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Original Research Article

Comparative study of mini chromosome maintenance deficient-5 and urine cytology as urinary biomarkers for the diagnosis of bladder cancer

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ABSTRACT

Background: Bladder cancer is the 9th most common cancer worldwide and the 13th most common cause of death accounting for 145,000 deaths worldwide. In Sokoto, Nigeria, bladder cancer is the most common male cancer and the area is endemic for schistosomal infestation. Mini chromosome maintenance deficient 5 (MCM5) is a potential urinary biomarker for bladder cancer diagnosis, study of this biomarker is essential to compare its effectiveness in diagnosing bladder cancer with voided urine cytology.
Methods: Patients presenting at the urology out-patient clinic of the Usmanu Danfodiyo University Teaching Hospital, Sokoto between February 2,2018 and February 1, 2019 with clinical and radiological suspicion of bladder cancer who met the inclusion criteria and gave informed consent were recruited for the study. Data analysis was done using IBM statistical package for the social sciences (SPSS) version 20.0 computer software package and diagnostic validity indicators of each marker was computed.
Results: A total of 65 patients were recruited into the study with a mean age of 51.9 years and standard deviation of ±14.7. The male to female ratio was 6:1. The commonest histological type of bladder cancer seen was squamous cell carcinoma (70.8%). The biomarker MCM5 was found to be more sensitive in diagnosing squamous cell carcinoma than the other histological types of bladders.
Conclusion: The biomarker MCM5 is more sensitive but less specific than voided urine cytology in the diagnosis of bladder cancer. Also, MCM5 is more sensitive in diagnosing squamous cell carcinoma than other histological types of bladder cancer.

Keywords: Bladder cancer, Voided urine cytology, MCM5, Cystoscopy, Biopsy

INTRODUCTION

The incidence and prevalence of urothelial cancer increase with age, with exposure to environmental toxins as part of the risk factors. Histologically, 90% of bladder cancers are of urothelial origin, 5% are squamous cell carcinoma and less than 2% are adenocarcinoma or other variants.[1] In Sokoto, bladder cancer is the most common male cancer and the incidence is rising.[2,3] Patients come predominantly from rural and agricultural areas of the region known to be endemic for urinary schistosomiasis.[3] The male to female ratio is 11.1:1, this is higher than the reported ratio from other Nigerian centers.[3-6] The mean age was 46 years with a range of 20-82 years.[3] The histological types were mostly

differentiated squamous cell carcinoma which comprised 65.1% of cases and these demonstrated histological evidence of chronic Schistosomiasis in 50% of squamous cell carcinoma variant.[3] Currently, bladder cancer is diagnosed by cytology and cystoscopy with biopsy.[7] Urine cytology has high specificity but low sensitivity, it is cytopathologist dependent and can give false positives in the presence of inflammation. Cystoscopy with biopsy is sensitive and specific for most papillary and solid tumours but it is invasive, uncomfortable, costly and can result in urinary tract infection in up to 5% of cases.[8] Therefore, there is a need for a biomarker for the diagnosis of bladder cancer that is more sensitive than cytology, non-invasive but with similar specificity like cystoscopy and biopsy, and such biomarker can be used for early diagnosis of bladder cancer and surveillance.[9] Intensive research for urinary biomarkers is ongoing with the aim of fulfilling this.

The family of mini chromosome maintenance proteins constitutes a potential new tool in the assessment of bladder cancer cell proliferation rate. They are highly conservative widespread group of proteins with a well-known important role in DNA synthesis with components of the family ranging from 2 to 7. They have been well documented to interact with each other forming heterohexamer complex.[10] Elevated levels of mini chromosome maintenance deficient 5 (MCM5) were highly predictive of bladder cancer with results superior to cytology.[11]

A study of this potential urinary biomarker is thus essential to know it's validity in diagnosing bladder cancer histologically confirmed by cystoscopy and biopsy. It also offers an opportunity to determine the expression of MCM5 by bladder cancer of the squamous cell carcinoma variant which is prevalent in our region as most of the studies previously conducted elsewhere were on transitional cell carcinoma variant of bladder cancer.

Objectives

The objectives of the study were to compare the sensitivity and specificity, negative predictive value (NPV) and positive predictive value (PPV) of MCM5 and voided urine cytology and to determine if the diagnosis of bladder cancer using MCM5 is affected by the histological type of bladder cancer.

METHODS

It was a prospective comparative cross-sectional study carried out at the Urology unit, Department of Surgery, Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria between 02 February 2018 and 01 February 2019. Patients with clinical and radiological features of bladder cancer who met the inclusion criteria and gave informed consent were recruited for the study. A structured proforma was used to collect data on the relevant clinical details from the patients involved in the study including history to identify risks and classical presentation, investigations, MCM5 assay, urine cytology and cystoscopy with biopsy.

Inclusion criteria

Inclusion criteria included clinical and radiological features of bladder cancer (haematuria, necroturia, ultrasound finding of bladder mass).

Exclusion criteria

Exclusion criteria included haematuria from other genito-urinary malignancies– prostate, urethra, ureter, kidney, patients too ill to withstand anaesthesia and patients who refused consent.

Urine cytology and assay for MCM5 were done prior to cystoscopy and biopsy.

Assay for MCM5 was done at the Centre for Advanced Medical Research and Training (CAMRET) of the Usmanu Danfodiyo University (UDU)Sokoto, Nigeria. Urine cytology and histological analysis of the cystoscopy and biopsy samples were done at the Histopathology Department of Usmanu Danfodiyo University Teaching Hospital (UDUTH) Sokoto. Approval to carry out the study was obtained from the Research and Ethics Committee of Usmanu Danfodiyo University Teaching Hospital, Sokoto prior to the commencement of the study. The IBM statistical package for the social sciences (SPSS) version 20.0 (SPSS Inc; Chicago, IL, USA) computer software was used for the data analysis. Frequencies and proportions of socio-demographic variables were reported. Positive and negative predictive values were used to test diagnostic accuracy.[12]

RESULTS

A total number of 65 patients participated in the study. The age range of the patients was 16-80 years with mean age of 51.9 years and standard deviation of 14.7. There were 56 males and 9 females with male to female ratio of 6:1. The commonest occupation of the patients was farming seen in 27 patients (41.5%). Details of the socio-demographic characteristics are shown in Table 1.

Receiver operating characteristics curve for MCM5

The effectiveness of the urinary biomarker MCM5 in diagnosing bladder cancer was assessed using the receiver operating characteristics (ROC) curve, which is a plot of sensitivity against specificity.

The performance of the marker was assessed using it`s area under the curve (AUC). The closer the area under the curve for a biomarker is to 1, the better the diagnostic effectiveness of that biomarker. The AUC for MCM5 was found to be 0.628, which shows that the biomarker is effective in diagnosing bladder cancer.

Using the ROC curve, the optimal cut off value for MCM5 that will give the best sensitivity and specificity was found to be 231.75 pglml (Figure 1).

Table 1: Socio-demographic characteristics of patients.

Variables	Frequency (%), n=65
Mean age±SD	51.86±14.7
Sex	
Male	56(86.2)
Female	9 (13.8)
Marital status	
Single	3 (4.7)
Married	62 (95.3)
Occupation	
Student	2 (3.1)
House wife	7 (10.8)
Farmer	27 (41.5)
Civil servant	11 (16.9)
Business man	16 (24.6)
Fisherman	2 (3.1)

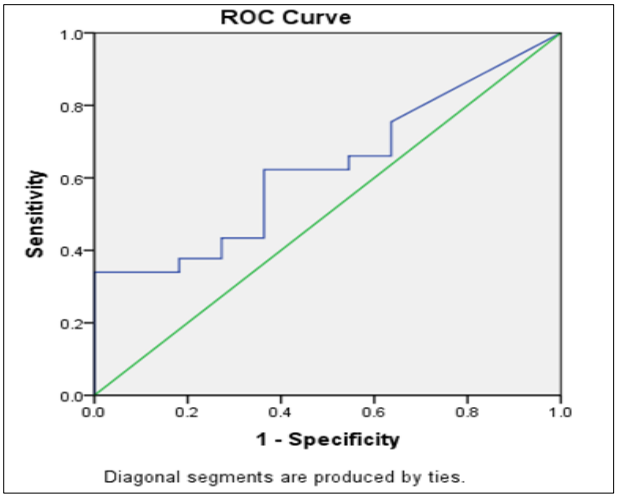

Figure 1: ROC curve for MCM5.

Sensitivity, specificity and predictive values of MCM5 and voided urine cytology

Using the cutoff point value of 231.75 pglml for MCM5, its diagnostic indicators were calculated as follows.

$$Sensitivity\ (true\ positive\ rate)\ (a/a+c\ or\ TP/TP+FN) = 34/34+20 = 0.63\ or\ 63\%$$

$$Specificity\ (true\ negative\ rate)\ (d/d+b\ or\ TN/TN+FP) = 7/7+4 = 0.64\ or\ 64\%$$

$$Positive\ predictive\ value\ (a/a+b\ or\ TP/TP+FP) = 34/34+4 = 0.90\ or\ 90\%$$

$$Negative\ predictive\ value\ (d/d+c\ or\ TN/TN+FN) = 7/7+20 = 0.26\ or\ 26\%$$

The diagnostic indicators for voided urine cytology were calculated as follows.

$$Sensitivity\ (true\ positive\ rate)\ (a/a+c\ or\ TP/TP+FN) = 11/11+43 = 20.3\ or\ 20\%$$

$$Specificity\ (true\ negative\ rate)\ (d/d+b\ or\ TN/TN+FP) = 10/10+1 = 0.91\ or\ 91\%$$

$$Positive\ predictive\ value\ (a/a+b\ or\ TP/TP+FP) = 11/11+1 = 0.92\ or\ 92\%$$

$$Negative\ predictive\ value\ (d/d+c\ or\ TN/TN+FN) = 10/10+43 = 0.19\ or\ 19\%$$

These findings were summarized in Table 2.

Comparison of the concentration of MCM5 with the Gleason's grade and stage of bladder cancer

The highest concentration of the marker was found at the advanced stage of bladder cancer (stage 4) while for the grade of bladder cancer, the highest concentration was found at grade 2.

Comparison of the histopathological types of bladder cancer with the concentration of MCM5

The highest concentration of the marker was seen at the squamous cell carcinoma histological type of bladder cancer. Also, 67% of patients histologically diagnosed with squamous cell carcinoma were positive for bladder cancer using MCM5 test, this was followed by adenocarcinoma which was 50% and lastly transitional cell carcinoma which was 33%. Details of these are seen in Tables 3 and 4.

Table 2: Comparison of sensitivity, specificity, positive and negative predictive values of MCM5 and voided urine cytology.

Variable	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
MCM5	63	64	90	26
Voided urine cytology	20	91	92	19

Table 3: Comparison of the histopathological types of bladder cancer with MCM5 concentration.

MCM5 (pglml)	Transitional cell carcinoma	Squamous cell carcinoma	Adenocarcinoma	Total
0-181.90	4	15	1	20
273.60-565.30	0	11	0	11
575.90-1109.00	1	10	1	12
1133.60-1219.00	1	3	0	4
1231.60-3585.30	0	7	0	7
Total	6	46	2	54

Table 4: Sensitivity of MCM5 in diagnosing the various histological types of bladder cancer.

Histological type of bladder cancer	Number of diagnosed cases	Percentage of patients diagnosed with bladder cancer using MCM5 (%)
Squamous cell carcinoma	46	67
Adenocarcinoma	2	50
Transitional cell carcinoma	6	33

DISCUSSION

The mean age of the patients in the study is similar to the mean age of patients in studies done at schistosomiasis endemic areas of Sokoto and Plateau states.[3,5] The earlier age of onset of bladder cancer noticed in these patients when compared with the global mean age of onset of bladder cancer was due to childhood exposure to schistosomiasis. The late onset of bladder cancer globally may be attributed to occupational exposure to aromatic hydrocarbons and cigarette smoking, as these risk factors occur in adults.

The male to female ratio in this study was lower that the ratio reported in the study done in this environment where they reported 11.1:1.[3] This however was higher than the ratio reported in some Nigerian centers (2.5:1) as well as the worldwide reported ratio of 4:1.[5,13] The higher prevalence in males was due to their increased involvement in farming which was reported as the commonest occupation from a study done in this environment.[3]

The commonest occupation of the patients was farming which is in keeping with the study done in this environment.[3] This was believed to be due to the fact that these rural farming communities' dwell at riverside areas so are more predisposed to schistosomal infestation and re-infestation even when treated, this thus may progress to bladder cancer which is one of the complications of schistosomiasis.

The optimal cut off value for urine MCM5 using the ROC curve was used to calculate its diagnostic indicators. Thus, using this, the sensitivity and specificity of MCM5 are lower than the result gotten by Stoeber and colleagues where the sensitivity and specificity of MCM5 were 87% respectively.[14] However this is similar to the sensitivity result gotten by Burling et al that reported MCM5 sensitivity of 69%.[15] Another study revealed sensitivity and specificity of 83% and 77% respectively for MCM5 which are both higher than the results of the current study.[16]

The sensitivity of MCM5 is higher than the sensitivity of voided urine cytology from this study while the specificity of MCM5 is lower than the specificity of voided urine cytology from this study. This shows that in the diagnosis of bladder cancer, MCM5 is more sensitive than voided urine cytology while voided urine cytology is more specific than MCM5.These findings are similar to findings of other studies done that also compared urinary biomarkers with voided urine cytology in the diagnosis of bladder cancer.[9,17-20] This is however different from the result of the study done in this environment on urinary survivin where the sensitivity of urinary survivin and urine cytology were 100% and 29.1% respectively while the specificity of urinary survivin and urine cytology were both 100% respectively.[21]

The positive predictive value of MCM5 is slightly lower than that of voided urine cytology from this study while the negative predictive value of MCM5 is higher than that of voided urine cytology. This shows that voided urine cytology has a better positive predictive value than MCM5 while MCM5 has a better negative predictive value than voided urine cytology. The negative predictive value of MCM5, although higher than the negative predictive value of voided urine cytology is lower than that of previous studies done on the biomarker.[15,16] This may be due to the small sample size of the current study. A similar study done in this environment on urinary survivin revealed the positive predictive values of urinary surviving and cytology as 80.2% and 96.2% respectively while their negative predictive values were 80% and 25.6% respectively.[21]

The highest concentration of the biomarkers was seen at the advanced stage of bladder cancer (stage 4) while the highest concentration was found at Gleason`s grade 2. This

positive correlation between the concentration of MCM5 and the stage of bladder cancer is in keeping with previous studies on urinary biomarkers for the diagnosis of bladder cancer.[22] This thus reveals that the higher the stage of the bladder cancer, the higher the concentration of MCM5 and thus the higher the sensitivity of this biomarker in diagnosing bladder cancer. The inverse relationship between the concentration of MCM5 and grade of bladder cancer is contrary with the finding from previous studies.[9,22] This may be due to inter-observer variation as noted by international society of urological pathology, so most of the G2 tumours may actually be G3 tumours.[23]

On comparing the concentration of MCM5 with the histological types of bladder cancer, it was found that the highest concentration of MCM5 was seen in the squamous cell histological type of bladder cancer which was the prevalent histological type of bladder cancer from this study. This thus reveals that MCM5 is more sensitive in diagnosing the squamous cell carcinoma histological type of bladder cancer than the other histological types of bladder cancer. Also, 67% of patients histologically diagnosed with squamous cell carcinoma were positive for bladder cancer using MCM5 test. For adenocarcinoma and transitional cell carcinoma histological subtypes, 50% and 33% of patients diagnosed with these histological subtypes respectively were positive for bladder cancer using MCM5 test.

Therefore, this also buttresses the fact that from this study, MCM5 is more sensitive in diagnosing squamous cell histological type of bladder cancer than the other histological subtypes. This biomarker thus will be useful in our environment as the predominant histological subtype of bladder cancer in our environment is squamous cell carcinoma.

Limitations

The study is limited by small sample size done over a short duration of time and in a single center. There is need for large and long-term multi-centre randomized control trials in our environment to determine clearly the effectiveness of MCM5 as a urinary biomarker in early diagnosis of bladder cancer.

CONCLUSION

The urinary biomarker MCM5 is more sensitive but less specific than voided urine cytology in the diagnosis of bladder cancer. The urinary biomarker MCM5 is more sensitive in diagnosing squamous cell histological subtype of bladder cancer than the other histological subtypes.

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