



NON- UROTHELIAL BLADDER CANCERS: OUR EXPERIENCE

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ABSTRACT

Non urothelial bladder cancers are no less than a histological surprise, owing to the rarity of this group. The article presents a case series of 25 patients of non urothelial urinary bladder cancers presented in JIPMER Hospital, Puducherry over a period of four years (2014-2017) . Details of patients were reviewed from medical record section and Pathology department. Total 25 patients were included in the study. 20(80%) were males and 5 (20 %) were females (M: F :: 4:1). Mean age of the patients was 58.3 years ranging from 30 to 80 years. Seveteen (68.0%) out of twenty five patients had hematuria as their presenting complaint. Out of 25, there were 14 (56.0 %) squamous cell carcinoma, four had small cell carcinoma(16.00%), six adenocarcinoma(24.00%) and one leiomyosarcoma(4%) . Twenty four (96.0 %) patients out of 15 were referred for upfront surgery . One pt. was not willing for any treatment. This study highlights the role of surgery and status of adjuvant therapies in the management of non urothelial bladder cancers.

KEYWORD

Squamous cell Carcinoma (SCC), urachal (U), non urachal (NU), American Joint Committee on Cancer (AJCC)

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Introduction:

Bladder cancer is a disease of age and environment.It accounts for 7% of all cancers worldwide. There is a wide spectrum of histological subtypes albeit transitional type contribute to majority(95%).

Squamous cell Carcinoma (SCC) of bladder can be further classified as bilharzial and nonbilharzial based on the etiology of cancer due to Schistosomiasis hematobium which is endemic in Egypt and other African regions. However nonbilharzial SCC is associated with chronic irritation of bladder from urinary stasis due to bladder outlet obstruction, recurrent urinary tract infections, bladder stones, indwelling catheters and cyclophosphamide exposure.

Adenocarcinoma of urinary bladder can further be classified as urachal (U) and non urachal (NU). Features which favour the diagnosis of urachal adenocarcinomas are tumor of the dome, absence of cystitis glandularis cystica, primary involvement of muscle or deeper structures, an intact or ulcerated epithelium, presence of suprapelvic mass, sharp demarcation between tumor and normal surface epithelium, presence of urachal remnants and tumour branching into the space of Retzius.

Sarcoma constitutes the most usual mesenchymal malignancy of the bladder, with leiomyosarcomas being the most common type of sarcoma in adults.

Small cell carcinomas of urinary bladder accounts for 0.35–0.70 % of all bladder tumors. There is no standard treatment approach to the management of the same. Carcinosarcoma is another rare malignancy of urinary bladder which is characterised by an intimate admixture of carcinoma and malignant soft tissue neoplasm .

Classification of Bladder tumours according to histologic type (WHO,2004)

Urothelial neoplasia	Pseudostratified stroma
Benign	Stronal osseous or cartilaginous metaplasia
Urothelial papilloma	Osteoclast-type giant cells
Inverted papilloma	With prominent lymphoid infiltrate
Papillary urothelial neoplasia of low malignant potential	Squamous cell carcinoma
Malignant papillary	Usual type
Papillary carcinoma, low grade	Variants
Papillary carcinoma, high grade	Verrucous
Papillary carcinoma with squamous or glandular differentiation	Basoid
Malignant nonpapillary	With sarcomatoid features
Flat carcinoma in situ	Adenocarcinoma (from bladder mucosa, urachal, with ectrophy)
Invasive carcinoma	Usual intestinal type
Variants of invasive carcinoma	Mucinous (including colloid)
Nested pattern	Signet ring cell
Small tubular pattern	Clear cell
Microcystic pattern	Hemoid
Inverted pattern	Mixture of aforementioned patterns
Squamous differentiation	Adenocarcinoma NOS
Glandular differentiation	Tumors of mixed cell types
Monopapillary	Undifferentiated carcinoma*
Sarcomatoid carcinoma	Small cell carcinoma
Clear cell urothelial carcinoma	Large cell neuroendocrine carcinoma
Plasmacytoid	Lymphoepithelioma-like carcinoma
With syncytiotrophoblasts	Giant cell carcinoma
With unusual stromal reactions	Undifferentiated carcinoma NOS
	Metastatic carcinoma

*Stains to tumors that are undifferentiated by light microscopy
NOS, not otherwise specified
Modified from Iroon-Hubman & Bladder cancer: clinical and molecular entities. *Recent Adv Nephrol* 2008; 218:95-100.

Material and methods

All patients whose final histology came out be NUBC were studied retrospectively from a period of January 2012 to October 2016. Details were retrieved from Medical record section , Pathology department and Hospital Information Systemportal.

Patients were evaluated with history, physical examination, biochemical tests, imaging studies CT scan (abd. +pelvis), chest X ray, Cystoscopy and TURBT.

Patients' parameters which were considered are age, gender, cystoscopic findings, primary modality of treatment, recurrence, and survival were considered. Staging was done according to the American Joint Committee on Cancer (AJCC) staging manual.

Based on the stage and performance, patients were referred for radical cystectomy i.e. cystectomy with bilateral pelvic lymphnode dissection up to the bifurcation of common iliac vessels, concurrent chemoradiation or radiation.

Immunohistochemistry was done in four patients of small cell tumor (neuroendocrine origin).

Only patients of stage 3 and 4 were referred for adjuvant radiation or chemoradiation. Stage 1 and 2 were advised observation. All the patients with recurrence or residual

lesion were referred for palliative care. Patients were followed up monthly after completion of the treatment for 3 months and three monthly thereafter for 2 years. Families of patients who failed to follow up were contacted on phone and enquired about their survival and condition. Simple percentage and frequencies have been used to interpret the data. Also the article reviews few studies on NUBC, SCC and adenocarcinoma of urinary bladder.

Observation:

Total 25 patients were included in the study. 20 (80 %) were males and 5 (20 %) were females (M:F :: 4:1). Mean age of the patients was 51.3 years ranging from 22 to 65 years. Seventeen (68.00 %) out of twenty five patients had hematuria as their presenting complaint. Other presenting symptoms seen were lower abdominal mass seen in three (12%) patients; pain, irritable bladder seen in seven (28.0 %) patients each. Urinary tract infection (pyuria) and obstructive uropathy were seen in two (8.0 %) patient.

On cystoscopy, though the tumor involved more than one area in most of the cases, on broad classification, three patients had tumor in the dome of bladder out of which two had adenocarcinoma and one had Leiomyosarcoma. Fourteen patients had multicentric disease and twelve of them were squamous cell carcinoma. Nine patients had involvement of the trigone out of which two were small cell carcinoma, four SCC and three Adenocarcinoma and one. Two patients had bladder diverticulum as additional finding one of which had adenocarcinoma and the other had SCC.

Out of 25, there were six (24.00 %) adenocarcinoma, fourteen (56.00%) were SCC and four (16.00 %) small cell carcinoma and one (04.00%) leiomyosarcoma.

Out of 6 patients who had poorly differentiated adenocarcinoma four had stage 4 disease and one had stage 2 disease who later lost to follow up. Three out of PD stage 4 patients died in the course of follow up and the remaining one is on palliative care. Two of moderately differentiated (MD) adenocarcinoma patients had stage 1 disease and one had stage 4 disease. One lost to follow up (stage 1) and remaining three are on follow up.

Out of the 14 patients of SCC, 9 belonged to stage 2, 3 patients were of stage 3 and 2 had stage 4 disease.

One patient of stage 2 had developed internal iliac artery aneurysm and angioembolisation was done for the same ; however the same patient had perineal recurrence and was underwent total penectomy with stage 1 urethroplasty. However patient succumbed to death and was not able to receive adjuvant therapy.

2 patients of stage 2 had lost follow up. 2 had died and 4 pts. are in regular follow up with us.

All the patients of stage 3 and 4 had died.

Of the remaining five patients, 4 patients belonged to small cell carcinoma, 1 to Leiomyosarcoma group.

Of small cell carcinoma group 3 patients were positive for CD 56 and synaptophysin and one was positive for Pan CK and Ki 67 besides synaptophysin.

Solitary Leiomyosarcoma patient was Desmin IHC marker positive and is under regular follow up.

Only one patient was referred for neoadjuvant chemotherapy i.e. one with Adenocarcinoma tumor however patient could not complete the therapy as he died within 2 months of the diagnosis.

Twenty two (88.0 %) patients out of 25 were referred for upfront surgery. 21 patients from this group underwent radical cystectomy with bilateral pelvic lymphnode dissection. One partial cystectomy with bilateral pelvic node dissection was done.

Out of remaining three (12.00 %) patients from the non surgical group two were referred for definitive concurrent chemoradiation. One patient of adenocarcinoma (non urachal) was referred for palliative chemotherapy as lung secondaries were found on initial workup.

Most of the patients i.e. 16 (72.3 %) out of 22 had stage 2 disease, one (4.5 %) patients with stage 1 and 3 patients with stage 3 disease. Two patients (9.0 %) patients had stage 4 disease. Two pts. were advised adjuvant chemotherapy and they died within 2 and 3 months of the surgery.

Amongst the patients who underwent surgery, two (23.07 %) recurrences were reported. One was local and one distant recurrence. The distant recurrence was in the perineal region in a patient of squamous cell carcinoma.

Four (16.0 %) out of 25 patients lost to follow up and could not be traced (one had adenocarcinoma and three had SCC). Rest of the patients either died in the course of follow up or are still following up. The longest follow up in the series is 32 months and shortest follow up is one month. Out of 22 patients who followed up 14 (63.6 %) died. Out of all these 14 patients, 5 pts. were of stage 3 or stage 4 rest all belonged to stage 2. Eight deaths belonged to SCC group, four to Adenocarcinoma and two to small cell carcinoma.

Discussion and Review

Review on adenocarcinoma by Grignon et al. [2] concluded that non urachal adenocarcinoma outnumbers the urachal variety. In his study there were 48 non urachal adenocarcinoma and only 4 had the Urachal variety.

Histologic subtypes in their study included enteric, signet ring, mucin secreting, unspecified and mix of two or subtypes. Surgery was the mainstay of treatment as 40 pts. were operated, 15 received Radiation therapy, 2 received chemotherapy and 23 did not receive any adjuvant treatment.

Only radiotherapy was given to 12 patients, 8 patients received only chemotherapy and one patient received concurrent chemoradiation, seven patients were subjected to TURBT alone. No treatment could be offered to 3 patients. It was concluded from the study that stage of the tumor was the strongest prognostic predictor and distinction between urachal and non urachal variety did not affected the survival.

A study by Dahm et al from Germany found SSC to be the commonest non urothelial subtype ranging between 3 to 5%. Adenocarcinoma and small cell carcinoma constitutes 0.5 – 2% and <0.5% respectively.

Calculus, foreign bodies and urinary stasis being the chief causative factors for Nonbilharzial SCC. (1)

Study by Kassouf et al. had 27 patients of nonbilharzial SCC with a median age of 67 years between the ages of 36 to 79 years. In this study 5 patients had T4 disease, 9 patients had T3 disease and 13 patients had T2 disease.

Eight patients received upfront chemotherapy and /or radiotherapy and were planned for surgery after ; however in 5 patients surgery cannot be done due to rapid progression of disease and death.

2 out of 3 patients (67%) who received neoadjuvant therapy

were downstaged at cystectomy and had remained disease free.

15% patients (3 out of 20) who underwent radical cystectomy had a node positive disease.

Disease recurrence was seen in 10 patients out of total 20 (who underwent radical cystectomy), recurrence was reported with a median duration of 5.1 months. Death occurred in 7 patients due to local recurrence in 3 patients, distant recurrence in 1 and 3 patients had both.

Sheldon et al.(9) in his study made a interesting hypothesis that presence of mucus (gross/microscopic) in urine is suggestive of adenocarcinoma. However it was seen in only one fourth of the patients. In this study majority of the patients were in the age group 10- 70 years and 65 % were males. They also concluded that for urachal tumours inclusion of posterior rectus sheath and peritoneum along with en bloc removal of urachus and bladder (partial/total) constitutes optimal surgery for this subtype.

Other lesser subtypes of non -TCC subtypes are very rare (carcinosarcoma, small cell ,neuroendocrine and spindle cell) and portend a bad prognosis due to inherent aggressive nature of the disease. Adjuvant chemotherapy may provide improved survival benefits as compared to surgery alone. (6,7,10)

In our series, SCC histology was highest in no. i.e fourteen out of twenty five.

Adenocarcinoma was seen in 6 pts, 4 patients belonged to small cell carcinoma and one to Leiomyosarcoma.

In SCC subgroup mean age of the patient is 57.21 years which is much below the western study of about 67 years. Male to female ratio was found to be with 5:1 in our study as opposed 14:13 in study by Kassouf et al. Nine out of fourteen patients died after a mean follow up of 12.6 months and three lost follow up. Remaining eight are well at present and have been following up for 32, 11 and 3 months.

In our group of surviving pts. Five (62.5%) are of stage 2, two (25%) of stage 3 and one (12.5%) of stage 4

In adenocarcinoma subgroup mean age was 59.7 years (46-80 years), which is slightly above the western studies. However 83.3% were males which is higher than in above studies Five pts. had died after a mean follow up of 6 months and one pt. is in our of regular follow up since 4 months. Four out of six pts. had stage 2 disease one had stage 3 and one patient had stage 4 due to M1 disease.

Grade in our series (both SCC & adenocarcinoma) did appear to make a significant impact on survival, however the observation was diluted by fact that all the patients with poorly differentiated carcinoma presented in higher stage of the disease making it difficult to interpret that poor survival was attributed to poor grade or higher stage. Urine cytology has a role in screening of urothelial bladder cancers and it indicates the higher grade of urothelial malignancy however its role in non urothelial bladder cancer is not well defined. Cytologic examination fail to lead to a diagnosis of malignancy in 18 % of primary adenocarcinoma cases in a study of 46 patients done by Bardales et al. [11]. A large number of metastatic adenocarcinomas of the colon and prostate have sufficient cytologic features to suggest the correct diagnosis in urine samples. The cytomorphology of primary bladder adenocarcinoma is not as easily characterized. The role of studying abnormal squamous cells in urine samples for detection of squamous cell cancer of

urinary bladder remains equivocal [12].

Conclusion:

It is not possible to relate all the data to treatment in a scientific and meaningful manner because various treatments and histologies resulted in numerous groups each containing too few patients for reliable analysis. There is a lack of randomized studies on adenocarcinoma and nonbilharzial SCC of urinary bladder hence most of the treatment strategy in these conditions is from the extrapolation of data from the SCC & adenocarcinoma at other sites in body where abundant patients are available.

Hence in view of this case series and review of literature it is concluded that surgery appears to be a better option in terms of recurrence and survival. Role of adjuvant or neoadjuvant treatment remains undefined.

Poor grade correlates with recurrence and less survival but this is confounded by the fact that most of the higher grade tumors presented in advanced stage.

S.no	Age	Gender	Presenting symptom	Cytoscopy	TURBT Biopsy	Neoadjuvant treatment	Primary modality of treatment	Staging	Adjuvant treatment	Recurrence	Follow up
1	58	M	Hematuria+obst. Urinary on b1 PCN since 2 months	Large growth occupying whole bladder ; b1 ureteric orifices engorged in the growth	Squamous cell carcinoma	Nil	Radical cystectomy with orthotopic neobladder(D N) (Abol Chemis-AF)	T2BNOM 0	Chemotherapy	Peritoneal	Died
2	48	M	Hematuria since 2 months	3x4 cm well defined mass at the rt. post. Lat wall extending to rt. VUJ	Small cell carcinoma	nil	Radical cystectomy + ileal conduit - RC	T2BNOM X	no	nil	Follow up
3	51	M	Hematuria since 1.5 months	7.5 X 7.5 cm growth in the lt. lateral wall and base of bladder	Small cell carcinoma	Nil	Radical cystectomy + ON (AG)	T2BNOM X	No	Nil	Follow up
4	62	M	Hematuria+obst. LUTS	7.5 cm x 5 cm growth in dome of bladder	Leiomyosarcoma	Nil	Radical cystectomy with orthotopic neobladder- Studer Neobladder - SN	T2BNOM X	NO	Nil	Follow up
5	58	M	Hematuria+AS 4. Pain since 3 months	4x4 cm growth near rt. VUJ	Squamous cell carcinoma	Nil	Radical cystectomy + ileal conduit - RC	T2BNOM X	No	Nil	Lost to Follow up
6	55	M	Abd. Pain +lower abd. mass+voiding LUTS	Growth involving the bladder neck circumferentially with involvement of b1 anteroventral wall with multiple trabeculations present	Squamous cell carcinoma	Nil	Radical cystectomy + ileal conduit - RC	T2N1MX	Chemotherapy	Nil	Died
7	59	F	Hematuria since 2 months+ UTI	5x4 cm growth present at lt. lateral wall	Squamous cell carcinoma	Nil	Radical cystectomy + ileal conduit - RC	T2BNOM X	Nil	Nil	Died
8	72	F	Hematuria since 4 months	6x4 cm growth present in the right posteroventral wall	Squamous cell carcinoma	Nil	Radical cystectomy + ileal conduit - RC	T2N1M0	Chemotherapy	Nil	Follow up
9	38	M	Lower abdominal mass +voiding LUTS since 3 months	7x4 cm polypoidal mass in lateral wall of bladder	Squamous cell carcinoma	Nil	Radical cystectomy + ileal conduit - RC	T2BN0 MX	Nil	Nil	Died
10	65	M	Hematuria +voiding LUTS since 3 months	4x6 cm growth in the lt. lateral wall	Small cell carcinoma	Nil	Radical cystectomy + ileal conduit - RC	T2BNOM X	Nil	Nil	Died
11	55	F	Hematuria since 2 months	5x2 cm growth present in lt. lateral wall	Squamous cell carcinoma	Nil	Radical cystectomy + ileal conduit - RC	T2BNOM X	Nil	Nil	Lost to Follow up
12	50	M	Hematuria with voiding	6x2 AND 5x2 CM growth present	Sq. cell carcinoma	Not operated	NA	NA	NA	Nil	Died

References

1. Dahm P, Gschwend JE (2003) Malignant non-urothelial neoplasms of the urinary bladder: a review. Eur Urol 44:672–81
2. Grignon DJ, Ro JY, Ayala AG et al (1991) Primary adenocarcinoma of the urinary bladder. A clinicopathologic analysis of 72 cases.
3. Cancer 67:2165–72
3. El-Bolkainy MN, Mokhtar NM, Ghoneim MA et al (1981) The impact of schistosomiasis on the pathology of bladder carcinoma.
4. Cancer 48:2643–8
4. Kassouf W, Spiess PE, Siefker-Radtke A, Swanson D, Grossman
10. HB, Kamat AM et al (2007) Outcome and patterns of

- recurrence of
11. nonbilharzial pure squamous cell carcinoma of the bladder: a
 12. contemporary review of The University of Texas M D Anderson
 13. Cancer Center experience. *Cancer* 110:764–9
 14. 5. Labanaris AP, Zugor V, Meyer B, Nützel R, Helmus S, Labanaris
 15. PG et al (2008) Urinary bladder leiomyosarcoma in adults. *Int Urol*
 16. *Nephrol* 40:311–6
 17. 6. Choong NW, Quevedo JF, Kaur JS (2005) Small cell carcinoma of
 18. the urinary bladder. The Mayo Clinic experience. *Cancer*
 19. 103:1172–8
 20. 7. Lopez-Beltran A, Pacelli A, Rothenberg HJ et al (1998)
 21. Carcinosarcoma and sarcomatoid carcinoma of the bladder:
 22. clinicopathological study of 41 cases. *J Urol* 159:1497–503
 23. 8. *AJCC Cancer Staging Manual*. 7th edition. 2010. p497–502
 24. 9. Sheldon CA, Clayman RV, Gonzalez R, Williams RD, Fraley EE
 25. (1984) Malignant urachal lesions. *J Urol* 131:1–8
 26. 10. Quek ML, Nichols PW, Yamzon J, Daneshmand S, Miranda G, Cai
 27. J et al (2005) Radical cystectomy for primary neuroendocrine
 28. tumors of the bladder: the University of Southern California experience.
 29. *J Urol* 174:93–6
 30. 11. Bardales RH, Pitman MB, Stanley MW, Korourian S, Suhrland MJ
 31. (1998) Urine cytology of primary and secondary urinary bladder
 32. adenocarcinoma. *Cancer* 84:335–43
 33. 12. Manabu H, Yukari N, Masumi T, Hirokuni K, Kazumasa M,
 34. Makoto O et al (2011) Cytological significance of abnormal squamous
 35. cells in urinary cytology. *Diagn Cytopathol*.