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Original Article

Rare tumours of the bladder: A Saudi registry based descriptive study

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الملخص

أهداف البحث: كان هناك نقص في الأدبيات التي تركز على خصائص وسلوكيات أورام المثانة خارج الأشكال الثلاثة الشائعة، مثل سرطان الظهارة البولية وسرطان الخلايا الحرشفية والسرطان الغدي. تقدم الدراسة المقدمة تحليلا وصفيًا لأورام المثانة النادرة في المملكة العربية السعودية.

طرق البحث: شملت هذه الدراسة الأترابية الاستعادية جميع المرضى الذين يعانون من ورم المثانة الأولي النادر من 1 يناير 2008 إلى 31 ديسمبر 2017. تم الحصول على البيانات من سجل الأورام السعودي. تم إنشاء الترددات والنسب المئوية للمتغيرات الفئوية. تم حساب الوسائل والانحرافات المعيارية للمتغيرات الكمية.

النتائج: تم تحديد 65 مريضا. الغالبية [35 مريض، 53.8٪] كانت أعمارهم 60 سنة فما فوق. الغالبية من الذكور [53 مريض، 81.5٪]. الغالبية تعيش في المنطقة الغربية [26 مريض، 40٪]. أكثر أشكال الورم التي تم تشخيصها كانت سرطان الخلايا الصغيرة لدى البالغين [11 مريض، 16.92٪] والساركوما العضلية المخططة الجنينية عند الأطفال [14 مريض، 21.5٪] وكانت طريقة التشخيص السائدة هي أنسجة الورم الأولي في 98.5٪. كانت معظم الأورام موضعية [30 مريض، 46.2٪] ومتعددة البؤر [34 مريض، 52.3٪]. كان معدل الوفيات الإجمالي 24.6٪ مع تشخيص شامل لفترة الوفاة 1.14 + 0.75 سنة ومع سرطان الخلايا الصغيرة هو الأقصر [0.84 + 0.24].

الاستنتاجات: لا تزال هناك فجوة في الأدبيات المتعلقة بأورام المسالك البولية غير الشائعة. إن إلقاء الضوء عليها سيساعد في زيادة فهم أنماط سلوك هذه الأورام في المنطقة. سيسمح هذا بتحسين استراتيجيات الفحص القائم على المخاطر والاستجابة وتحقيق نتائج أكثر ملاءمة. ينصح أيضا بصياغة سجل عالمي لمثل هؤلاء المرضى.

الكلمات المفتاحية: أورام المثانة؛ أورام نادرة؛ أورام المسالك البولية؛ سجلات الأورام؛ المملكة العربية السعودية

Abstract

Objective: There is limited literature focusing on the characteristics and behaviours of bladder tumours outside of the common three morphologies, that is, urothelial carcinoma, squamous cell carcinoma, and adenocarcinoma. The presented study provides a descriptive analysis of rare bladder tumours in KSA.

Methods: This retrospective cohort study included all patients with a primary rare bladder tumour between 1 January 2008 and 31 December 2017. The data were acquired from the Saudi Tumour Registry. Frequencies and percentages were then generated for the categorical variables, while means and standard deviations were calculated for quantitative variables.

Results: The study included 65 patients. The majority (n = 35, 53.8%) were aged 60 years and older. The patients were predominantly male (n = 53, 81.5%) and the majority lived in the Western region (n = 26, 40.?%). The most diagnosed tumour morphologies were small cell carcinoma in adults (n = 11, 16.9%) and embryonal rhabdomyosarcoma in children (n = 14, 21.5%), with the dominant diagnosis method being histology of primary tumour in 98.5% of the patients. Most tumours were localised (n = 30, 46.2%) and multifocal (n = 34, 52.3%). The overall mortality rate was 24.6%, with an overall diagnosis to death interval of 1.14 ± 0.75 years wherein small cell carcinoma was the shortest (0.84 ± 0.24) days.

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Conclusion: There remains a gap in the literature regarding uncommon urologic tumours. Shedding light on these factors will aid in further understanding the patterns of tumour behaviour in the region. This will facilitate enhanced risk-and response-based screening strategies and more favourable outcomes. Additionally, formulating a global registry for such patients is recommended.

Keywords: Bladder tumours; KSA; Rare tumours; Tumour registries; Uro-oncology

Introduction

Each year, more than 18 million new cases of cancer are diagnosed worldwide.[1] Bladder cancer is one of the leading cancers in prevalence and has been increasing since the last decade.[1] The Global Cancer Observatory ranks bladder cancers as the 11th leading cancer based on the number of new cases in KSA.[1] Bladder cancers as an entity represent a spectrum of diseases.[2] Approximately 70% of organ-confined bladder cancers are non-muscle-invasive bladder cancer (NMIBC), while the remaining are muscle-invasive bladder cancers.[2] Bladder cancer can either be a low-grade tumour with a low progression rate requiring minimal treatment and surveillance or a high-grade tumour, progressing quickly, leading to significant mortality and morbidity.[2,3]

Bladder cancer has multiple identified reversible and irreversible risk factors. Cigarette smoking is the most established risk factor for bladder cancer.[2] Smoking increases the risk of developing bladder cancer by up to four times.[2] Although smoking is a well-established risk factor, other factors play a major role too. Occupational hazards account for approximately 20% of those factors.[2,4] Occupations, such as aluminium production, rubber industry, and certain chemical-related jobs have been identified to impose a greater risk for bladder cancer.[2,4] Males have a three to four times higher risk of developing bladder cancer, while females have a higher risk of developing more advanced stage of disease.[2,4,5]

Bladder cancer is mostly classified based on histology. More than 80% of bladder cancers are caused by urothelial cancers.[6] The remaining 20% are caused by non-urothelial cancer, also called 'variant histology'.[6] This variant histology bladder cancer tends to behave more aggressively, has worse clinical outcomes, and is diagnostically challenging.[6,7] The most common subtypes of non-urothelial carcinoma of the bladder include squamous cell carcinoma and adenocarcinoma.[7,8] Another infrequent type is small cell carcinoma, which has a poor prognosis due to advanced local disease and distant metastasis.[8,9] Embryonal rhabdomyosarcoma is a subtype of bladder cancer that is generally present in children and rarely in adults.[10,11] It is managed aggressively, similar to other rare bladder tumours and tends to have a less favourable prognosis in children.[10,11]

In the global literature, there have been limited studies to improve the clinical outcomes of bladder tumours outside of the more common three morphologies, that is, urothelial carcinoma, squamous cell carcinoma, and adenocarcinoma. This may be attributed to the rarity of other malignancies. The presented study aims to provide a descriptive analysis of rare bladder tumours in the KSA.

Materials and Methods

This retrospective cohort study included patients diagnosed with primary bladder adenosquamous carcinoma, carcinosarcoma, clear cell adenocarcinoma, embryonal rhabdomyosarcoma, epithelioid leiomyosarcoma, epithelioid sarcoma, granular cell carcinoma, hemangioendothelioma, hemangiosarcoma, leiomyosarcoma, malignant rhabdoid tumour, neuroendocrine carcinoma, paraganglioma, primitive neuroectodermal tumour, signet ring cell carcinoma, small cell carcinoma, or undifferentiated sarcoma, between 1 January 2008 and 31 December 2017. Patients diagnosed with metastatic bladder tumours were excluded from the study. The data were collected from the Saudi Cancer Registry (SCR), which collects tumour data from all private, military, and Health Ministry hospitals in KSA through five regional offices. The variables were grouped according to the year of diagnosis, gender, age, marital status, region, nationality, tumour's site of origin, tumour histological subtype, tumour behaviour, tumour grade, tumour extent, tumour laterality, basis of the diagnosis, and survival. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corporation, NY, USA). Frequency and percentage were used to display the categorical variables, and mean and standard deviation for the continuous variables.

Results

A total of 65 patients were included in the study. Table 1 shows the socio−demographic profiles of the patients. The majority (n = 35, 53.8%) were aged 60 years and older. The mean age of the patients was 50.5 ± 27.7 years. Regarding gender, the population was predominantly male (n = 53, 81.5%). Considering nationality, 52 patients (80.?%) were Saudi, and 13 patients (20.?%) were non-Saudi. Regarding marital status, 15 patients (23.1%) were single, 64.6 patients (42%) were married, one patient (1.50%) was divorced, and 7 patients (10.8%) did not have a documented marital status. For the place of residency, 15 patients (23.1%) lived in the Central region, 11 patients (16.9%) in the Eastern region, 4 patients (6.20%) in the Northern region, 26 (40.0%) in the Western region, and 9 patients (13.8%) lived in the Southern region.

The tumour profiles of the patients are shown in Table 2. It shows the location of the tumour wherein one patient (1.50%) was in the trigone of the urinary bladder, one patient (1.50%) in the dome of the urinary bladder, 6 patients (9.20%) in the lateral wall of the urinary bladder, two patients (3.10%) in the anterior wall of the urinary bladder, two patient (3.10%) in the posterior wall of the urinary bladder, and 53 (81.5%)

Table 1: Socio-demographic profile of the patients (n = 65).

Demographical Characteristics	n	%
Age groups		
18 years and younger	15	23.10
19–39 years	3	4.60
40–59 years	12	18.50
60 years and older	35	53.80
Gender		
Male	53	81.50
Female	12	18.50
Nationality		
Saudi	52	80.00
Non-Saudi	13	20.00
Marital status		
Single	15	23.10
Married	42	64.60
Widowed	1	1.50
Unknown	7	10.80
Place of residency		
Central region	15	23.10
Eastern region	11	16.90
Northern region	4	6.20
Western region	26	40.00
Southern region	9	13.80
Age		
Mean	50.49	
Standard deviation	27.74	

Table 2: Tumor profile.

	n	%
Location		
Trigone of urinary bladder	1	1.5
Dome of urinary bladder	1	1.5
Lateral wall of urinary bladder	6	9.2
Anterior wall of urinary bladder	2	3.1
Posterior wall of urinary bladder	2	3.1
Multifocal	53	81.5
Grade		
Grade I (Well differentiated)	4	6.2
Grade II (Mod differentiated)	4	6.2
Grade III (Poor differentiated)	16	24.6
Grade IV (Undifferentiated anaplastic)	7	10.8
Unknown	34	52.3
TNM		
Extension		
Localized	30	46.2
Regional: Direct extension	12	18.5
Regional: Lymph node	1	1.5
Regional: Lymph node and direct extension	3	4.6
Distant metastasis	14	21.5
Unknown	5	7.7
Lateralization		
Not paired	65	100
Base of diagnosis		
Histology of metastases	1	1.5
Histology of primary tumor	64	98.5
Year of diagnosis		
2008	6	9.20
2009	1	1.50
2010	11	16.90
2011	1	1.50
2012	8	12.30
2013	7	10.80
2014	7	10.80
2015	8	12.30
2016	7	10.80
2017	9	13.80

were multifocal tumours. Regarding the grades of tumours, 4 patients (6.20%) had grade I tumours (well-differentiated), 4 patients (6.20%) had grade II tumours (moderately differentiated), 16 patients (24.6%) had grade III tumours (poorly differentiated), 7 patients (10.8%) had grade IV tumours (undifferentiated anaplastic), while 34 patients (52.3%) did not have a documented grade of the tumour. Regarding the extension of the tumour, 60 patients (46.2%) had a localised tumour, 12 patients (18.5%) had a tumour with regional direct extension, one patient (1.50%) with regional lymph node extension, three patients (4.60%) with regional lymph node and direct extension, 14 patients (21.5%) had a tumour with distant metastasis, and 5 patients (7.70%) had no documentation of the extension. Furthermore, the most common method used for the base of diagnosis was histology of the primary tumour in 64 patients (98.5%). For the year of incidence, 6 patients (9.20%) were diagnosed in 2008, one patient (1.50%) in 2009, 11 patients (16.9%) in 2010, one patient (1.50%) in 2011, 8 patients (12.3%) in 2012, 7 patients (10.8%) in 2013, 7 patients (10.8%) in 2014, 8 patients (12.3%) in 2015, 7 patients (10.8%) in 2016, and 9 patients (13.8%) were diagnosed in 2017.

Table 3 displays the various tumour morphologies. Among those younger than 18 years, 14 (21.5%) had embryonal rhabdomyosarcoma, while one patient (1.50%) had a malignant rhabdoid tumour. For those aged 18 years and older, two patients (3.10%) patients had adenosquamous carcinoma, 5 patients (7.70%) had carcinosarcoma, 4 patients (6.20%) had clear cell adenocarcinoma, one patient (1.50%) had epithelioid leiomyosarcoma, one patient (1.50%) had epithelioid sarcoma, one patient (1.50%) had granular cell carcinoma, three patients (4.60%) had malignant hemangioendothelioma, two patients (3.10%) had hemangiosarcoma, two patients (3.10%) had leiomyosarcoma, 6 patients (9.20%) had neuroendocrine carcinoma, two patients (3.10%) had malignant paraganglioma, one patient (1.50%) had primitive neuroectodermal tumour, 8 patients (12.3%) had signet ring cell carcinoma, 11 patients (16.9%) had small cell carcinoma, and one patient (1.50%) had undifferentiated sarcoma.

Regarding patients' last contact status, 49 patients (75.4%) were alive, while 16 patients (24.6%) died. All the deceased patients had cancer as the cause of death. Among the participating patients who died from cancer, the overall mean of the interval from diagnosis to death was 1.14 ± 0.75 years. The mean interval for each subtype was 1.08 ± 0.69 years for carcinosarcoma, 1.43 ± 0.62 years for signet ring cell carcinoma, and 0.84 ± 0.24 years for small cell carcinoma. The interval for other subtypes could not be calculated due to insufficient mortality numbers.

Discussion

This study suggests that both age and gender can predict the presence of rare bladder tumours, as 58.?% of the patients included in this study were over the age of 60 years, while

Table 3: Morphology of tumors.

	n	%
For those Younger 18 years old		
Morphology		
Embryonal rhabdomyosarcoma	14	21.54
Malignant rhabdoid tumor	1	1.54
For those 18 years and older		
Morphology		
Adenosquamous carcinoma	2	3.08
Carcinosarcoma	5	7.69
Clear cell adenocarcinoma	4	6.15
Epithelioid leiomyosarcoma	1	1.54
Epithelioid sarcoma	1	1.54
Granular cell carcinoma	1	1.54
Malignant hemangioendothelioma	3	4.62
Hemangiosarcoma	2	3.08
Leiomyosarcoma	2	3.08
Neuroendocrine carcinoma	6	9.23
Malignant paraganglioma	2	3.08
Primitive neuroectodermal tumor	1	1.54
Signet ring cell carcinoma	8	12.31
Small cell carcinoma	11	16.92
Undifferentiated sarcoma	1	1.54

male patients accounted for 81.5% of the cohort. Most patients identified were Saudi nationals (80.0%), single (42.0%), and resided in the western region (40.0%). Moreover, the tumour profile of each patient varied considerably, where 81.5% had multifocal tumours while 52.3% did not have a documented tumour grade. Regarding the extension of the tumour, a significant proportion of patients (46.2%) had a localised tumour. The most prevalent method of diagnosis was histology of the primary tumour, which was utilised in 98.5% of patients. Further, the tumour morphologies varied widely, with the most common presentations being embryonal rhabdomyosarcoma (21.5%), small cell carcinoma (16.9%), and signet ring cell carcinoma (12.3%). Almost a quarter of the patients (24.6%) included in this study died because of their cancer, while the mean interval from diagnosis to death in these patients was 1.14 years.

The male majority apparent in our study is reflected in the current literature, with a systematic review by Ismaili et al. reporting on the incidence of small cell carcinoma. This rare bladder malignancy has a mean sex ratio of 5:1, ranging from 1:1 to 16:1 in the studies discussed in this review.[9] However, a study by Fang et al. contradicts gender as a risk factor for rare bladder tumours, with the patient demographics in this study indicating a 3:1 female-to-male incidence of pan-urothelial cell carcinoma.[12] Despite this contradiction, their study supports our findings that the prevalence of rare tumours of the bladder is enhanced in those over 60 years of age, with Fang et al. reporting a mean age of 64.5 years in a cohort of 45 patients.[12]

However, it has been suggested that age is significantly related to the histological subtype of rhabdomyosarcoma. Gaal et al. assessed the impact of age on the outcome of both embryonal and alveolar rhabdomyosarcoma patients in a multicentre study, and the data indicated that patients over 16-years had a higher rate of alveolar subtypes and tumours arising at unfavourable sites. Moreover, the incidence of lymph node involvement, rate of distant metastasis, and incidence of relapse were all significantly higher in those over the age of 16 years compared to the patients under 16 years.[13] Although not directly corroborating our findings—suggesting that the elderly population is at a greater risk of developing rare bladder tumours—their study provides evidence that children and adolescents have a greater possibility of complete remission.

A study by Shaaban et al. had similar purpose as this study and assessed the incidence of squamous cell carcinoma of the urinary bladder in patients treated at the Riyadh Armed Forces Hospital between 1979 and 1995. Several similar results about patient demographics were noted. First, among the patients under study, the proportion of Saudi nationals diagnosed with transitional cell carcinoma was 71%, while 68% had squamous cell carcinoma. Moreover, the male-to-female ratio was 8:1 for transitional cell carcinoma patients and 4.2:1 for those with squamous cell carcinoma.[14] These findings align with those of our study.

Detecting bladder cancer encompasses several diagnostic measures, including cytology and morphology-based assays, in addition to biochemical and molecular markers. Cystoscopy is widely accepted as the gold standard for the detection of bladder tumours; however, several studies have highlighted the importance of histology in diagnosis, as numerous tumour types reflect a characteristic histological appearance.[15,16] Hence, histology, as the most prevalently employed method in the diagnosis of bladder cancer utilised in our cohort, was validated by the evidence presented in the literature.

Concerning tumour characteristics, the current literature corroborates the high incidence of patients with multifocal tumours, and several studies have also suggested that this multifocality is a determinant of disease prognosis. Wu et al. evaluated this hypothesis in a meta-analysis of patients with upper tract urothelial carcinoma. The findings provided evidence that both ureteral and multifocal tumours can be defined as independent prognosticators of disease progression and cancer-specific survival of patients with upper tract urothelial carcinoma.[17] This reduced survival of patients with multifocal tumours, provides a rationale for the high mortality rate (24.6%) among patients included in this study. The current literature also suggests other poor prognostic factors for this disease, including lymph vascular invasion, recurrence, large tumour size, presence of urothelial carcinoma in situ, and multicentricity.[18]

There were some limitations to this study. First, because it was retrospective, the research team members had to rely on other individuals for accurate and safe record keeping. Second, the issue of underreporting might be present, which may reduce the validity of our findings and the literature and is generally defined as a source of systematic error in cancer research. Third, the diagnosis to death interval could not be calculated for all morphologies due to an insufficient number of mortalities among them.

Conclusion

Formulating a global registry for such patients is advised to facilitate extensive investigations to improve our knowledge about the diagnosis and treatment of such rare entities. Additionally, future studies should focus on biomarker

findings with translational and clinical implications. Similar to the available literature, the tumours discussed in the study have been associated with a poor outcome and a short diagnosis to death interval, possibly due to the lack of investigations providing a level one evidence for management methods. There remains a gap in the literature regarding uncommon urologic tumours. Shedding light on them will aid in a better understanding of the patterns of tumour behaviour in the region. This will allow for enhanced risk-and response-based screening strategies and more favourable outcomes.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

The study was approved by the Institutional Review Board of King Abdullah International Medical Research Center, Ministry of National Guard Health Affairs, Riyadh, KSA (approval number NRC21R/085/03) on March 23rd, 2021. Patient confidentiality was ensured, and the patients' data were collected and used by the research team only. Serial numbers were used instead of medical record numbers to ensure anonymity. Due to the retrospective nature of the study and the use of anonymised patient data, the requirement for informed consent was waived.

Authors contributions

MAQ, MAG, ZFM, SMW, and AA formulated the idea, designed methods, validated the study, and provided research materials. MAQ, ZFM, and AA curated and analysed the data, interpreted, and presented the results. MAG and SMW wrote the original draft of the manuscript. AA critically revised the original draft for important intellectual content, supervised, and administered the project. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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