Original Article

Bladder Cancer in a Tertiary Health Institution in Northwestern Nigeria: A Thirty-Year Histopathological Review.

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Abstract

Malignant neoplasms of the bladder rank below common cancers such as breast, colon, cervix, liver, non-Hodgkin lymphoma and constitute less than 5% of all malignant tumours in most centres in Nigeria. The study analyzed all diagnosed malignant urinary bladder neoplasms in the departmental registry and clinical biodata were added. Consultants reviewed previously diagnosed cases, retrieved broken or faded tissue blocks, and stained them with Haematoxylin and Eosin. Tumours were classified according to the 2016 WHO classification of urinary bladder neoplasms. A total of 308 malignant urinary bladder neoplasms were found in 775 urinary bladder biopsies, with an annual prevalence of 39.7%. The most prevalent malignancies were infiltrative urothelial carcinoma and squamous cell carcinoma, which together accounted for 169 (54.9%) cases and 37.7% of all cases, respectively. The least frequent types of tumours were mesenchymal and glandular, accounting for 4.2% of cases. Males between the ages of 40 and 59 had the highest incidence. This study confirms that urinary bladder malignancies are uncommon as it was recorded in other centres in the country. It also shows that infiltrative urothelial carcinomas and squamous cell carcinomas are slightly equal in percentage with 46.4% and 45.6% respectively.

Keywords: - Bladder neoplasms, urothelial cancers, squamous cell carcinoma.

INTRODUCTION

Bladder cancer is the tenth most common cancer worldwide, accounting for 573,278 new cases and 213,000 reported deaths in 2020[2]. There are significant differences in the incidence rates of bladder cancer in various parts of the world. Bladder cancer is very common in North America, Southern and Western Europe, and both. Greece is the country with the greatest global incidence of bladder cancer in men, whereas Hungary is the country with the highest incidence in women. With 5.8 cases per 100,000 females and 26.6 cases per 100,000 men diagnosed annually, Southern Europe has the highest bladder cancer incidence rates in the world.[3] In contrast, bladder cancer is less common in areas like Middle East, Africa, South Central Asia, and Western Africa, which are mainly composed of nations with lower-than-average Human Development Index scores. Bladder cancer is more common in developed nations and mostly affects men, with incidence rates four times greater than in women. The relative frequency of

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urinary bladder neoplasms in Northern Nigeria from a short survey in Zaria ranges from 6.4% to 11.7% [4,5] . A study by Malami et al in Sokoto, North-west Nigeria revealed that bladder cancer was the commonest malignancy in males accounting for 19.3% of all malignancies and the sixth in females accounting for only 3%.[5] In Kano, North-west Nigeria, Ochicha et al found that bladder cancer accounted for 6.4% of all diagnosed cancers and was second to prostate cancer.[6] In a study on urological tumours, Mandong et al, North Central Nigeria, also made similar observation that urinary bladder malignancies weresecond to prostate cancer with a relative frequency of 31.7%.[7] Also, a study by Adesuwa et al conducted in Benin showed that malignant bladder neoplasm accounted for 1.85% of all malignant tumours, and transitional cell carcinoma accounted for 67.5%, squamous cell carcinoma 15%.[8] In Lagos, Anunobi et al found that bladder cancers accounted for 0.86% of all malignancies diagnosed in the department of pathology. Transitional cell carcinoma accounted for 61.5% whilesquamous cell carcinoma accounted for 20.5%.[9]

In Kenya, the disease forms 0.92% of all reported cancers in the early seventies.[10] In the United States, primary bladder neoplasms account for 2-6% of all malignancy and is commonly seen in men aged 50–70 years. Ninety-five percent of these neoplasms arise from the urothelium.[10] The most common subtype is urothelial carcinoma which accounts for 90% of all cases with varying geographic rates. Squamous cell carcinoma (SCC) accounts for 2%– 15% while the adenocarcinomas subtype which may be primary bladder, urachal,or metastatic represents less than 2%. The SCC and adenocarcinoma often occur in the setting of chronic bladder irritation and infection especially schistosomiasis. Mesenchymal tumours represent 5% of all bladder tumours. The commonest histological types are rhabdomyosarcoma in children and leiomyosarcoma in adults. Other rare mesenchymal tumours include paraganglioma, lymphoma, leiomyoma and solitary fibrous tumour.[12]

Smoking and occupational exposure to carcinogens such as aniline dyes, aromatic amines and benzidine are risk factors for bladder cancer. Most urothelial neoplasms are low-grade papillary tumours which tend to be multifocal with a high propensity for recurrence however, with a relatively good prognosis. On the other hand, high-grade invasive tumours are less common and have poorer prognosis.

MATERIALS AND METHOD

This thirty-year retrospective analysis was based on all diagnosed bladder biopsies submitted to the Department of Pathology of the hospital from 1st January 1991 to 31st December 2020. The hospital is a referral center for the Northwestern region of the country as well as a referral Oncology centre for the country.

The histopathology reports of all bladder biopsies and some of the case notes were extracted from the departmental and central hospital records. Relevant histology-stained slides were retrieved and viewed. Freshly stained slides were made from stored blocks in cases of missing slides. Special stains such as mucicarmine, alcian blue and periodic acid-Schiff (PAS) were done to demonstrate acid mucopolysaccharide especially in poorly differentiated adenocarcinomas to further characterized the tumour using current WHO 2016 edition diagnostic criteria for bladder neoplasms. Patients' biodata including age and sex were extracted from the accompanying case cards.

Analysis of the collected data was carried out using Statistical Program for Social Sciences (SPSS) Version 16.0. Data were presented in frequency distribution tables and figures including photomicrographs with legends.

Ethical clearance was obtained from the Ethics and Scientific Committee of the Ahmadu Bello University Teaching Hospital, Shika-Zaria for the study.

RESULTS

Seven hundred and seventy-five (775) urinary bladder biopsies were received during the same period.Of these 308 (39.7%) were malignant and accounted for 2.9% of all malignant neoplastic lesions in the same period. Three hundred and eight (308) malignant tumours of

Table 1: Sex distribution of histologic variants of malignant bladder neoplasms

Histologic variants	Males (%)	Females (%)	Total (%)
Infiltrative urothelial carcinoma	141 (45.8)	128 (9.1)	169 (54.9)
Squamous cell carcinoma	99 (32.1)	17 (5.5)	116 (37.7)
Glandular carcinoma	8 (2.6)	3 (1.0)	11 (3.6)
Mesenchymal tumours	1(0.3)	1 (0.3)	2 (0.6)
Metastatic tumours	10 (3.2)	-	10 (3.2)
Total	259 (84.1)	49 (15.9)	308(?)

the urinary bladder were analysed. The infiltrative urothelial carcinoma accounted for 169 (54.9%) cases andsquamous cell carcinoma (SCC) accounted for 116 (37.7%) cases while mesenchymal and glandular tumours accounted for 2 (0.6%) and 11 (3.6%) cases respectively. Only 10 (3.2%) metastatic cases were recorded. (Table 1)

Sex Distribution

There were 259 males and 49 females with a M; F ratio of 5.3:1. The commonest histological variant amongst both sexes is infiltrative urothelial carcinoma which accounted for 141 (45.8%) cases and 28 (9.1%) cases in males and females respectively. Well differentiated SCC was the second commonest in both sexes with 99 and 17 cases accounting for 32.1% and 5.5% in males and females respectively. Infiltrative urothelial carcinoma with micro-papillary differentiation and infiltrative urothelial carcinoma with sarcomatoid changes were seen in males only. The only case of leiomyosarcoma occurred in a 45-year-old female. (Table 2)

Table 2: Age Distribution of Histologic Variants of Malignant Bladder Neoplasms

AGE (YEARS)	HISTOLOGIC VARIANTS					
	IUC	SCC	GC	MT	MTT	Total
0-19	-	-	-	1	-	1
20-39	22	29	3	-	2	56
40-59	80	67	7	1	4	159
60-79	60	19	1	-	4	84
>80	7	1	-	-	-	8
TOTAL	169	116	11	2	10	308

Age Distribution

The patients' ages ranged from 1 to 87 years with a mean of 51 years. The peak age distribution of the two commonest tumour types, infiltrative urothelial carcinoma and SCC shared the same peak age distribution in the 5th and 6th decades while the solitary case of Rhabdomyosarcoma occurred in a one-year-old boy. Fifty percent (50%) of all the metastatic tumours were seen in the 6th and 7th decades of life. (Table 2)

One hundred and sixty-nine cases were recorded with a M:F ratio of 141:28 (10:2). Of these, 23 exhibited squamous differentiation with a M:F ratio of 13:3, while six (16) and three (3) cases respectively showed micro-papillary and glandular differentiation. The highest frequency of these tumours occurred inthe 5th to 7th decade with M:F ratio of 6.4:1. (Tables 2)

Table 3: Comparison of Current Study with Previous Local, Regional and International Studies

STUDIES	HISTOLOGICAL TYPES					
	UC	SCC	AC	PDC	S	SN
Nigerian studies						
			-	6.2%	-	
Eni et al, Maiduguri (65 cases)	23%	70.8%				
Ochicha et al, Kano (51 cases)	35%	53%	4%	8%	2%Ÿ	
Mungadi et al, Sokoto (43cases)	27.9%	65.1%	4.7%	2.3%§	-	
Mandong et al, Jos (97 cases)	50.5%	43.3%	3%	-	3%¥	
Anunobi et al, Lagos (39 cases)	61.5%	20.5%	5.1%	5.1%	7.8%¢	
Thomas et al, Ibadan (71 cases)	46.5%	47.9%	4.2%	1.4%		
Other African studies						
Klufio, Ghana (117cases)	50.4%	44.4%	1.7%	2.6%	0.9%†	
Bowa et al, Zambia (158cases)	23.4%	46.2%	22.2%	8.2% (Others)		
International studies						
Gupta et al, India (481cases)	97.7%	1.03%	1.2%			
Hnatko et al, Canada (660 cases)	92%	5%	2%	1% (Others)		
Index study (237cases)	46.4%	45.6%	3.8%	-	0.8%	3.4%

UC= Urothelial Carcinoma; SCC= Squamous cell Carcinoma; AC=Adenocarcinoma; PDC= Poorly Differentiated Carcinoma; S=Sarcoma; SN=Secondary Neoplasia; §=Signet ring Carcinoma; Ÿ= Leiomyosarcoma; ¥= Spindle cell tumour; ¢= Rhabdomyosarcoma. †=Angiosarcoma.

Tumour Types

Infiltrative Urothelial Neoplasms

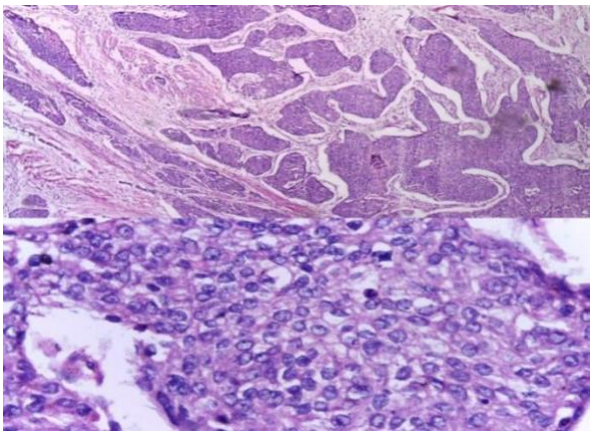

Fig 1: Infiltrative urothelial carcinoma showing nests and sheets of malignant urothelial cells (Top: H&E X100) and (Bottom: H&E x400)

Squamous Cell Neoplasms

One hundred and sixteen cases were recorded, and this accounted for 37.7% with M:F ratio of 99:17. The highest incidence is in the 5th and 6th decade and commoner in males than females with a ratio of 5.8:1.

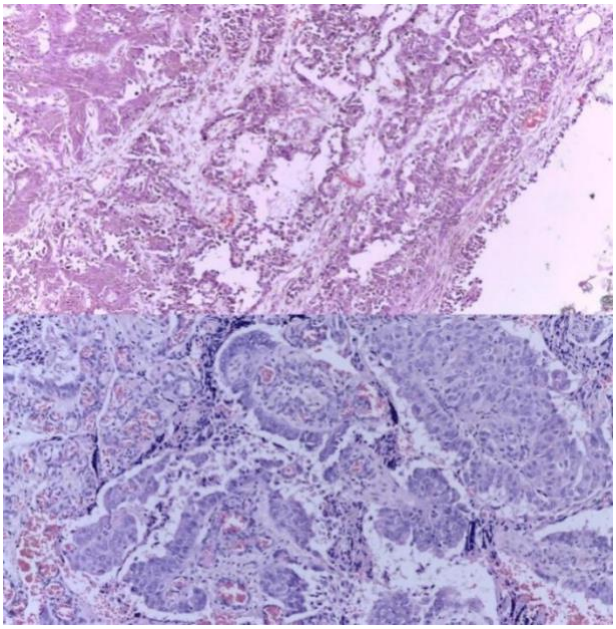

Fig 2: Infiltrative urothelial carcinoma with glandular differentiation: solid sheets of urothelialcells and glandular formation (Top: H&E x200) and Micropapillary infiltrative urothelial carcinoma: papillary fronds and tips (Bottom: H&E x200**).**

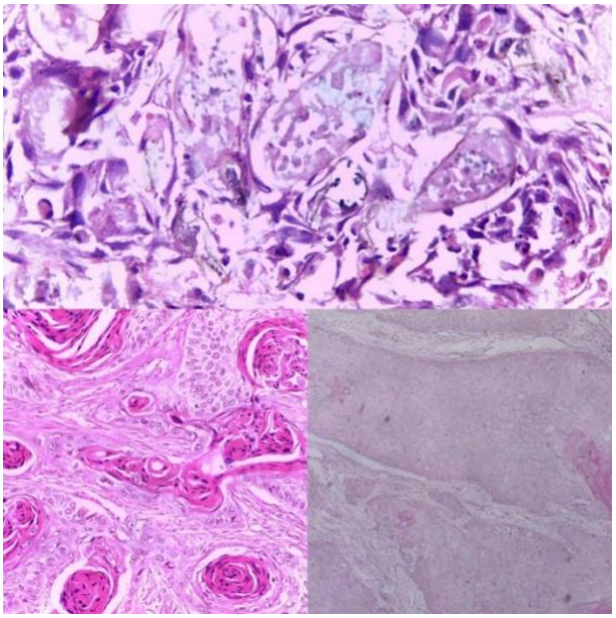

Fig 3: Well differentiated SCC with Schistosomiasis (Top: H&E x400), Well differentiated SCC with keratin pearls (Bottom left: H&E x400); Verrucous carcinoma: acanthotic squamous sheets and nests with minimal stroma (Bottom right: H&E x200)

Well differentiated SCC had the highest frequency with 69 (22.4%) cases and moderatelydifferentiated SCC cases were 26 (8.4%) while poorly differentiated SCC were 21 (6.8%) cases.(Tables 2 and 3)

Glandular Neoplasms

Eleven cases of urothelial adenocarcinoma were recorded. They accounted for 3.6% of all the caseswith M:F ratio of 2.7:1. The peak age distribution was in the 5th to 6th decade of life. (Table 2 and 3)

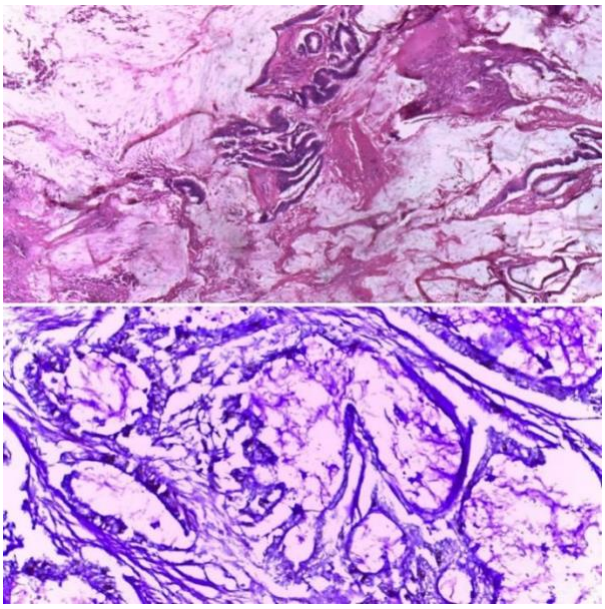

Fig 4: Adenocarcinoma of the urinary bladder: tubules formation within mucinous stroma (Top: H&E, x100; Bottom: PAS x200).

Mesenchymal Neoplasms

A solitary case of rhabdomyosarcoma and leiomyosarcoma were seen in a 1-year-old boy and a 45-year-old female respectively. (Tables 2 and 3)

Metastatic Neoplasms

Ten metastatic prostatic adenocarcinomas to the bladder were recorded and this accounted for 3.2% of all the cases. Eighty percent (80%) of this metastasis occurred in the 6th to 8th decades of life. (Tables 2 and 3)

Schistosomiasis and Malignant Bladder Neoplasms

Thirty-nine (12.7%) cases of schistosomiasis were

seen in association with varied malignant bladder neoplasms. 33 were seen in males and 6 cases only in females. Of the 39 cases, thirty-two were associated with SCC, while six cases were seen in infiltrative urothelial carcinoma. Only one case was seen with urothelial adenocarcinoma.

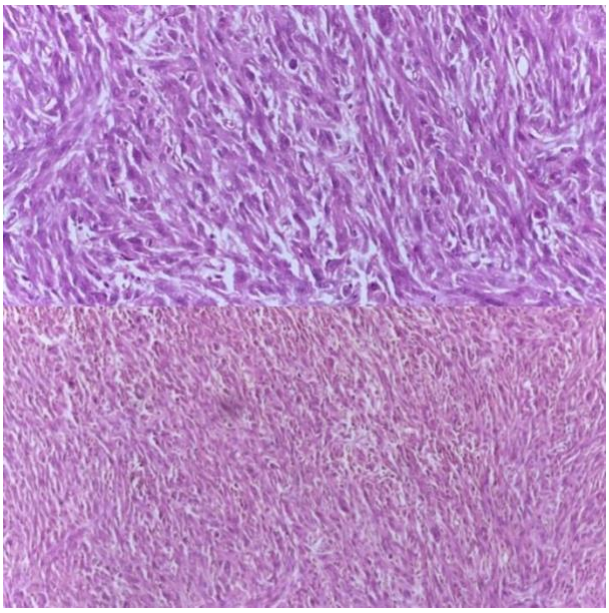

Fig 5: Infiltrative urothelial carcinoma, Sarcomatoid variant: spindle tumour cells admixed withanaplastic cells (Top: H&E x200); Leiomyosarcoma of the urinary bladder: fascicles of malignant spindle cells having hyperchromatic nuclei with moderate cytoplasm and giant cells (Bottom: H&E x200)

DISCUSSION

A total of 775 bladder biopsies were recorded out of which 308 were malignant bladder neoplasms.In this centre we recorded 308 malignant bladder neoplasms representing annual frequency of 10.3within the 30 years of the study. An average of 10.3 cases per year was recorded in this study which is one of the highest compares to the study conducted by Anunobi et al in which they recorded 54 cases of bladder biopsies over 15 years with a yearly average of 3.6 cases.[8] The yearly averagewas higher in Kano where 22.3 cases were recorded yearly by Ochicha et al.[3] this is a more comprehensive study than other centres which limited their studies to 5, 10 and 15 years. This is a reflection of a hospital-based study.

The global frequency of malignant urinary bladder neoplasms is low compared to other malignancies. However, World Health Organization documented global frequency rate of 3.2% which is lower than the 11.9% found in this study which is a hospital-based study.[1] Hospital studies in various centres in Nigeria namely Kano, Lagos and Jos also documented a frequency rate of 6.4%, 0.86% and 2.5% respectively. These low frequencies thus further supporting the rarity of these neoplasms.[3, 6, 8, 64]

Malignant bladder neoplasm is predominantly a male disease. This male preponderance is well documented by many studies; thus, our finding is not an exception. Although, Alhassan et al in their study reported a significant M: F ratio of 18:1 which is 3 times the ratio (5.3:1) found in this study.[4]

The peak age incidence of these tumours is the sixth decade of life and our mean age in this pilot study was 51years while the peak age of occurrence was between the 5th and 6th decades. We also recorded a wide age spectrum from 1yr to 85yrs. This wide age spectrum is significant because traditional malignant neoplasms such as infiltrative urothelial neoplasms are uncommon in youngage group. The single case documented in the 1st to 2nd decades was a 1year old boy with embryonal rhabdomyosarcoma a tumour which commonly affect hollow organs such as bladder and the orbit and is often seen in these age groups. Reports from Kano and Jos support our finding.[3, 6, 65] About twenty percent of cases of malignant bladder neoplasms were documented in the first four decades of life in this study.

The male to female ratio for malignant neoplasms in this study was 5.3: 1 which is higher than most studies from Nigeria which range from 2:1 to 5.2:1.[3, 8, 66-68] The highest ratio was documentedin the findings of Mungadi and Malami where they recorded a very high male to female ratio of 11.1:1.[15] The male predominance could be due to higher exposure to risk factors such as being farmers, workers in industries that uses aniline dyes, being swimmers and fishermen in water bodies where *Schistosoma* are endemic and cigarette smoking. The attributable risk of tobacco smoking in males is 66% as against 30% in females as documented by Eble et al in the WHO series.[51]

It was previously reported that urinary bladder malignancies accounted for 6.4% of all malignancies in Zaria.[2] In the present study, they accounted for 2.9% of all malignancies. This is higher than the 0.86% reported from Lagos and 0.92% from Kenya.[8, 9] and was lower than the relative frequencies of 2.5%-3.5% in Jos, 6.4% in Kano and 8.7% in Sokoto.[3, 4, 69] The higher relative frequencies in the Northern part of Nigeria compared to the South could be due to the endemic schistosomiasis in the predominantly agrarian population of the north. In support of this hypothesis, a high relative frequency of 30.3% was documented at the National Cancer Institute, Cairo where there is endemicity of schistosomasis.[70]

The commonest histologically diagnosed category of malignant bladder neoplasms was infiltrativeurothelial carcinoma and its variants which

accounted for 54.9% of cases. This comprised 36.7% infiltrative urothelial carcinoma, 7.5% of infiltrative urothelial carcinoma with squamous differentiation, 5.2% of micropapillary carcinoma, 1.0% of infiltrative urothelial carcinoma with glandular differentiation, 0.3% of infiltrative urothelial carcinoma with sarcomatoid differentiationand 4.0 % of poorly differentiated urothelial carcinoma. Similar studies in Nigeria by Mandong et al in Jos and Anunobi et al in Lagos showed higher frequency of urothelial carcinoma with 50.5% and 61.5% respectively.[6, 8] Also similar findings were recorded by Klufio et al in Ghana, Gupta et al in India and Hnatko et al in Canada also shows higher frequency rates of 50.4%, 97.7%, 92% respectively.[18, 71, 72]

Infiltrative urothelial carcinoma with squamous and glandular differentiation accounted for 7.5%and 1.0% respectively in our study. Zhai et al in Houston, USA reported a frequency of 21% and 6% respectively and their high figure may be attributed to their highly industrialized environment.[73] Sultana et al from Bangladesh documented 18% and 5.3% for squamous and glandular differentiation in urothelial carcinoma, we found 7.5% and 1.0% respectively.[74]

The frequency of occurrence of both infiltrative urothelial carcinoma and squamous cell carcinoma varies with a frequency of 54.9% and 37.7% respectively in this study. This slight rising trend in the incidence of Infiltrative Urothelial Carcinoma may be attributable to the increasing rate of urbanization and industrialization. Also, the increasing incidence of cigarette smoking amongst the young population further exposes the populace to carcinogenic agents such as Aromatic amines benzidine and 2-naphthylamine.[16, 75-77] While, improvement in water treatmentand supply, modern diagnostic and accurate prompt treatment of schistosomiasis may play a role in the decreasing incidence of squamous cell carcinoma a well-known sequela of schistosomiasis. Though, Ochicha et al and Mungadi et al in Kano and Sokoto respectively reported a higher incidence in SCC. This may be attributable to high incidence of schistosomiasis in both settings.[3,15,]

Squamous cell carcinoma was the second commonest malignancy accounting for 37.7% of cases which is higher than what is found in Lagos (20.5%). Previous studies showed its predominance with relative frequencies of 53% in Kano, 65.1% in Sokoto and 70.8% in Maiduguri. In Egypt, therelative frequency of squamous cell carcinoma was 59%.[70] In the western world, the relative frequency is 3-7%.[70,72] Gupta et al reported a low frequency of 1.0%.[78] The relatively high frequency of squamous cell carcinoma in Nigerian and Egyptian studies compared to the lower frequency in Western and Indian studies is probably attributable to endemicity of schistosomiasis in areas of Western and Northern Africa. In support of this hypothesis, in Egypt, with active treatment, management and prevention of schistosomiasis, a changing trend from squamous cell carcinoma to transitional cell carcinoma was also noticed.[79]

Similar to studies from the Southwest Nigeria, the modal age of patients with urinary bladder cancers in this study was 60-69 years.[18] The modal age in *Schistosoma* endemic areas are a decade or two younger.[14,53,94] In this study, 39 cases had *Schistosoma* ova of which 33 were squamous cell carcinoma, 5 were urothelial carcinoma and a case of adenocarcinoma. Similar to reports from Maiduguri, there is statistical association between Schistosomiasis and squamous cell carcinoma. In a critical appraisalof casual relationship between schistosomiasis and carcinoma of the bladder, Attah and Nkposong found association between schistosomiasis and all varieties of urothelial carcinoma.[80],[32-34] This association is attributed to chronic irritation of the urothelium due to the schistosome ova, altered metabolism of elevated urinary levels of carcinogenic metabolites and N-nitroso compounds as well as elevated urinary levels of beta-glucuronidase.[81] SCC carries poorer prognosis and occurs in younger age group than urothelial carcinomas. Similar to other studies, patients with squamouscell carcinoma were younger than patients with other histological variants.[3, 8, 16] The modal age group in this study for squamous cell carcinoma was 50-59 compared to the 60-69 years for urothelial carcinoma.

Bladder adenocarcinoma constituted 3.6% more than the reported 2% in the literature. This usually arises on the background of cystitis glandularis, cystica and urachal remnants or ectopia vesica. This is commensurate with reports from Ochicha et al and Mandong et al with 4% and 3% frequency rates respectively.[1, 3, 6]

Sarcomas of the urinary bladder are uncommon and constitute less than 1% of all bladder malignancies. Of the sarcoma variants, leiomyosarcoma is the commonest documented in the bladdder.[82-84] Though we recorded a solitary case of leiomyosarcoma a disease of the elderly as seen in our case. The two sarcoma cases accounted for 0.6% of our cases thus supporting literature. Unlike the reports from Lagos, the embryonal type was the commonest.[8, 85]

CONCLUSION

This thirty-year retrospective analysis of bladder cancer cases in a referral hospital in Northwestern

Nigeria sheds light on the prevalence, types, and demographic distribution of this disease in the region. The study revealed a higher frequency of bladder cancer cases compared to prior reports in Nigeria, emphasizing the significance of this health issue in this specific area.

The predominance of infiltrative urothelial carcinoma and squamous cell carcinoma aligns with findings from similar studies in Nigeria. These two primary histological variants, especially squamous cell carcinoma, demonstrated an association with schistosomiasis, indicating the influence of environmental factors on cancer occurrence in the region.

The higher incidence among males, typically occurring in the 6th decade of life but with occurrences observed across a wide age range, highlights the need for continued vigilance and tailored preventive measures.

This study underscores the importance of ongoing surveillance, targeted interventions, and awareness programs focusing on risk factors like schistosomiasis, occupational exposures, and lifestyle habits to address and potentially reduce the burden of bladder cancer in Northwestern Nigeria. Further research and collaborative efforts are essential to better understand the disease's dynamics and implement effective preventive strategies in this region.

The study highlights the higher frequency of malignant bladder neoplasms in Nigeria compared to some other regions, possibly due to the endemicity of risk factors such as schistosomiasis, presence of dye industries in the Northern Nigeria and tobacco smoking. Schistosomiasis was associated with squamous cell carcinoma, emphasizing the importance of addressing this parasitic infection in the prevention and management of bladder cancer.

The findings of this study contribute to the understanding of bladder cancer epidemiology in Nigeria and provide useful information for healthcare professionals and policymakers. Efforts should focus on raising awareness about risk factors, promoting early detection and diagnosis, and implementing preventive measures to reduce the burden of bladder cancer in the country.

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