

## **Clinicopathological characteristics of urinary bladder cancer as seen at Kilimanjaro Christian Medical Centre, Moshi-Tanzania**

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**Background:** *Urinary Bladder Cancer (UBC) is a common disease worldwide which ranks ninth in worldwide cancer incidence with highest incidence in developed countries. This study aimed at describing clinicopathological characteristics of urinary bladder cancer as seen at KCMC.*

**Methods:** *This was an eight years hospital based descriptive, retrospective study conducted from 2006 to 2013 by using a structured data extraction form. The data were analyzed using SPSS software.*

**Results:** *A total of 120 subjects were included in the study. Majority 90 (75%) had TCC followed by SCC (18%). Forty nine percent of subjects with TCC presented with non muscle invasive bladder cancer (NMIBC). Majority (87%) of subjects with non-muscle invasive TCC of bladder experienced recurrence within a period of one year after diagnosis. Multifocality and recurrence at first follow up cystoscopy are determinants of recurrence. Patients with NMIBC were lost to follow up giving an attrition bias of 29.5%.*

**Conclusion:** *TCC is still the most common histological type in our set up followed by SCC. Majority of patients with TCC presents with advanced cancer, moreover intravesical recurrence after TURBT is high for those with non-muscle invasive TCC and influenced by multifocality and recurrence at first follow up cystoscopy. We need a large prospective study to confirm recurrence, progression and determinants of recurrence in our set up.*

### **Introduction**

The urinary bladder is an extra peritoneal organ surrounded by pelvic fat. Its wall consist of four layers; urothelium, lamina propria, muscularis propria and adventitia. The urothelium consists of three to seven layers of transition cells. The lamina propria is very vascular layer and the muscularis propria consist of bundles of smooth detrusor muscle, sub divided into outer and inner layer. UBC is a common disease worldwide which ranks ninth in worldwide cancer incidence (2002) with highest incidence in developed countries; however the burden is expected to increase in developing countries<sup>1</sup>.

Occurrence of UBC in developing countries is predominated by histological type that is related to infection and presents at advanced stage. This is expected to change as a result of economic growth which goes together with change and increase in prevalence of risk factors. Non muscle invasive bladder cancer (NMIBC) is characterized by high recurrence rate and this which made bladder cancer to be most expensive cancer to manage. The incidence of UBC has been rising over the last 60 to 70 years. The overall incidence (not age-specific incidence) of UBC in developing countries is lower due to several reasons one being low life expectance. Unfortunately, the incidence rate is rising faster in developing countries as a result of increased incidence of cigarette smoking, urbanization and industrialization. An estimated 386,300 new cases of UBC occurred in 2008 worldwide. The highest incidence rates were found in the

countries of Europe, North America, and Northern Africa. Epidemiological studies are unavailable in most African countries, however Africa was found to have low incidence of around 22,053 cases with Sub Saharan Africa having 45.5%(10,042) of cases. The prevalence of UBC is difficult to assess due to recurrence nature of the disease. Globally at any given point in time, 2.7 million people have a history of UBC<sup>1-3</sup>.

Hereditary component of bladder cancer is probably due to inheritance of low penetrance genes (N-acetyl transferase and glutathione-S-transferase polymorphism) which makes an individual susceptible to carcinogenic exposure. N-acetyl transferase (NAT-2) is enzyme needed to detoxify nitrosamine which is urinary bladder carcinogen. Slow acetylators have increased risk of UBC than fast acetylators. Glutathione- S- Transferase M1 (GSTM1) plays an important role in detoxification. It conjugates reactive chemicals such as arylamines and nitrosamines. Null GSTM1 is associated with increased risk of UBC. Also it is well documented that second degree relative of individual with UBC have 2 times higher risk of developing UBC compared to general population<sup>4</sup>.

The percentage of UBC attributable to tobacco smoking varies between countries according to local habits. In Europe it accounts for 66% of cases in males and 30% in females. In UK (2010) cigarette smoking account for 38% and 34% of UBC cases in male and female respectively<sup>5-6</sup>.

In Germany cigarette smoking account for 50% of TCC while in Kenya it account for 29%. Squamous cell carcinoma (SCC) has also been related to cigarette smoking. Not only Active smoking but also passive smoking is related to UBC<sup>4,7-8</sup>. Strong link exists between amount and duration of cigarette smoking. Smokeless tobacco (snuff or chewable) use is also linked to UBC, whereby it was found to account for 51% of UBC in female. The causative agents are thought to be  $\alpha$ - and  $\beta$ -naphthylamine, which are secreted into the urine of smokers. In addition to tobacco use, there are other established bladder carcinogens including exposure to drugs like cyclophosphamide used in chemotherapy and consumption of high amount of phenacetin containing analgesics. Acroline which is a metabolite of cyclophosphamide is responsible for UBC as well as hemorrhagic cystitis. Therapeutic irradiation in the pelvic region as in treatment of testicular cancer or cervical cancer has been implicated in UBC<sup>8-9</sup>.

Like any other cancer, diagnosis of UBC depends on pathological evaluation of resected specimen. Cystoscopic appearance of the tumour can be classified according to characteristic of tumour surface, which can either be solid or papillary. The grade and stage of the tumour can be predicted with reasonable accuracy by its cystoscopic appearance<sup>10</sup>. UBC is usually staged using Tumour Nodal and Metastasis (TNM) staging system. The system considers the depth of invasion of bladder (T), regional lymph node status (N), and whether the disease has spread to distant organs other body parts (M). TNM is a quick, acceptable and detailed system of staging cancer.

Staging can be done clinically or pathologically. Pathological staging/surgical staging is based on histopathological finding after surgical resection of the bladder tumour and of adjacent lymph nodes. Clinical stage reflects pathological finding at transurethral resection of bladder tumour (TURBT), radiological finding and EUA. During EUA any tumour which involves other organs or fixed to pelvic bone is considered to be stage T4 tumours. Stage T2/T3 tumours are bimanually palpable and mobile after TURBT. Despite its superficial location, CIS has more aggressive behavior, progressing to more advanced disease, often skipping directly to dissemination. Bacillus Calmet Guerin (BCG) is the preferred initial treatment option for CIS. Over a 10-year period, approximately 30% of patients remain free of tumour progression or recurrence. TURBT is effective in some cases. Due to recurrent and progressive behavior of the disease,

intravesical immunotherapy or chemotherapy has great role in reducing recurrence and progression. Intravesical agents provide direct access to the tumour for therapy<sup>11-13</sup>.

Radical cystectomy is the standard treatment for MIBC; T2-T4a, N0-NX, and M0. Other indications are high-risk NMIBC (T1 G3 and BCG-resistant CIS) and extensive papillary disease that cannot be controlled with conservative measures. Radiation as monotherapy is usually offered to patients who are poor surgical candidates due to advanced age or significant comorbid medical problems. Radiotherapy is an alternative to radical cystectomy in well-selected patients with MIBC however risk of local recurrence is high. Stage T2 bladder cancer has excellent disease control when treated with radical cystectomy. While stage T3 or greater is at substantial risk for failure (pelvic failure 38% at 3 years) after cystectomy only. The aim of treatment in metastatic disease is palliative with systemic combination chemotherapy as the primary treatment modality<sup>14-15</sup>.

Most of the work in managing UBC patients especially NMIBC, results from the frequent follow up cystoscopies that are considered to be necessary for the detection of recurrent disease and the endoscopic resection of any tumours so found. Potential for disease recurrence and progression even in the long term necessitates lifelong follow-up. Varieties of different follow-up protocol have been advocated, many urologists follow a defined pattern for follow up cystoscopy: every three months for one year, every six months for the second, and then annually unless tumours recur, in which case the sequence starts again. Some advocates a follow up scheme according to the patient's degree of risk<sup>16</sup>.

In Egypt an area endemic for schistosomiasis, 70 and 60% of patients with SCC and TCC of bladder respectively are peasants. Most primary UBC are epithelial in origin, accounting for up to 95% of all UBC. TCC is a most common (90%) type of UBC in developed countries while SCC is common in developing countries especially in schistosoma endemic areas where it accounted for 72% of UBC. Egypt reported an increase in frequency of TCC and decrease in SCC within five years period from 20 to 66% and 73-25% respectively<sup>17-19</sup>. Tanzania also reported reversal in histological type whereby the frequency of SCC was found to be 65.7% and 21.5% for TCC, ten years later the frequency of SCC dropped to 40% while TCC increased to 50%. A recent study done in Tanzania showed that SCC account for 55.1%<sup>20-21</sup>.

Adenocarcinoma is a rare tumour which account for 0.5-2% of all UBC subcategorized as either urachal or non-urachal in origin as in bladder exstrophy. Often localized at the time of diagnosis, but muscle invasion is usually present. Non-epithelial UBC accounts for 5-10% of UBC and it includes rhabdomyosarcoma, teratoma, leiomyosarcoma and chondrosarcoma. Non-muscle invasive TCC of bladder is characterized by high recurrent rate which makes UBC to be most expensive cancer to manage. Studies on recurrence rate vary broadly as a result of different patient's characteristics and duration of follow up. For example, in Pakistan and Greece it was 68.4% and 35% respectively. However we could not find published study in Africa looking at the recurrence of UBC. One of the goals of treating NMIBC is to prevent disease progression to muscle invasive and metastasis. Progression varies according to characteristic of study population as well as duration of follow up, for instance in Korea it was found to be as high as 11.5% while in Pakistan progression in terms of upstaging was 4.3%<sup>18,22-25</sup>.

Multiplicity of the tumour is a prognostic factor for recurrence. In additional to multiplicity, grade of the tumour is also a prognostic factor with high grade lesion having high recurrence rate compared to low grade lesions. Other prognostic factors associated with high risk of recurrence include having history of previous recurrence and presence of CIS<sup>26-29</sup>. Our study aimed to describe clinical and pathological characteristics of urinary bladder cancer at KCMC.

## Patients and Methods

This was a descriptive; hospital based retrospective study that evaluated all case notes of patients treated for urinary bladder cancer from 2006 to 2013. All case notes of patients treated for urinary bladder cancer at Kilimanjaro Christian Medical Centre from Jan 2006 to Dec 2013 were reviewed. Case notes with incomplete information which does not fulfill the requirement of this study were excluded from the study.

Ethical clearance and permission was obtained from Kilimanjaro Christian Medical University College and Urology department at KCMC Referral Hospital. All patients' information was kept confidential; no patient's direct identifiers were used in the data collection instrument. A structured questionnaire was used to collect data from patient's case notes. Data were entered into computer for analysis where by SPSS version 16 was used to analyze the information. Cross-tabulations were generated, and where comparisons were made, significance was considered at p-value of less than 0.05.

### **Study limitations.**

This study was done at Kilimanjaro Christian Medical Centre in Moshi, thus the findings may not reflect a true image of urinary bladder cancer country wise. Incomplete documentation denied review of some case notes.

## Results

A total of 120 case notes of patients treated for urinary bladder cancer during the study period of eight years were reviewed. Males were the majority at 69% (83/120) with a male to female ratio of 2.2:1. Their age ranged from 4 to 90 years with mean age of 58.45 years. Most 85(71%) of the subjects were peasants. The mean age at diagnosis of SCC was 49.3 years with male to female of 0.9:1 while for TCC the mean age was 62.01 years with male to female ratio of 2.9:1 (Table 1).

Of the 90 subjects with TCC, 44(48.9) had non-muscle invasive TCC. All subjects with stage Ta/T1 were managed by complete TURBT while stages T2/T3 and T4 were subjected to either radical cystectomy or palliative radiotherapy after TURBX. All subjects with SCC, Adenocarcinoma, mixed TCC/SCC and other histological types had muscle invasive cancer at presentation (Table 2). Of the 44(48.9%) subjects with superficial TCC, 13 (29.5%) were lost to follow up and hence they were excluded from the analysis. Of the remaining 31 subjects, 27 (87.1%) experienced recurrence at least one recurrence. Among the 27(87.1%) subjects who suffered recurrence, 4 (13%) of them had T stage progression (Table 3).

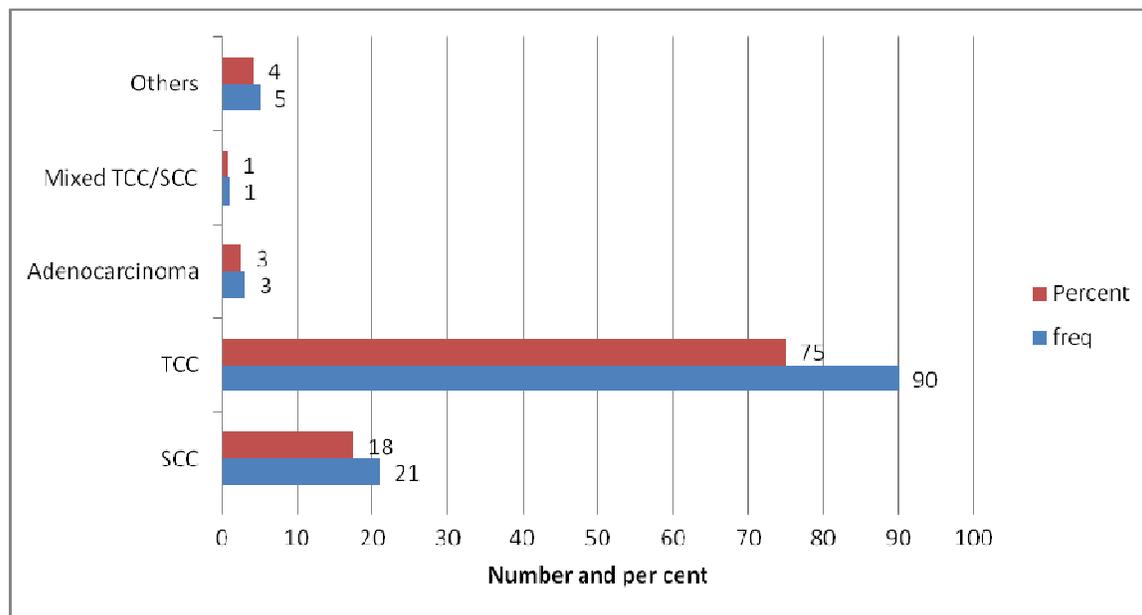
Twenty four patients had low grade TCC at diagnosis while the remaining seven had high grade TCC. All the seven patients with high grade TCC experienced recurrences (p value=0.338). Twenty three patients had recurrence at first check cystoscopy and all of them experienced recurrences in the subsequent follow ups (P values = 0.002). Sixteen subjects (52%) had multiple lesions at cystoscopy and all of them suffered recurrences (p value=0.043). Concomitant CIS was noted in 3 patients who also experienced recurrences in the course of one year of follow up (p value=0.65). (Table 4)

**Table 1.** Social demographic characteristics (n=120).

Variable	Values	Number	Percentage (%)
Age (years):	Mean	58.45	-
	Range	4-90	-
Sex:	Male	83	69
	Female	37	31
Sex ratio	Male: Female	2.2:1	-
Occupation	Peasant	85	71
	Not known	7	6
	Others*	28	23

\*Others =teachers, medical doctor, pastor, market vender, student and accountant.

Transition cell carcinoma (TCC) was the most common histological type 90 (75%) while mixed TCC/SCC was the least common. [Figure 1].



Others =Rhabdomyosarcoma& lymphoma

**Figure 1.** Histological types of bladder cancer (N=120)

**Table 2.** Stages against Histological Types

Stages at presentation	Histological type of bladder tumour					
	SCC n (%)	TCC n (%)	Adeno. n (%)	Mixed TCC/SCC n (%)	Others n (%)	Total n (%)
Ta/T1	0(0)	44(48.9)	0(0)	0(0)	0(0)	44 (36.7)
T2/3	12(57.1)	25(27.8)	1(33.3)	0(0)	2(40)	40(33.3)
T4	9(42.8)	21(23.3)	2(66.6)	1(100)	3(60)	36(30)
Total	21(100)	90(100)	3(100)	1(100)	5(100)	120(100)

Others=rhabdomyosarcoma& lymphoma

**Table 3.** Cancer Progression and Recurrences (N=31).

Progression of cancer		
No	Yes	Total
27(65)	4(12.9)	31(100)
Recurrence		
4(12.9)	27(87.1)	31(100)

**Table 4.** Determinant of Recurrence (N=31).

Variables		Recurrence		
		No (4)	Yes (27)	P values
Grade	Low grade	4	20	0.338
	High grade	0	7	
Recurrence in 1 <sup>st</sup> check cystoscopy	Yes	0	23	0.002
	No	4	4	
Number of lesion at diagnosis	Single	4	11	0.043
	Multiple	0	16	
Presence of CIS	No	4	24	0.65
	Yes	0	3	

## Discussion

Although our study did not aim at giving the latent period from exposure to carcinogens to development of UBC, this contributes to the higher prevalence of this condition in elderly people with mean ages of 60.2 and 61.9 years in India and Iran respectively similar to mean age of 58.45 years in this study.<sup>30-31</sup> This is contrary to the findings in Nigeria of a mean age of 52

years. In the Nigerian study there was higher percentage of SCC compared to our study, which presents at an age of 10-20 years earlier than TCC.<sup>19</sup>

The male to female ratio in different parts of world is varied. The ratios generally range between three and five.<sup>31</sup> It exceeded six in some areas in Asia <sup>30</sup>but it was less than two (1:0.9) in parts of East Africa.<sup>21</sup> An analysis of our data has revealed a ratio of 2.2:1. Greater exposure to risk factors like cigarette smoking and industrial carcinogens may explain the male preponderance. The higher sex ratio in Asia is probably due to higher tendency of males to smoke cigarettes and females tend to present to hospital less frequently due to social reason. Relatively high percent of SCC was documented by previous investigator in East Africa, and it affects males and females almost equally due to equal exposure to schistosomiasis in childhood.<sup>20</sup>

TCC is the most common variant accounting for >90% of bladder cancer in the world literature.<sup>30</sup> Prevalence of SCC varies widely in different parts of the world but is higher in Africa especially in areas endemic for schistosomiasis like Egypt which accounts for 25% of bladder cancer<sup>19</sup>. In Lake Zone of Tanzania, an area endemic for schistosomiasis, the frequency of TCC and SCC were 40.5% and 55.1% respectively.<sup>21</sup>

Previous investigators in Africa observed a shift of histological type toward TCC<sup>19, 20</sup>. One of the studies which were done at KCMC hospital fifteen years ago found frequency of TCC to be 50% and SCC to be 40%. The current study, we also observed the shift in histological type, contribution of TCC raised to 75% while that of SCC decreased to 18%. This means the shift is still in process and in the future the frequency of TCC and SCC might resemble those of western countries. Adenocarcinoma and mixed carcinoma remained rare in our study similarly to other studies.<sup>20, 32</sup>. Eradication of schistosomiasis has been thought to contribute to the change of histological type of UBC resembling those of western countries<sup>33</sup>. An effort has been made in Tanzania to control schistosoma infestation which is highly associated with SCC<sup>21</sup> Furthermore urbanization which goes together with industrialization and smoking can as well explain increase in TCC. This has to be looked into in our population.

The frequency of recurrence in our study was 87%, which is in contrary to recurrence of 68.3% in another study<sup>34</sup>. In the comparative study, they excluded patients with concomitant CIS and they looked at recurrence at three month after diagnosis. Although we had 3 patients with concomitant CIS, the number can be higher than that as we did not perform random bladder biopsies to detect CIS<sup>24</sup>. Another study documented a much lower recurrence of 32% after follow up for two years after diagnosis<sup>24</sup>. In that study they included young adults and some of the patients were given intravesical instillations which can explain the difference in recurrence observed.

Progression after mean follow up of 28 months in patient with high grade superficial UBC has been found to be 27.1% in Pakistan<sup>26</sup>, which is higher than our progression of 13%. This difference can be contributed by characteristics of study population as well as duration of follow up. Definition of progression can also contribute because in the previous study they define progression as tumour involving the detrusor muscle, nodal or distant metastasis. However others have found progression rate of 4.3% <sup>23</sup>, which is low compared to our finding. The lower progression is probably due to the fact that in the comparative study they included patients who were on intravesical therapy and excluded CIS cases.

There are a lot of controversies on factors which can predict accurately intravesical recurrence of urinary bladder cancer. It is difficult to compare studies because different investigator use

different definitions for recurrence, different populations and these patients are managed differently. A study of patients with Ta and T1 without CIS showed that recurrence occurs in most patients with previous recurrences<sup>35</sup>. This finding was solidified by another study which concluded that, negative first follow up cystoscopies have a significantly lower recurrence rate than those with recurrence at first cystoscopy in patients with stage T1 and Ta TCC<sup>36</sup>. We found the same in our study, having recurrence at first follow up cystoscopy is a predictor of subsequent recurrences.

Number of tumour is the predictors of recurrence in patients with superficial TCC of bladder<sup>28,37</sup>. Multifocality is associated with high rate of recurrence in high grade superficial lesions<sup>26</sup>. In our analysis multifocality was related to recurrence. This high recurrence rate in multiple tumours can be contributed by incomplete resection of tumour at diagnosis or aggressiveness of the disease.

In a retrospective study of 110 patients with TCC who were not on intravesical therapy in Turkey, recurrence was related to grade of cancer with high grade cancer having high recurrence rate<sup>38</sup>. A similar finding was documented in a Chinese study<sup>39</sup>. This was different from our study which had 7 patients with high grade cancer and all experienced recurrence. However statistical test revealed no statistical significant association between grade and recurrence. We noted that the cooperative study conducted in Turkey was looking at both intravesical and extravesical recurrence. The difference can also be due to small number of patients with superficial TCC in our study. In our analysis three out of thirty one patients had concomitant CIS and all of them experienced recurrence in the first year of follow up after diagnosis. However statistical test did not show any significant association between recurrence and CIS.

### Conclusion

TCC is still the most common histological type in our set up followed by SCC. Majority of patients with TCC presents with advanced cancer, moreover intravesical recurrence after TURBT is high for those with non-muscle invasive TCC and influenced by multifocality and recurrence at first follow up cystoscopy. We need a large prospective study to confirm recurrence, progression and determinants of recurrence in our set up.

### Acknowledgement

We thank the Good Samaritan Foundation of KCMC for sponsoring this study without competing interest.

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