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RESEARCH ARTICLE

HISTOPATHOLOGICAL STUDY OF URINARY BLADDER TUMORS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Introduction: Urinary bladder cancer ranks 9th in worldwide cancer incidence. It is the 7th most common malignancy in men and the 17th most common in women. (1) Urinary bladder carcinoma accounts for 5.6% of cancer in males and 1.8% of cancer in females in India. ***Aims and objectives:*** To study the histopathological pattern of urinary bladder tumors and to compare the histopathological spectrum of urinary bladder tumors in various age groups and genders at a tertiary care hospital in Kashmir valley (SKIMS). ***Materials and Methods:*** The study was conducted in the Department of Pathology at the Sher-i-Kashmir Institute of Medical sciences (SKIMS), Kashmir and included retrospective data analysis for 4 years and a prospective study over a period of 1 year. The specimens/biopsies for urinary bladder tumors received in the Department of Pathology were properly labeled, numbered and then subjected to gross and detailed histopathological examination. The specimens/ biopsies were fixed in 10% buffered formalin. Biopsies were measured. The specimens (partial cystectomy/ cystectomy) were measured and a detailed gross examination was carried out. Gross photographs of the specimens were taken. The tissue was processed as per standard procedure 4-5 micron sections were cut on microtome and stained by haematoxylin and eosin stain and special stains like PAS was done when required. The findings were then analyzed. Microphotographs of tumors were to represent various histological types. ***Results:*** A total of 433 cases were received. Out of those 413 cases (95.7%) were TUR biopsies followed by cystectomy specimens i.e. 13 cases (3%). Cases received for review were 4 (0.9%). Partial cystectomy specimens were least common specimens received i.e. 3 cases (0.7%). Of the total of 433 urinary bladder specimens/ biopsies studied, 411 (94.92%) were found to be neoplastic and 22 (5.08%) were non -neoplastic. Thus majority of urinary bladder lesions comprised of neoplastic lesions. Out of 379 cases of TCC, 315 cases (83.11%) were primary and 64 cases (16.89%) were recurrent. Of the 353 urinary bladder lesions in males, non- neoplastic lesions seen were 18, benign were 16 and 319 were found to be malignant, including 310 TCC cases. ***Conclusion:*** Higher number of Bladder tumors are found in males as compared to females. The most common clinical presentation was hematuria followed by lower urinary tract symptoms, pain abdomen and retention of urine. Right posterolateral wall was the most common site of tumor in Radical cystectomy specimen. Transitional cell carcinoma was the most common tumor type. Muscle invasion was seen in 22.89% of malignant cases and there was increasing trend of cases annually.

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INTRODUCTION

Urinary bladder cancer ranks 9th in worldwide cancer incidence. It is the 7th most common malignancy in men and the 17th most common in women (Parkin *et al*., 2002). Urinary bladder carcinoma accounts for 5.6% of cancer in males and 1.8% of cancer in females in India. In India, it is the 9th most common malignancy (Kamarana *et al*., 2000). There is an increasing trend of urothelial carcinoma in developing countries while as in developing countries; there has been a decline in the number of new cases (Ploeg *et al*., 2009).

MATERIALS AND METHODS

The study was conducted in the Department of Pathology at the Sher-i-Kashmir Institute of Medical sciences (SKIMS), Kashmir and included retrospective data analysis for 4 years and a prospective study over a period of 1 year.

Inclusion criteria

All the cases of urinary bladder tumors received in the Department during the five years of study period were taken

for study. The retrospective study was taken over a period of 4 years from July 2009 to June 2013. The urinary bladder tumor cases were collected from the records section of the Department of Pathology at SKIMS. The histopathological reports of all such cases diagnosed during the above mentioned period, were collected. Name, age, sex address and MRD number and lab. number of patients was checked in the record section of the Department. Corresponding slides were collected. The prospective study of fresh cases of urinary bladder tumors consisting of TUR biopsies and cystectomy (radical/partial) specimens received in the Department was carried out over a period of one year from June 2013 to July 2014. In each case a brief clinical history along with evaluation of available relevant investigations was carried out.

The specimens/biopsies for urinary bladder tumors received in the Department of Pathology were properly labeled, numbered and then subjected to gross and detailed histopathological examination. The specimens/ biopsies were fixed in 10% buffered formalin. Biopsies were measured. The specimens (partial cystectomy/ cystectomy) were measured and a detailed gross examination was carried out. Gross photographs of the specimens were taken. In case of TUR biopsies, whole tissue was submitted for processing. In case of cystectomy specimens a minimum of four sections were taken from the tumor and sections were taken from ureters, urethra, lymph nodes (if present), adventitia and from prostate and seminal vesicles in males. The tissue was processed as per standard procedure and 4-5 micron sections were cut on microtome and stained by haematoxylin and eosin stain and special stains like PAS was done when required. The findings were then analyzed. Microphotographs of tumors were to represent various histological types.

Aims and objectives

To study the histopathological pattern of urinary bladder tumors and to compare the histopathological spectrum of urinary bladder tumors in various age groups and genders at a tertiary care hospital in Kashmir valley (SKIMS).

RESULTS

The study was carried out in the Department of Pathology at Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Kashmir. A total of 433 cases of TUR biopsies/ specimens received in the Department during the five years of study were included in the study.

Table 1. Distribution of different histological types

S. No	Histopathological Type	No.	%
1	Transtitional cell carcinoma	379	92.21
2	Carcinoma- in- situ	1	0.24
3	PUNLMP	12	2.92
4	SCC	1	0.24
5	Sarcomatoid carcinoma	1	0.24
6	Paraganglioma	1	0.24
7	Adenocarcinoma	4	0.97
8	Leiomyosarcoma	1	0.24
9	Metastatic	4	0.97
10	PNET	1	0.24
11	Papilloma	2	0.49
12	Inverted Papilloma	1	0.24
13	Leiomyoma	1	0.24
14	Hemangioma	1	0.24
15	Inflammatory myofibroblastic tumor	1	0.24

The observations made are as follows

A total of 433 cases were received. Out of those 413 cases (95.7%) were TUR biopsies followed by cystectomy specimens i.e. 13 cases (3%). Cases received for review were 4 (0.9%). Partial cystectomy specimens were least common specimens received i.e. 3 cases (0.7%). Of the total of 433 urinary bladder specimens/ biopsies studied, 411 (94.92%) were found to be neoplastic and 22 (5.08%) were non - neoplastic. Out of 379 cases of TCC, 315 cases (83.11%) were primary and 64 cases (16.89%), were recurrent. Of the 353 urinary bladder lesions in males, non- neoplastic lesions seen were 18, benign were 16 and 319 were found to be malignant, including 310 TCC cases. Of the total of 80cases, non-neoplastic lesions found in females were 4; benign were 3 and 73 were malignant, including 69 cases of TCC. Overall urinary bladder lesions were about 4 times common in males (81.52%) than in females (18.48%). Similarly TCC was also about 4 times more common in males. Maximum number of the males were in age group 50-60 years and maximum number of the females were in age group 40-50 years. Overall the maximum number of patients were in the age group of 50-60 years114 cases were located on right posterolateral wall followed by 81 cases on left posterolateral wall. 46 lesions were located on neck, 40 lesions on right anterolateral wall, 31 lesions on left anterolateral wall, 37 lesions on anterior wall, 34 lesions on posterior wall, 29 lesions on dome, 21 lesions on trigone and 22 cases on left lateral wall. One case was showing lesion on external aspect. Majority of TCC cases are located on right posterolateral wall (101 cases) followed by left posterolateral wall (77 cases). 319 cases (73.67 %) had single lesion and 113 cases (26.10%) had multiple lesions.

No definite lesion was found in 1 case (had recent history of TUR) Out of 433 cases, 236 cases (54.50 %) had a positive smoking history and 198 patients (45.50%) were non smokers. Smoking was more common in male cases compared to female cases. Smoking was also more common (58.5%) in TCC cases Out of 22 non- neoplastic lesions seen, inflammation & cystitis cystica were the most common lesions with 10 cases in each group (45.45%). There was one case each of mesonephroid metaplasia and foreign body granuloma (4.55%). Inflammation and cystitis cystica comprised of 2.31 % of all urinary bladder lesions, while Mesonephroid metaplasia and foreign body granuloma comprised of 0.23% of all the cases. Of the total of 411 neoplastic urinary bladder lesions, 392 (95.38%) were found to be malignant and 19 (4.62%) were benign.

Thus majority of the neoplastic urinary bladder lesions comprised of malignant lesions. Hematuria was the most common clinical presentation and was seen in 320 patient with malignant lesions and 13 patients with benign lesions, followed by LUTS seen in 67 patients with malignant lesions and 3 patients with benign lesions. 44 patients with malignant lesions and 4 patients with benign lesions had no symptoms. In cases of TCC hematuria was the most common presentation i.e. in 311 cases, followed by LUTS in 63 patients. 38 patients had no symptoms. Pain abdomen and retention of urine was seen in 12 and 11 patients respectively Transitional cell carcinoma was the most common tumor with 379 cases (92.21%) followed next by 12 cases (2.92%) of PUNLMP. 4 cases (0.97%) of metastatic disease including 2 cases (0.49 %) of metastasis from SCC cervix and 2 cases (0.49 %) of metastasis from prostatic adenocarcinoma, 4 cases (0.97%) of primary adenocarcinoma of urinary bladder, 2 cases (0.49%)

papilloma. 1 case (0.24%) each of primary SCC of urinary bladder, sarcomatoid carcinoma, paraganglioma, leiomyo sarcoma, inflammatory myofibroblastic tumor, inverted papilloma, leiomyoma, hemangioma, PNET. TCC was present in 310 males and 69 females. PUNLMP was also more commonly seen in males (11 males and 1 female). Four cases of primary adenocarcinoma of urinary bladder were seen in males, two cases of metastasis in males and two cases in females and two cases of papilloma in males. There was one case each of carcinoma–in-situ (60year old male), squamous cell carcinoma (60 year old female), sarcomatoid carcinoma (65 yr male), paraganglioma (35 yr male), leiomyosarcoma (65 yr male), inflammatory myofibroblastic tumor (37yr female), inverted papilloma (62 yr male), leiomyoma (55 yr male), hemangioma (74 yr female), PNET (5 yr male). Total number of TUR cases of TCC was 367. Out of them, 184 cases (50.14%), including 142 males and 42 females, had no invasion of muscle and in 84 cases (22.89%) including 72 males and 12 females, muscle invasion was seen. No muscle was identified in 99 cases (26.97%). Cases of muscle invasion were more common with increasing age.

All the 4 cases in the age group › 80years had muscle invasion. 234 cases (61.74%) including 193 males & 41 females were of low grade TCC & 145 cases (38.26%) including 117 males and 28 females were of high grade. With increasing age relative number of high grade tumors had an increasing trend. Of 234 cases of low grade TCC muscle was invaded in only 9 cases, free in 148 cases. No muscle was seen in 77 cases. Of 133 cases of high grade TCC muscle was invaded in 75 cases, free in 36 cases. No muscle was identified in 22 cases. Right posterolateral wall and posterior wall were most sites with 3 cases in each. 2 cases were located on left lateral wall. Neck and trigone, anterior wall were sites in 1 case each. In 1 case tumor was involving anterior and right posterolateral wall and in 1 case tumor was involving posterior and left lateral wall. No growth was identified in 1 case. 8 cases had tumor size 1-3cm, 3 had tumor size 3-5cm and in one case tumor size was more than 5cm. 10 cases had single growth, 2 cases had multiple growths.

In one case no growth was identified. Of 234 cases of low grade TCC muscle was invaded in only 9 cases, free in 148 cases. No muscle was seen in 77 cases. Of 133 cases of high grade TCC muscle was invaded in 75 cases, free in 36 cases. No muscle was identified in 22 cases. 8 cases had tumor size 1-3cm, 3 had tumor size 3-5cm and in one case tumor size was more than 5cm in cystectomy cases. 9 cases had ulceroproliferative growths and in three cases infiltrative growth was seen in 12 cystectomy cases In 11 cases cut-section through growth was grey-white and in 1case cut-section was variegated 12 cases were males and one patient was female. Tumor was grossly invading muscle in 9 cases and adventitia in three cases. Prostate is free in 9 cases and involved in two cases Invasion was limited to inner muscle in 6 cases, to outer muscle in 3 cases and invaded adventitia in 3 cases. All the cases were high grade TCC. LVI were present in 4 cases and PNI was seen in one case. Resection margin was involved in only 1 case (right ureteric margin). Prostate is involved in two cases and seminal vesicle (right seminal vesicle) is involved in 1 case. Lymph nodes were involved by tumor in three cases. 5 cases had pT2a stage, 1 case had pT2a m stage, 2 cases had pT2b stage, 1 case had pT2b m stage, 1 case had pT3a stage and 2 cases had pT4a stage. N0 stage was in 9 cases followed by N2 in 2 cases and N1 in 1 case. 7 cases had stage II, followed by 3 cases in stage IV. 2 cases had stage III.

DISCUSSION

In our study, out of the 433 cases of urinary bladder tissue samples received, 95.4% were transurethral resection biopsies, 3% were cystectomy specimens, 0.7% were partial cystectomy specimens and in 0.9% cases histopathological examination of TUR biopsies was already done outside the institution and were sent to the department for review. As per world literature TURBT is the most common procedure for urinary bladder tumors. Similar findings were noted by Beniwal *et al*. (2015) in their study who observed predominance of resection biopsies with 94.94% of the samples received comprising of resection biopsies and cystectomy specimens comprising 5.06%. Goyal VK *et al*. (2015) observed 4% of the cases comprising of non- neoplastic (inflammatory) lesions in their study. In our study, out of 433 cases 5.08% were non-neoplastic lesions and 94.92% were neoplastic, comprising majority of cases in our study. The findings of our study were in accordance with the above mentioned study. In our study, cystitis cystica and inflammation comprised of 45.45% of the non-neoplastic cases each. Pudasaini *et al*. (2014) observed 69.3% of non- neoplastic lesions comprised of cystitis cystica and rest comprised of inflammation. In our study 81.52% of the cases were males and 18.48% were females. This gender wise distribution was almost similar in non neoplastic and neoplastic (benign and malignant) lesions. The male to female ratio in cases of transitional cell carcinoma was 4.49:1. The gender wise distribution of our study was in accordance with study by Sehli *et al*. (2014) who observed 81.87% of cases with neoplastic lesions were males. Muhammad Mubarak *et al*. (2014) observed 84.2% cases in males and 15.8% in females. The gender ratio was 5.4:1 for transitional cell tumors. Urinary bladder cancer is about 4 times higher in males in the present study & is at par with Mungan *et al*. (2000) who found it 3 to 4 times more common in men than in women.

The most common site of lesions mostly comprising of transitional cell carcinoma on cystoscopic examination in our study was right posterolateral wall followed by left posterolateral wall, neck, anterolateral walls and trigone. In a series of 1000 cases Stephenson *et al*. (1990) found 37% lesions on lateral wall, 18% on posterior wall, 12% on trigone, 11% on neck, dome 8% and anterior wall 4%. In our study 315 cases (83.11%) were primary and 76 cases (16.89%) were recurrent out of total 379 TCC cases. All the cystectomy patients had at least once undergone resection (TURBT). Recurrence was more common in cases with previous diagnosis of high grade transitional cell carcinoma. Matalka I *et al*. (2008) studied a total of 115 patients and found recurrence in 22 patients (31.4 percent). 73.67% of the cases had single lesion on cystoscopy in our study and 26.10% had more than one lesion. Ghulam jeelani *et al*. (2005) conducted a study on urinary bladder lesions and found that 70% of the cases had single lesion and rest had more than one lesion. Auerbach and Garfinkel (1989) showed a correlation between smoking habits and the degree of nuclear atypia in urothelium. In our study 54.45% of the cases were smokers, most of them were males and smoking was more common in patients of transitional cell carcinoma (58.5% of TCC cases). In our study 392(95.37%) cases of the neoplastic lesions were malignant and 19(4.63%) of them were benign. Vaidya *et al* (2013) found

13.09% of all cases of urinary bladder tumors in their study were benign urothelial lesions.

In our study hematuria was the most common clinical presentation and was seen in 320(81.63%) patients with malignant lesions and 13(68.4%) patients with benign lesions, followed by lower urinary tract symptoms e.g. dysuria, urgency, strangury e.t.c. seen in 67 (17.09%) patients with malignant lesions and 3 patients with benign lesions.. Painless hematuria is most common symptom in most of the studies. Goyal VK *et al*. (2015), found hematuria was the most common clinical symptom in 91% cases, followed by strangury (48%), burning (39%) and pain in 38% of cases in their study (Goyal *et al*., 2015).

Fig .1. Gross of Radical cystectomy specimen

Fig. 2. Growth in posterolateral wall of bladder

Fig. 3. Growth in bladder infiltrating muscle

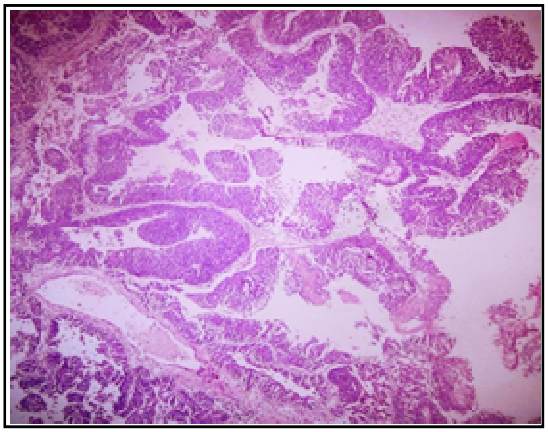

Fig. 4. Microscopy of Low Grade TCC (10x)

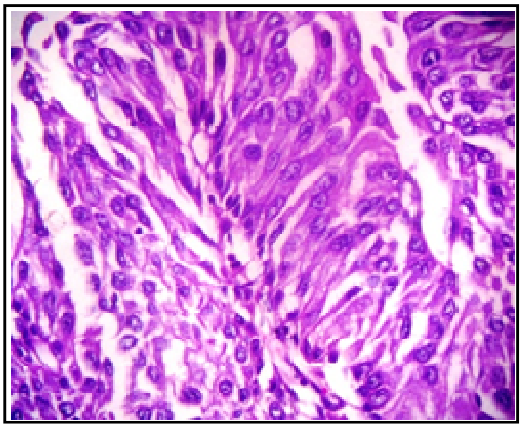

Fig. 5. Microscopy of High grade TCC (40x)

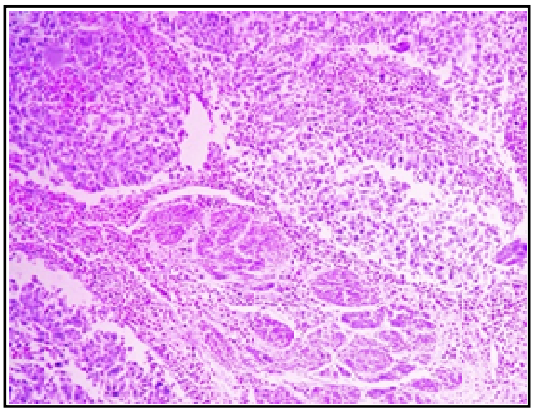

Fig. 6. Microscopy of TCC invading muscle (10x)

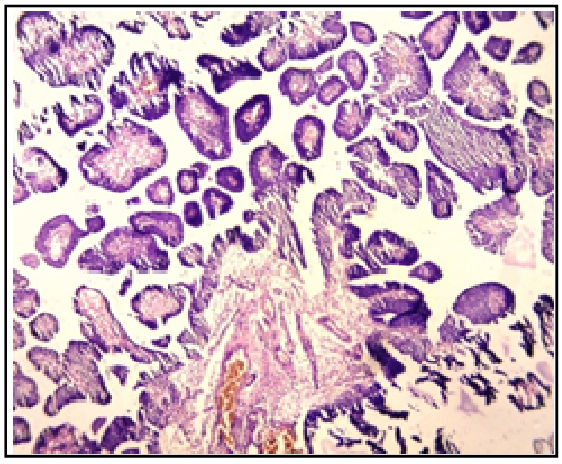

Fig.7. Microscopy of Transitional cell papilloma (10x)

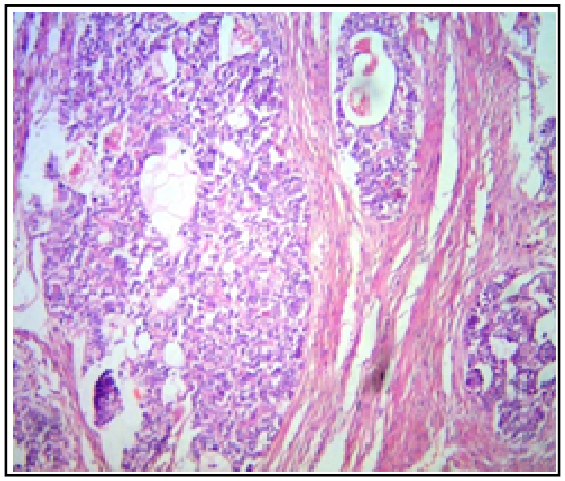

Fig. 8. Microscopy of Adenocarcinoma Bladder(10X)

Histopathological diagnosis of neoplastic lesions

We observed in our study that transitional cell carcinoma was the most common tumor with 379 cases (92.21%) followed next by 12 cases (2.92%) of papillary urothelial neoplasms of low malignant potential, 4 cases (0.97%) of metastatic disease including 2 cases (0.49 %) of metastasis from squamous cell carcinoma cervix and 2 cases (0.49 %) of metastasis from prostatic adenocarcinoma, 4 cases (0.97%) of primary adeno carcinoma of urinary bladder, 2 cases (0.49%) of papilloma. 1 case (0.24%) each of primary squamous cell carcinoma of urinary bladder, sarcomatoid carcinoma, paraganglioma, leiomyosarcoma, inflammatory myofibroblastic tumor, inverted papilloma, leiomyoma, Hemangioma and primitive neuroectodermal tumor. According to world literature transitional cell carcinoma comprises approximately 90% of all primary tumors of urinary bladder. Kong CH *et al*. (2008) observed in their study of 83 cases, the main histopathological type was transitional cell carcinoma (90.4%), followed by adenocarcinoma (6%), squamous cell carcinoma (1.2%), leiomyoma (1.2%) and myeloid sarcoma (1.2%).

In our study out of 367 transurethral resection cases of transitional cell carcinoma, 184 cases (50.14%) had no invasion of muscle and in 84 cases (22.89%) muscle invasion was seen. No muscle was identified in 99 cases (26.97%). Mubarak *et al*. (2014) observed in their study, majority of the cases (62%) presented with superficial (muscle non-invasive) disease, while in 38%, the disease was muscle-invasive when first diagnosed (Muhammed Mubarak *et al*., 2014). Alan R. Schned *et al*. (2008) reviewed 342 cases and observed, 25.7% of tumors were papillary urothelial neoplasms of low malignant potential, 34.3% low-grade papillary carcinomas, 22.6% high-grade papillary carcinomas, 10.1% non-papillary urothelial carcinomas and 5.5% carcinoma in situ. By WHO (1973) criteria, 52.5% of tumors were grade 1, 21.4% grade 2 and 26.1% grade 3. Two-thirds of all tumors were stage Ta, 20.8% stage T1 and 7.6% stage ≥T2. 100% of PUNLMPs were non-invasive, 6.3% of low-grade carcinomas were invasive and 64.9% of high-grade carcinomas were invasive (Schned *et al*., 2008).

Grading of transitional cell carcinoma

Of total 379 cases of transitional cell carcinoma, 234 cases (61.74%) were of low grade transitional cell carcinoma and 145 cases (38.26%) were of high grade. 5.84% of low grade urothelial carcinoma and 67.57% of high grade urothelial carcinoma were invading muscle. Mustafa *et al*. (2014) observed 51.4% were low grade and 21.4% were high grade transitional cell carcinoma in their study (Mustafa *et al*., 2014). Ahmed *et al*. (2002) performed a retrospective study which included 495 cases of transitional cell carcinoma of the urinary bladder and observed Grade II (46.6%) tumors were more than grade III, (28.1%) tumors in males while the frequency of the two grades was almost similar in females. In 94 (19%) out of 495 cases, no muscle was present in the biopsies. Invasion could only be assessed in 401 (81 % cases). None of the Grade I lesions were invasive. 10% of Grade II, 61.4% of Grade III and all Grade IV lesions were invasive and observed there is a definite correlation between advancing tumor grade & muscle invasion (Ahmed *et al*., 2002). Beniwal *et al*. (2015) reported that low-grade carcinoma was most common with 62.2% cases, followed by high grade with 28.4% cases (Beniwal *et al*., 2015). Husain *et al*. (2009) reported a high percentage of muscle invasion in higher grade tumors.

Cystectomy specimens

In our study we had 13 cases of cystectomy. 12 cases of them had high grade transitional cell carcinoma. All the 13 cases had pre-operative diagnosis of muscle-invasive high grade transitional cell carcinoma on previous TUR biopsy. Grossly 8 cases had tumor size 1-3cm, 3 had tumor size 3-5cm and in one case tumor size was more than 5cm. Right posterolateral wall and posterior wall were the most frequent sites with 3 cases in each.2 cases were located on left lateral wall. 9 cases had ulceroproliferative growths and in three cases infiltrative growth was seen. One case had no growth grossly. Tumor was grossly invading muscle in 9 cases and adventitia in three cases. Most of cases (7) were in age group 60-70 years, 4 cases in age group 50-60 years and 2 cases in group 40-50 years. 12 cases were males and one patient was female. Słojewski *et al*. (2000) conducted a study on patients who underwent cystectomy at the Department of Urology, Pomeranian Academy of Medicine, between 1989 and 1998 and observed 77 were males and 8 were females and mean age was 59.6 and concluded that the best candidates for radical cystectomy are patients with low or medium grade organ confined tumors and in other cases this is just a palliative procedure. In our study on microscopic examination 12 cases had high grade transitional cell carcinoma and one case had inflammation only on microscopy. There was a case of high grade TCC infiltrating muscle on resection biopsy and C.T. scan after TURBT showed perivesical fat stranding suggestive of infiltration. However, no growth was found in cystectomy specimen.

According to literature perivesical fat stranding may also be seen due to edema or inflammation and does not necessarily suggest T3b disease. Słojewski *et al*. (2000) in their study graded the tumors into Grade1, Grade 2 and Grade 3 and were found in 3.4%, 22.5%, and 74.1% of the cystectomy cases respectively. In our study, lymph nodes were involved by tumor in three cases. In one case, one node was involved by the tumor and in two cases multiple nodes were involved. Hautmann *et al*. (2006) observed positive lymph nodes were present in 143 patients (18%) and that patients with metastasis to regional lymph nodes (N1-3) were at significantly higher risk for bladder cancer recurrence and death. Kajiwara *et al*. (1997), observed sixteen patients (19.0%) out of 84 who underwent cystectomy, in their study, had pathologically proved nodal metastases. In our study, 7 of the cystectomy

cases had AJCC stage II, followed by 3 cases in stage IV. 2 of the cystectomy cases had stage III. In the study conducted by Słojewski *et al*. (2000), transitional cell carcinoma was present in 97.8% of the bladders and based on the pathologic stage and assigned patients to 2 groups: organ confined disease (pT2-3a, 41.3%) and perivesical or adjacent organ involvement (pT3b-4, 58.7%).

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