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ORIGINAL RESEARCH

A histopathological study of bladder cancer in Uganda

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Background: The incidence of squamous cell carcinoma (SCC) and adenocarcinoma of the bladder have been higher than that of urothelial carcinoma (UC) in several African countries for nearly five decades. However, this trend has changed over time, with various countries reporting rising numbers of UC against other forms of bladder cancer. We carried out a histopathological study of bladder tumours in Uganda to objectively realign the clinical and public health interventions.

Methods: We conducted a five-year descriptive cross-sectional study. In total, 117 samples that fit the inclusion criteria were consecutively selected and re-examined from a pool of 282 archived formalin-fixed paraffin-embedded (FFPE) bladder cancer tissue blocks. The independent variables studied were age and sex; the outcome variables were histological type, lymphovascular invasion and variant morphologies measured as proportions with their 95% confidence intervals. Crude associations between bladder cancer types and the independent variables were assessed using Pearson's chi-square and Fisher's exact tests accordingly. A p-value < 0.05 was considered statistically significant.

Results: The male-to-female ratio (M:F) was 1:1.7, whereas the mean and standard deviation of the participants' ages was 59 ± 15 years. The most common histological type was UC (107; 91.4%), of which 63 (58.9%) were muscle-invasive. SCC and adenocarcinoma had proportions of 6.0% (2.4–11.9) and 2.6% (0.5–7.3), respectively. The most common variant morphologies of UC were nested (14.3%), microcytic (12.7%) and squamous differentiation (7.9%). Lymphovascular invasion (LVI) was seen in 79.4% of the samples with muscle-invasive UC. There was no association between any bladder cancer type and age or sex.

Conclusion: Although SCC and adenocarcinoma were once the most common bladder cancer types in Uganda, current histopathological findings indicate that UC is now 15 times more frequent than SCC and 35 times more common than adenocarcinoma.

Keywords: bladder cancer, urothelial carcinoma, squamous cell carcinoma, adenocarcinoma

Introduction

More than 2.63 million people worldwide were diagnosed with bladder cancer in 2017, of which 200 000 died.[1] This makes it the ninth most frequently diagnosed cancer worldwide.[2]

The prevalence of the most common bladder cancer types (urothelial carcinoma, squamous cell carcinoma and adenocarcinoma) varies across Africa. Many African countries have high incidences of squamous cell carcinoma (SCC), for instance Nigeria, Zambia, Libya, Senegal and Zimbabwe, while in several African countries such as Egypt, Ethiopia, Kenya and Cameroon, urothelial carcinoma (UC) predominates.[3-7] It is worth mentioning that UC is the most common bladder malignancy diagnosed in Western countries.[4,8] It presents either as muscle-invasive or non-muscle-invasive. The latter comprises the bulk of patients (70–85%) seen in most of the countries.[5] This picture is quite different from what is seen in Uganda where the majority of UC cases present as the muscle-invasive form.

The neoplastic urothelium of the bladder can demonstrate enormous plasticity in the form of morphological variants and divergent differentiation. These rare histopathological patterns include nested, microcystic, clear cell, sarcomatoid, giant cell, lipid-rich, micropapillary, lymphoepithelioma-like, plasmacytoid, and poorly differentiated as well as divergent differentiation into squamous, glandular and trophoblastic forms.[9]

The only relatively similar study was done in Uganda approximately 50 years ago and indicated that out of the 138 cases reviewed from the national cancer registry at Mulago National Referral Hospital (MNRH), the majority (75; 54.3%) was SCC, followed by adenocarcinoma (26; 18.8%), UC (19; 13.8%) and other (18; 13.0%).[10] These trends have overtly changed with more cases of UC being diagnosed and very rarely SCC or adenocarcinoma. Therefore, we carried out a histopathological study of bladder cancer to aid in clinical and policy realignment.

Methods

This was a cross-sectional study conducted at the MNRH complex. The hospital is located on Mulago Hill in the northern part of Kampala, the capital of Uganda. This hospital complex has three repositories: Makerere University, Uganda Cancer Institute and Mulago Hospital pathology laboratories, all located within the campus of the MNRH complex. Nearly all patients with bladder cancer in Uganda are referred to and managed with super-specialised care at this hospital.

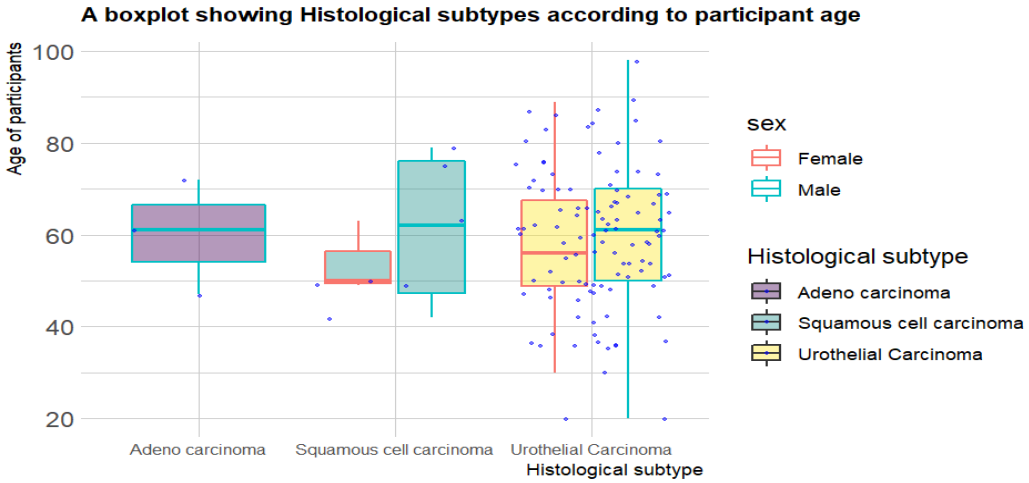

Figure 1: A box and scatter plot showing histological types according to the age of the participants separated by sex

From a collection of 282 archived formalin-fixed paraffin-embedded (FFPE) tissue blocks of bladder cancer over the last five years (2018–2022), we consecutively re-examined and recruited 117 samples. Two consultant pathologists independently read the slides using an Olympus BX50 Microscope with a field diameter of 0.52 mm. In case of a disagreement, a consensus was reached by re-examining the cases on a multi-headed microscope. Damaged tissue blocks, those with extensive necrosis, absent detrusor muscle in the specimen, or those with missing vital demographic data were excluded from the study.

Data management and analysis

Data were collected using a questionnaire and entered into REDCap (Research Electronic Data Capture)[11] and later exported as a comma separated values (CSV) file into RStudio for analysis. Graphs were drawn using the ggplot2-package.[12] Patients' ages were categorised into groups (i.e. < 40, 40–49, 50–59, 60–69, 70–79 and > 80) and thereafter summarised as mean and standard deviation or median and interquartile range (IQR). Categorical data were summarised as frequencies and proportions, and then presented in tables and graphs. We calculated the proportions of the histological types of bladder cancer as a proportion of each type of the total sample size. Crude associations between UC and the independent variables were assessed using Pearson's chi-square test for UC and Fisher's exact test for adenocarcinoma and SCC. A *p*-value < 0.05 was considered statistically significant.

Results

Overall, a total of 117 samples were included in the study. The majority of the samples were from male patients (74; 63.3%) (Figure 1). The mean and standard deviation of the participants' ages were 59 ± 15 years. There was no association between any bladder cancer type (UC, SSC or adenocarcinoma) and age or sex.

Table I: The proportion of histological types

Histological type	Frequency (*n*)	Proportion (95% CI)
Adenocarcinoma	3	2.6% (0.5–7.3)
Squamous cell carcinoma	7	6.0% (2.4–11.9)
Urothelial carcinoma	107	91.4% (84.8–95.8)

CI – confidence interval

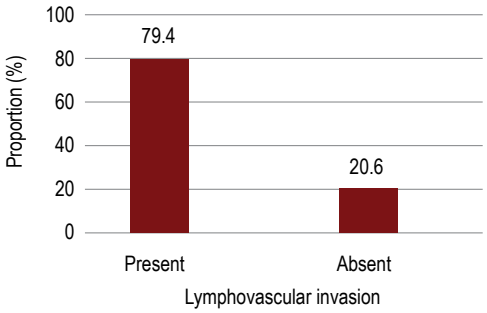

Figure 2: The proportion of lymphovascular invasion in the MIUC samples

The median (IQR) age of patients with adenocarcinoma was 61 (47–72) years, 50 (49–75) years for SCC and 60 (49–70) for UC. The median and IQR for male patients were slightly higher than for female patients for all histological types.

UC was the most common histological type of bladder cancer seen (91.4%), of which 63 (58.9%) were muscle-invasive urothelial carcinoma (MIUC).

Lymphovascular invasion (LVI) was present in most of the samples with MIUC (50/63; 79.4%). LVI was absent in all tissues with non-muscle-invasive urothelial carcinoma (NMIUC).

The majority of the tissues with MIUC exhibited variant morphologies (32/63; 50.8%). The most common were nested (14.3%), microcystic (12.7%) and squamous differentiation (7.9%).

Histopathological characteristics of some of the tissues examined

Papillary urothelial neoplasm of low malignant potential

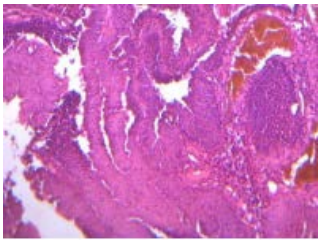

Image 1: x60

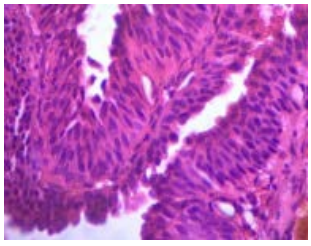

Image 2: x100

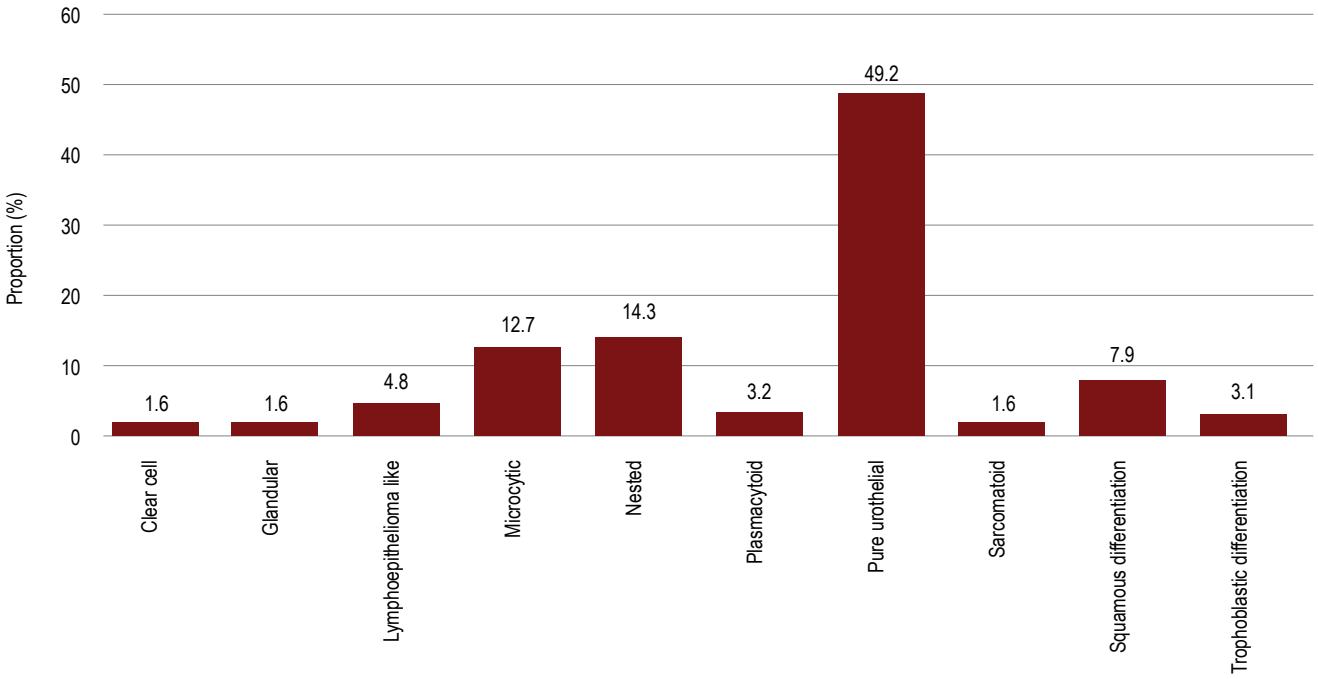

Figure 3: A bar graph showing the proportion of pure muscle invasive urothelial bladder cancer and the variant morphologies

Hyperplastic urothelium with well-matured polarity encasing a fibrovascular core, no LVI or stromal invasion (Images 1 and 2).

Non-muscle-invasive urothelial carcinoma, clear cell variant

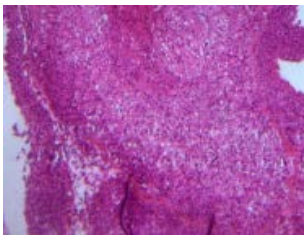

Image 3: x60

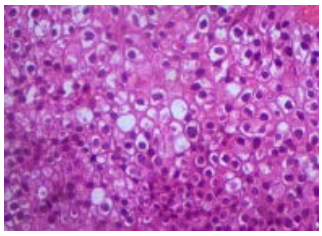

Image 4: x100

Papillary fronds lined with atypical urothelium (Image 3). The tumour cells depict cytoplasmic clearing with scattered mitotic figures (Image 4). No detrusor muscle invasion. No LVI; hence, the less likelihood of regional nodal metastasis.

Non-muscle-invasive urothelial carcinoma with glandular differentiation

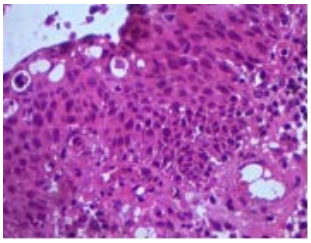

Image 5: x100

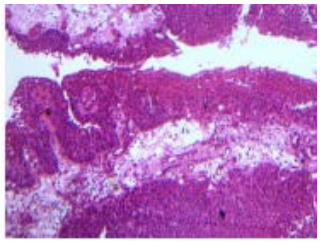

Image 6: x60

Papillary fronds lined with dysplastic urothelium (Image 5). There is cribriform glandular differentiation with extensive necrosis (Image 6). No invasion of the detrusor muscle. No LVI; hence, the less likelihood of regional nodal metastasis.

Micro-invasive urothelial carcinoma, lymphoepithelioma-like variant

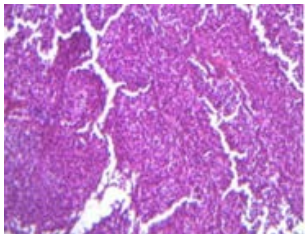

Image 7: x60

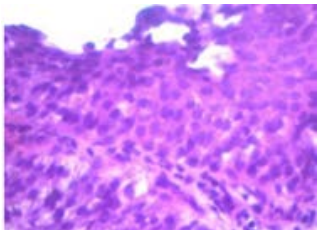

Image 8: x100

Sheets of cells arranged in syncytia separated by a prominent inflammatory infiltrate. The nuclei are large and vesicular (Images 7 and 8). Tumour extending 1 mm into the lamina propria. No LVI; hence, there is less likelihood of regional nodal metastasis.

Muscle-invasive urothelial carcinoma, nested variant

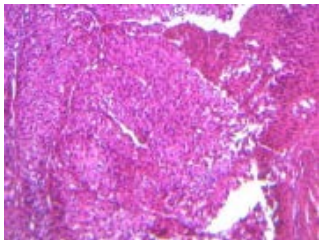

Image 9: x60

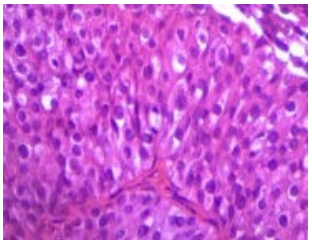

Image 10: x100

Highly dysplastic urothelium forming fragmented papillae and nests (Images 9 and 10). Detrusor muscle invasion, ≥ pT2. No LVI; hence, there is less likelihood of regional nodal metastasis.

Muscle-invasive urothelial carcinoma with squamous differentiation

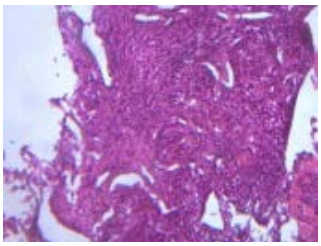
Image 11: x60

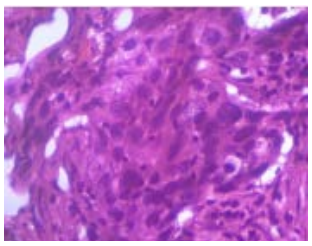
Image 12: x100

Tumour extending into the detrusor muscle, ≥ pT2 (Image 11). Solid papillary nests of dysplastic urothelium infiltrating and inciting desmoplastic stromal reaction (Image 12). There is prominent lymphovascular and perineural invasion, which entails a higher possibility of regional nodal metastasis and tumour extension out of the bladder wall, respectively.

Muscle-invasive urothelial carcinoma, microcystic variant

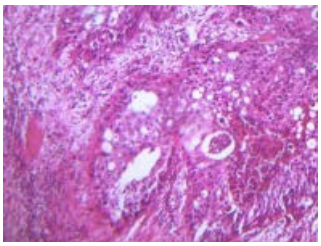
Image 13: x60

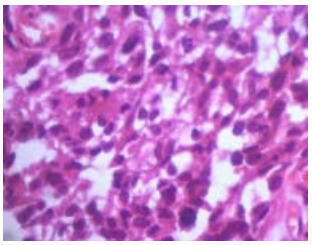
Image 14: x100

Tumour extending into the detrusor muscle, ≥ pT2. Prominent LVI; hence, possible regional nodal metastasis. There are variable-sized cysts lined with flattened cuboidal cells with intraluminal necrotic material (Images 13 and 14).

Muscle-invasive urothelial carcinoma, plasmacytoid variant

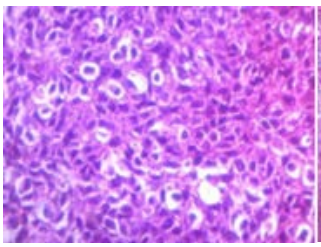
Image 15: x100

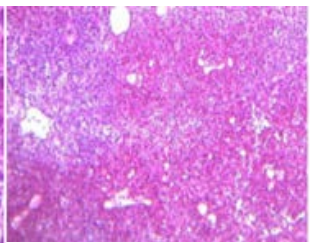
Image 16: x60

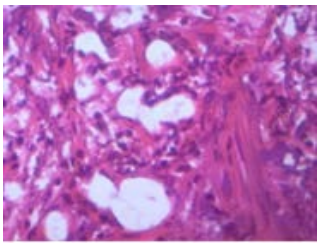
Image 17: x100

Polypoid projections comprised of urothelium with plasmacytoid features (Images 15 and 16). Tongue-like projections through the detrusor muscle, ≥ pT2 (Image 17). No LVI, entailing less likelihood of regional nodal metastasis.

Muscle-invasive urothelial carcinoma, sarcomatoid variant

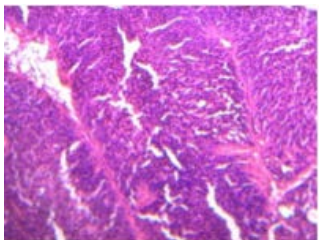
Image 18: x60

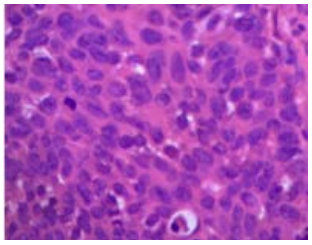
Image 19: x100

Solid sheets of large bizarre squamous cells infiltrating the detrusor muscle, ≥ pT2b (Image 18). Detrusor muscle invaded, ≥ pT2b, with 40% sarcomatous changes (Image 19). There is prominent LVI; hence, a high likelihood of regional nodal metastasis.

Discussion

From this study, the male-to-female ratio (M:F) has tremendously narrowed to 1:1.7, compared to 50 years ago when it was 1:8.1 in Uganda.[10] Regarding sex, there is a global preponderance of bladder cancer in males, i.e. four times more common.[4] However, it varies for different countries. For instance, bladder cancer is 2.2 times more common in Austrian males,[13] 7 times in Egyptian males,[14] and 8.8 times in Libyan males.[7]

Participants had a bimodal age distribution (Figure 1), the youngest being 37 years and the oldest 98 years with a mean age of 59 ± 15 years. The reasons for this observation are not yet clear. However, it can be postulated that genetics and environmental pollutants, among other multifactorial risk factors, may be implicated. The mean age is almost similar to the mean age of 54.8 years in the study done in Uganda five decades ago.[10] In Nigeria, the median age at diagnosis has progressively increased from 47.4 to 60.5 years.[15] In Libya, the mean age is 63.7 years,[7] while in Senegal it is 62.4 years,[16], and in Egypt it is 52 years.[17]

The majority of the cases of bladder cancer were UC (91.4%) with very few being SCC (6.0%) or adenocarcinoma (2.6%). These findings are a complete reverse of what was seen in the country 50 years ago when SCC was the most common (75; 54.3%), followed by adenocarcinoma (26; 18.8%) and UC (19; 13.8%).[10] Although the exact explanation for the current trends is beyond the confines of this study, the increasing levels of environmental pollution and risky lifestyle choices, like smoking among others, may be associated with the rising incidence of UC. It is worth noting that such findings are not unique to Uganda. For instance, many countries in the African Sahara region such as Egypt and Sudan, which were known to be hubs for SCC of the bladder, are currently seeing more UC cases than SCC and adenocarcinoma combined.[17,18]

From this study, the most common type of UC seen was MIUC, of which 50/63 (79.4%) had positive LVI and therefore a higher likelihood of regional or even distant metastases. In the Western world, the reverse findings are true, where 75–90% of UC cases managed are NMIUC.[19-21] Out of the 63 MIUC samples examined, the majority (51.8%) exhibited variant morphologies, a feature known to worsen prognosis.[22-24] This further explains one of the possible reasons for the high mortality rates from UC seen in

Uganda. The most common variant morphologies seen were nested (14.3%), microcytic (12.7%) and squamous differentiation (7.9%). The nested variant is rare with a reported incidence of 0.3% of all invasive bladder tumours.[23,25] On the other hand, squamous differentiation, known for its aggressiveness, is reported to be the most common variant and is seen in up to 20% of UC cases,[24] with some studies reporting it to be as high as 40%.[22] Although the microcystic variant is reported to be extremely rare and aggressive, with only 17 cases reported in literature,[26] there was a considerably high finding of 12.7% (8/63) in this study. Likewise, some studies reported higher numbers of glandular differentiation at 18%[22] and 5/46 (11%).[27] However, this study found that it was merely 1/63 (1.6%). Similar findings were noted for clear cell and sarcomatoid variants, with the latter reported to be less than 5% in other studies.[22,27] Trophoblastic differentiation, plasmacytoid and lymphoepithelioma-like variants were 3.1%, 3.2% and 4.8%, respectively, while some studies report these as less than 1% to as high as 20%.[22,27] We did not see any morphological patterns in the tissues suggestive of the micropapillary, poorly differentiated, giant cell or lipid-rich variants, although these have been reported in other studies.[22,27]

Study limitations

A retrospective study of histopathology samples spanning more than 10 years would be more informative. However, this was not possible due to various challenges at our repository that affect tissue quality, as well as missing demographic and clinical data of the stored samples.

Conclusion

The findings of this study confirm that UC has overtaken SCC and adenocarcinoma as the most common form of bladder cancer in Uganda. Moreover, the most frequently seen muscle invasive UC exhibits variant morphologies, with the most common being nested, microcystic and squamous differentiation. Pathologists should therefore look out for all these details in bladder cancer specimens to help urologists manage the affected patients better.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

Ethical approval was obtained from Makerere University School of Medicine's Research and Ethics Committee under protocol reference number **Mak-SOMREC-2021-257**.

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