Non Urothelial Bladder Cancers: A Case Series

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Abstract Non urothelial bladder cancers frequently present a diagnostic and therapeutic challenge. The article presents a case series of 21 patients of non urothelial urinary bladder cancers presented in our institute over a period of three years and review of literature on this rare condition. Details of patients were reviewed from hospital records of surgical, medical, radiotherapy and pathology departments. Simple percentage and frequencies have been used to interpret the data. Total 21 patients were included in the study. 12 (57.2 %) were males and 9 (42.8 %) were females (M: F :: 4:3). Mean age of the patients was 51.3 years ranging from 22 to 65 years. Eleven (52.3 %) out of twenty one patients had hematuria as their presenting complaint. Out of 21, there were nine (42.8 %) adenocarcinoma, nine (42.8 %) were SCC and one (4.76 %) each of carcinosarcoma, neuroendocrine tumor and sarcoma. Fourteen (66.6 %) patients out of 21 were referred for upfront surgery. Out of remaining seven (33.33 %) patients from the non surgical group three were referred for definitive concurrent chemoradiation, two for definitive radiotherapy. One patient of adenocarcinoma (non urachal) was referred for palliative chemotherapy. Remaining one patient of neuroendocrine tumor who was referred for neoadjuvant chemotherapy died before any definitive treatment could be considered. This study highlights the role of surgery and status of adjuvant therapies in the management of non urothelial bladder cancers.

Keywords Non Urothelial Bladder Cancer · Urinary Bladder cancer

Introduction

Non urothelial bladder cancers (NUBC) are uncommon tumors of urinary bladder accounting for less than 5 % of all the vesical tumors combined. The rarity of the tumor is to the extent that it may not be encountered within the life time of a practicing urologist [1]. World Health Organisation has classified bladder tumors according to the histology (Fig. 1) (Tables 1, 2, 3 and 4).

Adenocarcinoma of urinary bladder can further be classified as urachal (U) and non urachal (NU) based on the criteria described by Grignon et al. [2]. 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 tumor branching into the space of Retzius.

Similarly 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 [3, 4]. 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 [4].

Sarcoma constitutes the most usual mesenchymal malignancy of the bladder, with leiomyosarcomas being the most common type of sarcoma in adults [5]. Small cell carcinomas of urinary bladder accounts for 0.35–0.70 % of all

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Fig. 1 Low and high power view of adenocarcinoma.

bladder tumors. There is no standard treatment approach to the management of the same [6]. Carcinosarcoma is another rare malignancy of urinary bladder which is characterised by an intimate admixture of carcinoma and malignant soft tissue neoplasm [7].

Materials and Methods

All patients of carcinoma bladder with non urothelial histology presented in our institute from November 2008 to October 2011 were studied retrospectively. Details of patients were reviewed from hospital records of surgical, medical, radiotherapy and pathology departments. Patient evaluation consisted of history, physical examination, cystoscopy & biopsy/Transurethral resection of bladder tumor (TURBT), computerised tomographic scan of abdomen and pelvis, chest X ray. Colonoscopy was done in all the patients of adenocarcinoma. Urinary cytology was not done in any of the patients, as being a referral tertiary centre all the patients had come with the diagnosis or strong suspicion of carcinoma bladder.

Various parameters like 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 [8]

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. In patients of urachal adenocarcinoma the urachus was excised along with the bladder. Immunohistochemistry was done in two patients of small cell tumor (neuroendocrine origin) and

Table 1 World Health Organisation (WHO) histological classification of bladder tumors

I. Epithelial Tumors
A. Transitional cell papilloma
B. Transitional cell papilloma, inverted type
C. Squamous cell papilloma
D. Transitional cell carcinoma
E. Variants of transitional cell carcinoma
1. With squamous metaplasia
2. With glandular metaplasia
3. With glandular and squamous metaplasia.
F. Squamous cell carcinoma
G. Adenocarcinoma
H. Undifferentiated carcinoma.
II. Non epithelial Tumors:
A. Benign
B. Malignant
1. Rhabdomyosarcoma
2. Others
III. Miscellaneous Tumors
A. Pheocromocytoma/Paraganglioma
B. Lymphoma
C. Carcinosarcoma
D. Malignant Melanoma
E. Others
IV. Metastatic Tumors and Secondary Extensions
V. Unclassified tumors
VI. Epithelial Abnormalities
A. Papillary(polypoid cystitis) “cystitis”
B. Von Brunn’s nests
C. “Cystitis” cystic
D. Glandular metaplasia
E. “Nephrogenic” Adenoma
F. Squamous metaplasia
VII. Tumorlike Lesions
A. Follicular cystitis
B. Malakoplakia
C. Fibrous(fibroepithelial) polyp
D. Amyloidosis
E. Endometriosis
F. Hamrtoma
G. Cysts

Table 2 Details of patients

Serial No.	Age	Gender	Presenting Symptom	Cystoscopy	Biopsy	Neoadjuvant Treatment	Primary Modality of treatment	Staging	Adjuvant treatment	Recurrence	Followup
1	55	Female	Obstructive Uropathy B/I PCN	Diverticulum in Right lateral wall Mass in trigone and posterior wall	Adenocarcinoma MD (mucin Secreting) NU	Nil	Radical Cystectomy	pT1N0Mx (Stage 1)	Nil	Nil	6 months Lost to follow up
2	58	Female	Hematuria	Dome of Bladder	Adenocarcinoma PD (Signet ring) U	Nil	RT	cT2N0Mx (Stage 2)	Nil	Residual lesion	3 months Lost to follow up
3	55	Female	Abdominal Pain	Dome of Bladder & posterior wall	Adenocarcinoma MD (Mucin Secreting) NU	Nil	Partial Cystectomy + B/L PLND	pT1N0Mx (Stage 1)	Nil	Nil	Following up at present
4	22	Male	Hematuria	Dome of Bladder	Adenocarcinoma MD (Intestinal type) U	Nil	Radical Cystectomy	pT3N1Mx (Stage 4)	RT	Nil	Following up at present
5	55	Male	Mass in lower abdomen	Right Posterolateral wall	Adenocarcinoma PD (Intestinal type) NU + CGC	Nil	Inoperable? Palliative Chemotherapy	cT4aN2M1# (Stage 4)	-	-	1 month Expired
6	50	Male	Hematuria	Anterior wall upto base	Adenocarcinoma PD (Signet ring type) NU	Nil	CT + RT	cT3N2Mx (Stage 4)	Nil	2 months	Expired
7	45	Male	Irritation/Dysuria	Left Lateral wall	Adenocarcinoma MD(Intestinal type)NU+CGC	Nil	Radical Cystectomy	pT1N0Mx (Stage 1)	Nil	Following up at present	23 months Expired
8	45	Male	Mass in lower abdomen	Trigone & Right lateral wall	Adenocarcinoma PD (Signet ring) NU	Nil	Radical Cystectomy	pT4aN1Mx (Stage 4)	CT+RT	Inguinal Node	Expired
9	59	Male	Hematuria	Left Lateral wall	Adenocarcinoma PD (Mucin secreting) NU	Nil	Palliative Chemotherapy	cT4aN1M1* (Stage 4)	Nil	Following up at present	14 months Expired
10	32	Female	Hematuria	Dome of bladder with diverticulum	Squamous cell carcinoma MD	Nil	Radical Cystectomy	pT3aN0Mx (Stage 3)	RT	Local recurrence	Expired
11	45	Female	VV fistula	Trigone and proximal urethra + VVF	Squamous cell carcinoma MD	Nil	CT + RT	cT4aN1Mx (Stage 4)	Nil	Residual lesion	11 months Expired
12	45	Female	Abdominal Pain	Right lateral wall	Squamous cell carcinoma WD	Nil	Radical Cystectomy	pT1N0Mx (Stage 1)	Nil	Nil	Following up at present 5 months Expired
13	63	Male	Irritation & Dysuria	Multicentric tumor all over bladder	Squamous cell carcinoma MD	Nil	CT + RT	cT4aN2Mx (Stage 4)	Nil	Nil	Expired
14	60	Male	Hematuria	Left Lateral wall	Squamous cell carcinoma MD	Nil	Radical Cystectomy	pT2aN0Mx (Stage 2)	Nil	Nil	Following up at present 14 months Expired
15	57	Male	Hematuria	Right Posterolateral wall	Squamous Cell Carcinoma PD	Nil	Radical Cystectomy	pT3aN0Mx (Stage 3)	RT	Nil	Expired
16	60	Female	Hematuria	Dome of bladder		Nil			CT+RT	15 months	Expired

Table 2 (continued)

Serial No.	Age	Gender	Presenting Symptom	Cystoscopy	Biopsy	Neoadjuvant Treatment	Primary Modality of treatment	Staging	Adjuvant treatment	Recurrence	Followup
17	63	Male	Hematuria	Multicentric tumor all over bladder	Squamous cell carcinoma MD Squamous cell carcinoma MD	Nil	Radical Cystectomy RT	pT3aN1Mx (Stage 4) cT3N0Mx (Stage 3)		Local recurrence	Lost to follow up
18	56	Male	Hematuria	Multicentric tumor all over bladder	Squamous Cell Carcinoma MD	Nil	Radical Cystectomy	pT2N0Mx (Stage 2)	Nil	Nil	Following up at present
19	65	Female	Mass in lower abdomen pyuria	Dome, anterior, posterior wall & trigone	Spindle Cell tumor	Nil	Radical Cystectomy	pT3N0Mx (Stage 3)	Nil	Nil	Following up at present
20	25	Female	pyuria	Bladder full of tumor	Neuroendocrine tumor	Nepadjuvant Chemotherapy	Nil	cT3N1Mx (Stage 4)	-	-	Expired 1 month
21	64	Male	Hematuria	Right lateral wall &dome of bladder	Carcinosarcoma	Nil	Radical Cystectomy	pT3N1Mx (Stage 4)	Nil	Nil	8 months Expired

Table 3 Adenocarcinoma

Adenocarcinoma—9 patients
M:F :: 2:1
Mean Age: 49.33 years (22–59 years)
Pathology:
Moderately Diffrentiated (MD) -04
Poorly Diffrentiated (PD) -05
Out of nine, three each of signet ring, mucin secreting and intestinal subtypes
Urachal—02
Non Urachal -07

carcinosarcoma. In patient of sarcoma immunohistochemistry was not done due to some technical problem & hence the diagnosis remained as spindle cell neoplasm.

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 21 patients were included in the study. 12 (57.2 %) were males and 9 (42.8 %) were females (M: F :: 4:3). Mean age of the patients was 51.3 years ranging from 22 to 65 years. Eleven (52.3 %) out of twenty one patients had hematuria as their presenting complaint. Other presenting symptoms seen were lower abdominal mass seen in three (14.2 %) patients; pain, irritable bladder seen in two (9.52 %) patients each. Urinary tract infection (pyuria),

Table 4 Squamous cell carcinoma

Squamous Cell Carcinoma—9 patients
M:F :: 5:4
Mean Age: 53.44 years(32–63 years)
Pathology:
Well Diffrentiated—01
Moderately Diffrentiated (MD) -07
Poorly Diffrentiated (PD) -05
All cases described are non bilharzial

vesicovaginal fistula and obstructive uropathy were seen in one (4.76 %) patient each.

On cystoscopy, though the tumor involved more than one area in most of the cases, on broad classification, seven patients had tumor in the dome of bladder out of which three had adenocarcinoma, two had SCC and one each of carcinosarcoma and sarcoma. Three patients had multicentric disease and all three of them were squamous cell carcinoma. Five patients had involvement of the trigone out of which three were adenocarcinoma, one SCC and one sarcoma. Two patients had bladder diverticulum as additional finding one of which had adenocarcinoma and the other had SCC.

Out of 21, there were nine (42.8 %) adenocarcinoma, nine (42.8 %) were SCC and one (4.76 %) each of carcinosarcoma, neuroendocrine tumor and sarcoma.

Out of 5 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. Three 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 seven patients of MD SCC two had stage 2, two had stage 3 and three had stage 4 disease. One patient of MD stage 3 SCC lost to follow up, rest all the stage 3 and 4 MD SCC died in the course of follow up. Two patients of stage 2 disease are following up at present. Only patient of WD SCC had stage 1 disease and is following up at present. Also the only patient of PD SCC had stage 3 disease and is no more.

Remaining three (14.28 %) patients of the series had carcinosarcoma, neuroendocrine tumor (small cell carcinoma) and spindle cell tumor (sarcoma). Patients of sarcoma & neuroendocrine tumor were females aged 65 and 25 years respectively and that of carcinosarcoma was male aged 64 years. Biopsy from patient of small cell tumor was positive for synaptophysin and focally positive for chromogranin. Though immunohistochemistry was not done in the patient with spindle cell neoplasm however morphologically it appeared to be leiomyosarcoma.

Only one patient was referred for neoadjuvant chemotherapy i.e. one with neuroendocrine tumor however patient could not complete the therapy as she died within 1 month of the diagnosis.

Fourteen (66.6 %) patients out of 21 were referred for upfront surgery. 12 patients from this group underwent radical cystectomy with bilateral pelvic lymphnode dissection. One partial cystectomy with bilateral pelvic node dissection was done and the remaining one patient was declared inoperable because of metastatic peritoneal deposits present on the pelvic wall.

Out of remaining seven (33.33 %) patients from the non surgical group three were referred for definitive concurrent chemoradiation, two for definitive radiotherapy. One patient of adenocarcinoma (non urachal) was referred for palliative chemotherapy as lung secondaries were found on initial workup. Remaining one patient of neuroendocrine tumor who was referred for neoadjuvant chemotherapy died before any definitive treatment could be considered.

Most of the patients i.e. 10 (47.6 %) out of 21 had stage 4 disease, four (19.02 %) patients with stage 1 and 3 each. Three (14.28 %) patients had stage 2 disease.

Out of 13 operable patients, seven had stage 3 and 4 disease (three stage 3 and four stage 4). Five of them received adjuvant treatment in the form of chemoradiation or radiation. Specifically three received radiation and two received chemoradiation. Remaining two patients who did not receive any adjuvant treatment had sarcoma and carcinosarcoma in their histology.

Out of five patients who received primary radiation or chemoradiation two (40 %) had residual disease after completion of the therapy and were subsequently referred for palliative care. Amongst the patients who underwent surgery, three (23.07 %) recurrences were reported. Two local and one distant recurrence. The distant recurrence was in the inguinal nodes in a patient of adenocarcinoma.

Three (14.28 %) out of 21 patients lost to follow up and could not be traced (two had adenocarcinoma and one 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 25 months and shortest follow up is one month. Out of 18 patients who followed up 10 (55.55 %) died. All these ten patients had stage 3 or 4 disease. Six (60 %) of these ten patients were on palliative care. Three deaths in the adenocarcinoma group and five in SCC group were reported. Of the remaining 2 patients one had neuroendocrine tumor and the other had carcinosarcoma. Five out of these ten patients who expired had undergone definitive surgery, and four had taken adjuvant radiation or chemoradiation.

Discussion and Review of Literature

In a German Study by Dahm et al. [1] SCC was the most common NUBC i.e. between 3 to 5 %, followed by adenocarcinoma (0.5–2 %) and small cell carcinoma (<0.5 %). Rest of the histologies were seen in less than 0.1 % of the patients.

Nonbilharzial SCC mainly results from chronic bladder irritation from various causes e.g. stones, foreign body, urinary stasis etc. Even intravesical Bacillus-Calmette-Guerin (BCG) has been described as risk factor for SCC [1]. In a study by Kassouf et al. [4] 27 patients of non-bilharzial SCC were considered with median age of 67 years

in the range of 36 to 79 years. There were 14 males and 13 females in the study. 13, 9, 5 patients had cT2, cT3, cT4 lesions respectively. Eight patients received initial chemotherapy and/or radiation therapy with the intent of performing surgical consolidation. In 5 of these patients surgical consolidation was not performed due to rapid progression of disease and death. Of the 3 patients who were treated with neoadjuvant therapy (1 with chemotherapy, 1 with radiation, and 1 with chemoradiation) and had surgical consolidation, 2 (67 %) were downstaged at cystectomy and remain disease-free. Only three (15 %) patients out of twenty who underwent radical cystectomy had node positive disease. In 10 of 20 patients of radical cystectomy the disease recurred after a median duration of 5.1 months and 7 died: 3 of local recurrence, 1 of distant recurrence, and 3 of both.

In a study on adenocarcinoma by Grignon et al. [2], out of 72 patients twenty four patients had urachal and 48 patients had non urachal adenocarcinoma. They also divided the adenocarcinoma in five histologic types mainly enteric, mucin secreting, signet ring, not otherwise specified and lastly when tumor showed two or more types. Total 40 patients were treated with surgery. Out of these 40 patients 15 received radiation therapy, two received chemotherapy and remaining 23 did not receive any adjuvant treatment. 12 patients were treated with only radiotherapy, 8 patients received only chemotherapy, one received concurrent chemoradiation and seven underwent only TURBT. 3 patients did not receive any treatment. The study concluded that histological type and the distinction of U and NU did not affect the outcome significantly. Stage of the tumor was the strongest predictor of the outcome.

In another study by Sheldon et al. [9] gross or microscopic mucus in urine was described as an important symptom for adenocarcinoma but was present only in 25 % of the patients. Two thirds of the patients were in the age group of 41–70 years with 65 % of male patients. They also stated en bloc resection of urachus and bladder (partial or total) with or without umbilectomy, inclusion of posterior rectus sheath and peritoneum as the optimal surgery for urachal tumors.

As far as carcinosarcoma, neuroendocrine tumor, and spindle cell neoplasm of bladder are concerned, very less data is available. These are highly aggressive neoplasms with guarded prognosis. Adjuvant chemotherapy protocols may provide improved survival compared to cystectomy alone [6, 7, 10].

In our series, adenocarcinoma and SCC were present in equal proportion. Carcinosarcoma, spindle cell tumor and neuroendocrine tumor were also present in equal proportion but much less in number compared to the first two.

In SCC subgroup mean age of the patient is 53.44 years which is much below the western study of about 67 years. Male to female ratio appears comparable with 5:4 in our study and 14:13 in study by Kassouf et al. Five out of nine

patients died after a mean follow up of 11.8 months and one lost follow up. Remaining three are well at present and have been following up for 22, 9 and 2 months. One (11.1 %), two (22.2 %), four (44.4 %) and two (22.2 %) patients had (clinical, c or pathological, p) T1, T2, T3, T4 disease respectively. This converted to one patient with stage 1, two with stage 2, three each with stage 3 and 4. Three (33.33 %) out of nine patients had node positive disease. Patients presented at a much higher and advanced stage in our series as compared to the above study. However the sample size of the above study was three time that of ours for SCC.

In adenocarcinoma subgroup mean age was 49.33 years (22–59 years), which is slightly below the western studies. However about 66 % were males which is again comparable to above studies. Three out of nine patients died after a mean follow up of 8.66 months and two lost follow up. Remaining four are well at present and have been following up for 25, 23, 12, and 2 months respectively. Three patients had (c or p) T1 lesion, one had T2 and two had T3 and three had T4 lesion. Five (55.55 %) patients out of nine had node positive disease. Therefore three, one, five patients had stage 1, 2 and 4 disease respectively. Two of the stage 4 patients had M1 disease. The staging system used in the above studies is different and probably outdated therefore the staging has not been compared.

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 PD 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 it's 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 was not possible to relate all the data to treatment in meaningful manner because various treatments and histologies resulted in numerous groups each containing too few patients for reliable analysis. As there are no randomized control trials on adenocarcinoma and nonbilharzial SCC of

urinary bladder, 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 authors conclude 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.

Data for carcinosarcoma, neuroendocrine tumor and spindle cell tumor was inadequate to reach any conclusion.

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