, subtypes and divergent differentiations can affect patient prognosis and treatment decisions. Pathologists provide information to urologists and oncologists to help with risk stratification and treatment planning.

On the other hand, grading of bladder cancer by histopathology helps to determine how quickly the cancer is growing and how likely it is to spread. This information helps the clinician's plan of treatment and estimation of prognosis. Grading helps us to divide bladder cancer as low grade bladder cancer which are well differentiated, grow slowly and less likely to spread and less chance of recurrence and high grade which are poorly differentiated or undifferentiated, grow and spread quickly and high chance of recurrence.

Pathological staging of urothelial carcinoma is paramount importance because of invasive urothelial carcinoma involving the lamina propria (T1) is often treated with conservative intravesical therapy and mucosal resection but invasive urothelial carcinoma involving the muscularis propria (T2) is often treated with radical cystectomy[5].

In the light of above context, the aim of this study was to determine the pattern of bladder cancer with pathological staging and grading in admitted bladder biopsy cases which ultimately helps in proper diagnosis and treatment plan.

MATERIALS AND METHODS

A retrospective study were conducted of the admitted patients with clinically, radiologically and histopathologically diagnosed cases of bladder neoplasm at the department of histopathology, National Institute of Kidney Diseases and Urology, Sher-E-Bangla Nagar, Dhaka during the period of January 2019 to June 2020.
The histopathology reports of 250 bladder biopsy cases obtained by transurethral resection of bladder tumor (TURBT), radical and total cystectomy specimens were the study group. After confirmation of bladder neoplasm as benign, these cases were excluded for further studies. Relevant histology-stained slides were retrieved and viewed. Freshly stained slides were made from stored blocks in cases of missing slides.

The study analyzed all diagnosed malignant urinary bladder neoplasms found in the department of histopathology registry book. Pathologists reviewed previously diagnosed cases, retrieved broken and faded tissue blocks and stained them with Haematoxylin and Eosin. Special stain was done if necessary. The data also analyzed for the histologic subtyping and variants of bladder cancers diagnosed in the hospital. Bladder cancers were studied by categorizing three groups. Those bladder cancers that do not invade basement membranes or if invade upto lamina propria regarded as non-invasive, those bladder cancers invade upto muscularis propria and perivesical tissue within bladder regarded as invasive and those invade beyond the bladder tissue regarded as advanced bladder cancer.

In this study, bladder cancer also analyzed by pathological staging as follows:

pTa: noninvasive papillary carcinoma; **pTis**: carcinoma in situ; **pT1**: invades lamina propria; **pT2a**: invades inner half of muscularis propria; **pT2b**: invades outer half of muscularis propria; **pT3a**: microscopically invades perivesical tissue; **pT3b**: macroscopically invades perivesical tissue; **pT4a**: directly invades prostatic stroma, seminal vesicles, uterus or vagina; **pT4b**: directly invades pelvic wall or abdominal wall[12].

Lastly, all non-invasive and invasive TCC with different grades of differentiation were graded accordingly. Grading of tumor cells were obtained by observing increased N:C ratio, moderate to marked hyperchromasia, marked pleomorphism, coarse chromatin and increased abnormal mitosis. But invasive or non-invasive TCC of squamous, glangular, microcystic etc differentiation, morphologic variants of TCC or other histologic type of bladder cancer were excluded from grading of tumor cells. Data were analyzed under standard statistical method.

RESULTS AND OBSERVATIONS

A total of 250 histopathologically diagnosed cases of bladder neoplasm were studied in this study group. Of the 250 cases, 225 cases were obtained by TURB, 18 cases by total cystectomy and 07 cases by radical nephrectomy. Of the 250 cases, 224 cases (89.6%, n=250) showed malignant bladder neoplasm and 26 (10.4%) benign bladder neoplasm. Out of 250 cases, 201 cases were male and 49 were female. Male: female ratio was 4.1:1. The age ranged from 1yaer to 90 years and average 55 years.

Table-1: Distribution of bladder tumors obtained from different techniques of biopsy (n=250)

Biopsy specimens obtained	Total biopsy cases	Malignant, n=250 (%)	Benign, n=250 (%)
TURBT	225 (90%)	199 (79.6%)	26 (10.4%)
Total cystectomy	18 (7.2%)	18 (7.2%)	00
Radical cystectomy	07 (2.7%)	07 (2.8%)	00
Total	250 (100%)	224 (89.6%)	26 (10.4%)

Table-1 shows out of total 250 biopsy study case, 199 cases (79.6%, n= 250) were bladder cancer of different grades and pathological stages, those tissue obtained by TURBT (225 cases), total cystectomy (18 cases) and radical cystectomy (07 cases). Rest 26 cases (10.4%, n=250) of TURBT cases showed benign bladder neoplasm. No benign bladder neoplasm cases were found in total and radical cystectomy obtained biopsies. All radical nephrectomy 07 (2.8%) and total nephrectomy specimens 18 (7.2%) revealed high grade muscle invasive and advanced bladder cancer.

Over all 26 cases (10.4%, n=250) showed benign neoplasm of urinary bladder obtained only from 225 TURBT cases. Rest 224 cases (89.6%) were malignant bladder tumor. These 224 cases (89.6%) of malignant bladder neoplasm were analyzed according to tumor pattern, histological types of tumor cells, pathological staging and grading of tumor cells for further study.

Table-2: Distribution of bladder cancer among different techniques of biopsy (n=224)

	Total number	Malignant cases (n= 224)		
Biopsy obtained				
		Non-invasive	Invasive	Advanced
TURBT	199 (88.84%)	151 (67.41%)	29 (12.95%)	19 (8.48%)
Total cystectomy	18 (8.03%)	00	12 (5.35%)	06 (2.67%)
Radical cystectomy	07 (3.13%)	00		07 (3.13%)
Total	224 (100%)	151 (67.41%)	41 (18.30%)	32(14.28))

Table-2 shows that out of 224 cases of bladder cancer, 151 cases (67.41%) were non-invasive, 41 cases (18.30%) invasive and rest 32 cases (14,28%) advanced bladder cancer. Out of 18 (8.03%) total cystectomy muscle invasive bladder cancer, 12 cases (5.35%) were only muscle invasive and rest 06 cases (2.67%) were advanced bladder cancer. All of the 7 radical cystectomy cases (3.13%) were advanced bladder cancer. Twenty six cases (10.4%), all of which found in TURBT biopsies in this study group were excluded for further study because of benign bladder neoplasm only.

Table-3: Pathological staging of 224 bladder cancer found in this study group: (n=224)

Pathological stage Total bladder cancer 224 (89.6%)	Non-muscle invasive 151 (67.41%)	Muscle invasive 41 (18.30%)	Advanced 32 (14.28%)
pTis or CIS	12 (5.37%)	--	--
pTa	121 (54.01%)	--	--
pT1	18 (8.03%)	--	--
Total	151 (67.41%)	--	--
pT2a	--	18 (8.03%)	--
pT2b		11 (4.91%)	
pT3a	--	08 (3.57%)	
pT3b		04 (1.79%)	
Total	--	41 (18.30%)	---
pT4a	--	--	21(9.37%)
pT4b			11 (4.91%)
Total	**--**	**--**	**32 (14.28%)**

Table-3 shows 224 cases (89.9%) of bladder cancer distribution in different pathological stages with number and percentage. Out of 224 cases of bladder carcinoma, 151 cases (67.41%) were non-invasive cancer, 41 cases (18.30%) were only muscle invasive bladder cancer and rest 32 cases (14.28%) were advanced bladder cancer. Out of 151 cases (67.41%) of non-invasive cancer, most frequent cases were pTa stage group 121 (54.01%) followed by pT1 stage group of patients 18(8.03%). pTis stage group of cases were 12 (5.37%). Of the 41 cases (18.30%) of only muscle invasive cases, most frequent cases were in pT2a stage group 18 (8.03%) followed by pT_2b (4.91%) stage group of patients.

In this study group, there were 32 cases (14.28%) of patient who showed local or distant metastasis. Of these, most frequent cases were pT4a 21(9.37%) followed by 11 cases of pT4b group of patients.

Table-4: Histopathologic types of non-invasive bladder cancer n=151, (67.41%)

Histopathologic types	Number	Percentage
Transitional cell carcinoma	135	89.40
Squamous cell carcinoma	08	5.30
Mixed cell carcinoma (transitional and squamous)	06	3.98
Adenocarcinoma	02	1.32
Total	**151**	**100**

Table-4 shows different histological types of non-invasive bladder cancer occurred in this study. Transitional cell carcinoma was the most frequent cases 135 (89.40%) followed by squamous cell carcinoma cases 08 (5.30%). Interestingly, mixed cell carcinoma were 6 (3.98%).

Table-5: Histopathologic subtypes and morphologic variants of invasive bladder carcinoma (including advanced carcinoma) in the study; (n=73, (32.59%))

Histopathologic subtypes	Number	Percentage
Invasive TCC with different grades of differentiation	61	83.57
Invasive TCC with squamous differentiation	08	10.97
Invasive TCC with glandular differentiation	2	2.73
Sarcomatoid carcinoma	2	2.73
Total	**73**	**100**

Of all muscle invasive and metastatic group of patients 73 (32.59%), most frequent cases were invasive TCC with different grades of differentiation 61 (83.57%, n=73) followed by invasive TCC with squamous differentiation 08 (10.97%, n=73). There were 2.73% cases who exhibit both epithelial and sarcomatoid morphology called sarcomatoid carcinoma.

Table-6: Grading of TCC of both in non-invasive and invasive bladder cancer with different grades of differentiation.

Non-invasive bladder TCC (n=135)		Invasive bladder TCC (n=61)	
Grade-1	111 (82.22%)	Grade-1	12 (19.67%)s
Grade-2	19 (14.07%)	Grade-2	35(57.38%)
Grade-3	05 ((3.71%)	Grade-3	14 (22.95%)
Total	**135(100%)**	**Total**	**61 (100%)**

Grade- 1 TCC= Well differentiated transitional cell carcinoma
Grade-2 TCC= moderately differentiated transitional cell carcinoma
Grade- 3 TCC= Poorly differentiated transitional cell carcinoma

Table-6 shows grading of TCC of both non-invasive and invasive cases in the study group. Invasive or non-invasive TCC of squamous, glangular, microcystic etc differentiation, morphologic variants of TCC or other histologic type of bladder cancer were not included in this table. Most frequent transitional cell carcinoma with grade-1 were observed in non-invasive TCC cases followed by grade-2 TCC. Moderately differentiated transitional cell carcinoma (Grade-2) were the most frequent TCC in invasive bladder carcinoma. Out of advanced bladder cancer 32 cases (14.28%, n=224), 21 cases (65.63%, n=32) showed features of poorly differentiated transitional cell carcinoma, 08 cases (25%, n=32) were moderately differentiated transitional cell carcinoma and rest 3 cases (9.38%, n=32) were well differentiated transitional cell carcinoma.

DISCUSSION

A total of 250 biopsy cases of bladder neoplasm were studied. Out of 250 cases of bladder neoplasm, 26 cases (10.4%) were benign bladder neoplasm and rest 224 cases (89.6%) were malignant bladder neoplasm of different grades and stages. Our study showed 4 times male preponderance than female. Malignant bladder neoplasm is predominantly a male disease. This male preponderance is well documented by many studies. Thus, our finding is not an exception at all. Although, Alhassan et al in their study reported a significant M: F ratio of 18:1 which is more than 4 times the ratio 4.1:1) found in this study.[13]

The peak age incidence of these tumours is the sixth decade of life and our mean age in this study was 55years while the peak age of occurrence was between the 5th and 6th decades. We also recorded a wide age spectrum from 45yr to 90 yrs. This wide age spectrum is significant because traditional malignant neoplasms such as invasive urothelial neoplasm are uncommon in young age.[14]

This study revealed malignant bladder neoplasm of about 89.6% and benign bladder neoplasm 10.4% which is more or less similar to other studies.

In our study, out of 224 cases of bladder cancer, 151 cases (67.41%) were non-invasive, 41 cases (18.30%) invasive and rest 32 cases (14,28%) advanced bladder cancer. Out of 18 (8.03%) total cystectomy muscle invasive bladder cancer, 12 cases (5.35%) were only muscle invasive and rest 06 cases (2.67%) were advanced bladder cancer. All of the 7 radical cystectomy cases (3.13%) were advanced bladder cancer. Twenty six cases (10.4%), all of which found in TURBT biopsies in this study group were excluded for further study because of benign bladder neoplasm only.

Bladder cancer is a heterogeneous disease with a variable natural history. Our study showed lamina propria invasive malignant bladder neoplasm (8.03%), only muscle invasive (18.20%) and advanced bladder neoplasm (14.28%) –all three together about (40.51%).

Most frequent cases were invasive TCC with different grades of differentiation 57%, followed by invasive TCC with squamous differentiation 10.97%. There were 2.73% cases who exhibit both epithelial and sarcomatoid morphology called sarcomatoid carcinoma and only sarcomatoid carcinoma.In one study, the commonest urothelial carcinoma with its variants was 54.9% cases. This comprised 36.7% infiltrative urothelial carcinoma, 7.5% of infiltrative urothelial carcinoma with squamous differentiation, 5.2% of micropapillary carcinoma, 1.0% of infiltrative urothelial carcinoma with glandular differentiation, 0.3% of infiltrative urothelial carcinoma with sarcomatoid differentiation and 4.0 % of poorly differentiated urothelial carcinoma. Similar studies in Nigeria by Mandong et al in Jos and Anunobi et al in Lagos showed higher frequency of urothelial carcinoma with 50.5% and 61.5% respectively.[6,8] Also similar findings were recorded by Klufio et al in Ghana, Gupta et al in Indiaand Hnatko et al in Canada also shows higher frequency rates of 50.4%, 97.7%, 92% respectively.[15,16,17] Sultana et al from Bangladesh documented 18% and 5.3% for squamous and glandular differentiation in urothelial carcinoma, we found 10.97% and 2.73% respectively.[18]

The frequency of occurrence of both infiltrative urothelial carcinoma and squamous cell carcinoma varies with a frequency of 83.7% and 10.97% respectively in this study. This slight rising trend in the incidence of Infiltrative Urothelial Carcinoma may be attributable to the increasing rate of urbanization and industrialization[19,20-22]

Invasive urothelial carcinoma is the most frequent type of bladder cancer and may occur in pure or classical form or with the presence of variant or subtype histology and/or evidence of divergent morphology such as squamous, glandular, or trophoblastic differentiation. Squamous differentiation is the most frequent line of divergent histology seen in high grade urothelial carcinoma.

Like other studies, squamous cell carcinoma was the second commonest malignancy accounting for 5.30% of cases which is higher than in the western world, the relative frequency was 3-7% [23,24.25.] Gupta et al reported a low frequency of 1.0% of SSC.[25] SCC carries poorer prognosis and occurs in younger age group than urothelial carcinomas. Similar to other studies, patients with squamous cell carcinoma were younger than patients with other histological variants[16]

Overall, Ta tumors account for approximately 70% of superficial TCC. These tumors are composed of branching fibrovascular cores with more than 8 cell layers that display features of anaplasia. In general, pTa tumors are low-grade cancers. pT1 tumors, by definition, invade the lamina propria and account for approximately 30% of all superficial bladder tumors. pT1 lesions may have either a papillary or a broad-based appearance and are generally of higher grade than Ta tumors[9].

Our study shows, out of 151 cases (67.41%) of non-invasive cancer. Most frequent non-invasive cases were pTa stage group 121 (54.01%) followed by pT1 stage group of patients 18(8.03%). pTis stage group of cases were 12 (5.37%). More or less similar study were done by different authors. CIS is a high-grade tumor and comprises about 5-10% of all cases of superficial bladder cancer; over fifty percent of CIS multifocal[8]. The risk of progression to muscle invasive disease and subsequent metastases ranges from 40 to 80% with Tis depending on extent of disease. Usually, papillary bladder cancer of pTa stage group 60-70% of all tumors. Invasive into the submucosa, or lamina propria (pT1) diagnosed with 20% to 25% frequency. Between 35% and 48% of patients with pT1 bladder tumors progress to muscle-invasive disease within 3 years when treated by TUR alone. Patients with pT1 bladder tumors mandate repeat TUR to assure accurate staging and removal of any residual tumor burden [10].

In another study, it was showed that approximately 70–75% of patients present with noninvasive (pTa or pTis) or superficially invasive (pT_1) at the time of diagnosis, 20% present with muscle-invasive tumors (pT2–3) and rest 5-10% of the bladder cancers present with advanced bladder cancer [7].

Our study showed, a bit higher predominance of invasive and advanced bladder carcinoma because all of the 25 biopsy specimens (10.4%) obtained from total and radical cystectomy were previously clinically diagnosed invasive and advanced bladder carcinoma.

In our study, even 9.38% of the advanced bladder TCC were well differentiated TCC (grade-1). It can be explained that not all poorly differentiated TCC will metastasize. Because metastasis of an advanced cancer depends on many factors such as advanced tumor stage, atypical histologic features and presence of certain host factors (smoking, chemical exposure etc).

The findings of this study contribute to the understanding of bladder cancer pattern, histologic typing and its variants, staging and also grading in Bangladesh and provide useful information for healthcare professionals and policymakers. Efforts should focus on raising awareness about risk factors, promoting early detection and diagnosis, and implementing preventive measures to reduce the burden of bladder cancer in Bangladesh.

CONCLUSION:

Urothelial carcinoma subtypes and divergent differentiation impact patient outcome and their presence needs to be recognized and documented by the reporting pathologist. Recognition of these entities guide patient counselling and enable prognostic stratification. It can be envisaged that future bladder cancer pathology reporting should not only include the presence and quantity of subtypes/divergent features but also some adjunctive molecular analysis to further enable optimal and individualized therapy.

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