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Bladder cancer: Analysis of the 2004 WHO classification in conjunction with pathological and geographic variables

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KEYWORDS

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Abstract

Objectives: Bladder cancer (BCA) is a worldwide disease and shows a wide range of geographical variation. The aim of this study is to analyze the prevalence of schistosomal and non-schistosomal associated BCA as well as compare our findings with the 2004 WHO consensus classification of urothelial neoplasms and with other publications.

Patients and methods: The archival materials of 180 urinary bladder specimens were collected from Department of Pathology, King Abdul-Aziz University Hospital (KAUH), Jeddah, Western region, Saudi Arabia. The regional prevalence of this cancer was identified and studied, and a comparison between schistosomal and non-schistosomal associated BCA was made. Additionally, the study revised and classified these neoplasms according to the most recent 2004 WHO classification of urothelial neoplasms. The type of mural invasion either muscularis mucosae (MM) or muscularis propria (MP), other associated lesions as carcinoma in situ (CIS) as well as, metaplasia and schistosomal infestation were assessed.

Results: Urothelial cell neoplasms (UCN) comprised 161 cases (89.4%), squamous cell carcinoma (SCC) represented 12 cases (6.7%), adenocarcinoma 5 cases (2.8%), and sarcomatoid carcinoma detected in 2 cases (1.1%). Among all these cases schistosomal associated BCA represented 13 cases (7.2%), while the remaining 167 cases (92.8%) were non-schistosomal associated BCA. In the former category, 11 cases (6.1%) were squamous cell carcinoma and 2 (1.1%) urothelial cell carcinoma (UCC) whereas,

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non-schistosomal associated cancer that included UCN, SCC, adenocarcinoma, and sarcomatoid carcinoma found in 159, one case, 5, and 2 cases. Invasion of muscularis propria was detected in 30 cases (16.7%) and muscularis mucosae invasion in 45 cases (25%).

Conclusion: According to WHO classification of urothelial neoplasms accurate categorization of BCA is very important for both diagnostic and therapeutic values.

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Introduction

An estimated 68,810 new cases of BCA were diagnosed in the United States in the year 2008 and 14,100 deaths from it were estimated for the same year [1]. This tumor affects one in 4000 people and accounts 5% of all diagnosed cancers in human [2]. The incidence of this cancer varies worldwide that is highest in North America and Europe [3]. In spite of earlier diagnosis and better care, the incidence is still rising [4,5]. Due to its prevalence, morbidity and mortality previous studies investigated the strong association between schistosomiasis and smoking in the development of BCA [6–13].

Additionally workers in automobile industry, leather and apparel and petrochemical industries are associating with increased risk of BCA [14–17]. The manifestations of BCA are in the form of hematuria, irritative symptoms, constipation, fecal incontinence, back pain, and renal failure [18,19]. Schistosomal-associated BCA has distinctive clinicopathological features quite different from other regions worldwide. This tumor affects patients at a much younger age with male predilection [20–23]. In Egyptian patients SCC is the most common histological type and representing 76.6%. Since, it arises on top of squamous metaplasia which resulting from chronic bilharzial cystitis [21]. Previous studies were mentioned in spite that squamous cell carcinoma is the commonest histological type of BCA its percentage is in decline as with the strategy toward eradication of schistosomiasis [24,25]. Associated with these studies and others, the pattern of histopathology of BCA showed marked change, where SCC constituted less than 60% [26–28]. In Egyptian patients BCA ranks first in males representing 16.2% of male cancer [25,29]. Whereas, in Saudi patients and according to the tumor registry, BCA ranks the 10th among males and the 20th among females. The majority of this malignancy is conventional urothelial cell carcinoma [30].

Histologically BCA is including conventional UCC, squamous cell carcinoma, adenocarcinoma and small cell carcinoma. Urothelial cell carcinoma may be further subdivided into an additional 14 separate subtypes [31,32]. The World Health Organization/International Society of Urological Pathology (WHO/ISUP) described in the classification of urinary bladder tumors; mesenchymal neoplasms, lymphomas, and germ cell neoplasms [33]. As well as, 2004 WHO categorized non-invasive urothelial neoplasms into papillary urothelial neoplasm of low malignant potential (PUNLMP), low and high grades papillary urothelial carcinoma (PUC), and papilloma [34]. The diagnosis of UCC is compounded by the need for accurate pathologic staging. The identification of muscularis propria invasion is the most critical challenges in this theme [35–37]. Accurate recognition of muscularis propria invasion is crucial as it is the critical crossroad between conservative and aggressive management of these patients [38]. This pattern of invasion is sometimes difficult

and challenging particularly when inconsistent layers of muscularis mucosae were seen as hyperplastic bundles of muscles and mimicking the muscles of muscularis propria. In this condition the tumor staging may be difficult particularly in unoriented specimens as cystoscopic biopsies or transurethral resection specimens [39–41].

Subjects and methods

Setting and specimens

The material of the present study included 180 cases of urinary bladder specimens. These cases were seen and collected from the Department of Pathology, KAAUH, Jeddah, through the period, January 1995–April 2008.

The clinical data included the age, gender, clinical presentation, cystoscopic and radiological findings obtained from the patients files. All the patients were seen and examined clinically in the urology outpatient clinics, KAAUH.

Histopathological examination and interpretation

All the specimens received were fixed in 10% neutral buffered formalin solution. According to the type of the received material, TURB were weighed and measured, respectively, and then totally submitted. All the fragments of endoscopic biopsies were processed in many cassettes. The radical cystectomy specimens were weighed, inked, measured and processed in different cassettes. Five micron sections were taken and stained by hematoxylin and eosin (H&E). Then all the stained slides examined by two consultant pathologists for the evidence of BCA. Afterward the detected BCA in our study categorized according to the 2004 WHO consensus classification for urothelial neoplasms [34] (Table 1).

Table 1 Categorization of urothelial neoplasms according to the 2004 WHO classification.

PUNLMP	Low rate of recurrence ^a , low rate of grade and stage progression ^b
PUC, LG	Higher recurrence rate than PUNLMP ^a , stage as PUNLMP, grade lower than PUC, HG
PUC, HG	Have a significant risk of recurrence and progression ^a

PUNLMP: papillary urothelial neoplasm of low malignant potential; PUC, LG: papillary urothelial carcinoma, low grade; PUC, HG: papillary urothelial carcinoma, high grade.

Refs. [42,44].

^a Ref. [43].

^b Ref. [45].

As well as, all the cases were examined for mural invasion and for any calcified schistosomal ova. The specimens were investigated for other associated bladder lesions as such carcinoma in situ and metaplastic lesions.

Statistical analysis

The statistical analysis was performed using SPSS computer software (SPSS version 16 Microsoft windows). Z test was used for the comparison between two proportions. Results were considered to be statistically significant at $p < 0.05$.

Results

Clinical findings of all cases studied

The age of our patients ranged from 26 to 86 years with a mean of 55.3 years and regarding gender, there were 150 cases (83.3%) males and 30 cases (16.7%) females. All patients came to the urologic outpatient clinics at KAUH. The majority of them were complained of lower urinary tract symptoms that ranged from burning micturition to gross hematuria. After detailed clinical examination, the included cases were diagnosed as query BCA. Then all cases were investigated radiographically (plain X-ray, intravenous excretory urography and abdominal ultrasound), and laboratory investigations for clinical fitness aiming to suitable surgical procedures were performed. Afterward these cases underwent endoscopic examination where biopsies were taken.

Histopathological findings of all cases studied

The received specimens formed of 15 cases (8.3%) radical cystectomies, 20 cases (11.1%) TURB and the remaining 145 cases (80.6%) were cystoscopic biopsies. In this study the majority of the cases were urothelial neoplasms, which represented 161 (89.4%) whereas, the non-urothelial neoplasms which including squamous cell carcinoma, adenocarcinoma and sarcomatoid carcinoma were seen in 19 cases (10.6%) with P value < 0.001 that was highly significant. Among urothelial neoplasms, 15 cases (8.3%) were papillary urothelial neoplasm of low malignant potential (PUNLMP), low grade papillary urothelial carcinoma encompassed 95 cases (52.8%), and the high grade one was represented 51 cases (28.3%). In the same way, the first two types of non-urothelial neoplasms were included 12 cases (6.7%) squamous cell carcinoma and 5 (2.8%) cases adenocarcinoma. The relationship between these two variants was insignificant with P value 0.09. The third variant of non-urothelial neoplasms was sarcomatoid carcinoma that included 2 cases (1.1%) (Table 2).

Table 3 The comparison between papillary urothelial cell neoplasm and squamous cell carcinoma in all cases studied.

PUC	SCC	Total
146 (81.1%)	12 (6.7%)	180

PUC: papillary urothelial cell carcinoma; SCC: squamous cell carcinoma.

Regarding, the comparison between the main two histopathological types of BCA in this study that were papillary urothelial carcinoma and squamous cell carcinoma. The former was the most predominant that was followed by the later one which represented a lower prevalence. The relationship between them was significant with P value < 0.001 (Table 3). In the same theme, adenocarcinoma and sarcomatoid carcinoma were uncommon tumors affecting the urinary bladder among these patients.

Thirteen (7.2%) out of 180 cases showed calcified bilharzial ova in the tumor tissue. Among them 11 cases (6.1%) were squamous cell carcinoma, while the remaining 2 (1.1%) were papillary urothelial carcinoma. In the opposite direction, the remaining 167 cases (92.8%) were free from schistosomal ova. So, in this region schistosomal associated BCA showed a minor prevalence in comparison to non-schistosomal associated cancer. The relationship between these two groups of urinary bladder cancers was highly significant with P value < 0.001 . This finding may explain that there are other risk factors may be linked to the pathogenesis of BCA while, schistosomiasis implicated in a minor degree in the occurrence of this tumor among this location (Table 4).

Regarding malignant invasion 30 (16.7%) out of 180 cases revealed muscularis propria invasion and 45 cases (25%) had infiltration within the muscularis mucosae. in the opposite way, the remaining 105 cases (58.3%) were free from tumor invasion. The relationship between invasive and non-invasive types of BCA was significant with P value is 0.01. Surprisingly, all the cases of squamous cell carcinoma regarding its differentiation showed invasion in either muscularis propria or muscularis mucosae. Additionally 10 out of 180 cases (5.6%) were associated with carcinoma in situ, while the remaining 170 cases (94.4%) were free. The relationship between these two categories of BCA that included carcinoma in situ and the free one was highly significant with P value < 0.001 . For metaplastic changes 10 out of 180 cases (5.6%) showed squamous metaplasia, while 6 (3.3%) revealed glandular metaplasia of the covering urothelium (Table 5).

Table 2 Histological classification of BCA in all cases studied.

Histological categories						Total
Urothelial cell neoplasms			Non-urothelial cell neoplasms			
PUNLMP	PUC		SCC	Adeno.	S Ca	
	LG	HG				
15	95	51	12	5	2	180

PUNLMP: papillary urothelial neoplasm of low malignant potential; PUC, LG: papillary urothelial carcinoma, low grade; PUC, HG: papillary urothelial carcinoma, high grade; SCC: squamous cell carcinoma; Adeno.: adenocarcinoma; S Ca: sarcomatoid carcinoma.

Table 4 Relationship between schistosomiasis and BCA in all cases studied.

Bladder cancer								Total
Schistosomal-associated			Non-schistosomal-associated					
SCC	PUC	Total	UCN	SCC	Adeno.	S Ca	Total	
11 (6.1%)	2 (1.1%)	13 (7.2%)	159 (88.3%)	1 (0.6%)	5 (2.8%)	2 (1.1%)	167 (92.8%)	180 (100%)

SCC: squamous cell carcinoma; PUC: papillary urothelial cell carcinoma; UCN: urothelial cell neoplasm; Adeno.: adenocarcinoma; S Ca: sarcomatoid carcinoma.

Table 5 Invasion of BCA and other associated lesions in all cases studied.

Invasion		Associated lesions			Total
MP	MM	CIS	Metaplasia		
30 (16.7%)	45 (25%)	10 (5.6%)	Squamous 10 (5.6%)	Glandular 6 (3.3%)	180 (100%)

MP: muscularis propria; MM: muscularis mucosae; CIS: carcinoma in situ.

Discussion

The incidence of BCA is increasing, estimated to be the ninth most common cancer worldwide and the 13th cause of cancer related death [46]. Also, this cancer is the 5th most commonly diagnosed non-cutaneous solid malignancy [47,48].

The age of our patients was ranged from 26 to 86 years with a mean 55.3 also, 150 cases (83.3%) were males, and the other 30 (16.7%) were females. These findings are in agreement with [25,49] other studies from the Middle East where the mean age of their cases were 56 and 58 years. Additionally, these authors noted that these ages were less than reported in the literatures of other parts in the world. As well as in schistosoma free countries throughout the world the highest incidence of BCA is in the sixth or seventh decades of life with a peak between 65 and 72 years [50,51]. Our findings do not agree with what others mentioned in certain regions, such as Egypt, Sudan and Iraq as the mean age of the highest incidence is between 40 and 49 years [21,52,53]. In this study the gender ratio was 5:1 that does not equal to a higher one in endemic areas such as Egypt which is 3:1 [54]. In Jordan a study reported the highest incidence between 40 and 59 years with a percentage 35.9% [55]. In Saudi Arabia BCA affects 2.8/100,000 in Makkah region, which is the place of this study. In contrast the highest incidence of BCA in Saudi Arabia was in Tabuk region which was 5.5/100,000. While, in Northern and Eastern regions the incidence was between 4.5/100,000 and 2.6/100,000 [56].

In the current study, 15 cases (8.3%) were papillary urothelial neoplasm of low malignant potential, 95 (52.8%) low grade papillary urothelial carcinoma and 51 (28.3%) high grade papillary urothelial carcinoma, 12 (6.7%) squamous cell carcinoma, 5 (2.8%) adenocarcinoma, and sarcomatoid carcinoma detected in 2 cases (1.1%). Additionally, schistosomal associated BCA comprised 13 cases (7.2%), among them 11 (6.1%) were squamous cell carcinoma and the remaining 2 (1.1%) were papillary urothelial cell carcinoma. In the opposite side the remaining 167 cases (92.8%) were non-schistosomal associated BCA. Our results are comparable with those reported in KFSH & RC among 175 cases of radical cystectomies, 56% was diagnosed as papillary urothelial cell carcinoma, 34% squamous cell carcinoma, and 5% adenocarcinoma. Among these cases schistosomal associated BCA was 17% majority

of them were squamous cell carcinoma whereas, non-schistosomal associated BCA was 83% [30]. In the same manner other findings discussed urothelial tumors seen in 93%, SCC in 2.7%, and adenocarcinoma in 1.4% [57]. Also, our results were in agreement with a study done on Turkish patients and reported UCC found in 77.2%, non-schistosomal SCC in 8.9%, adenocarcinoma in 1.9% and sarcomatoid carcinoma in 0.8% [58]. As well as in Saudi Arabia and according to the Cancer Incidence Report (2004) the majority of BCA was urothelial cell carcinoma, NOS which was represented 51.8%, papillary urothelial cell carcinoma was 32.4%, squamous cell carcinoma encompassed 9% and adenocarcinoma 1.5% of all registered cases. In Japan urothelial cell carcinoma was detected in 92.1%, squamous cell carcinoma in 3.4%, and adenocarcinoma in 2% [59]. In the current study squamous cell carcinoma represented 6.7% out of all cases. This is not in parallel with a study performed in Cleveland clinic from the period 1981 to 2006 which found pure squamous cell carcinoma in 2% of cases [60]. As well as a similar range in other institution was reported [61]. In the same manner our results were in agreement with those mentioned in industrialized Western countries as urothelial cell carcinoma was seen in 90–95%, squamous cell carcinoma in 3–7% and adenocarcinoma in 1–2% [62]. Additionally schistosomal associated squamous cell carcinoma reported in 15% of cases in the developing countries [63]. A study done in Egypt during the years 1970–2007 revealed a significant decline in the frequency of BCA from 27.6% to 11.7%, urothelial cell carcinoma showed significant rise from 16% to 65.8% and a significant drop of squamous cell carcinoma from 75.9% to 28.4%. They linked these changes to the decline in squamous metaplasia of the urothelium as a result of decline in schistosomal infection [24]. The discrepancy between our findings and others may be explained by incrimination of many other risk factors in the occurrence of squamous metaplastic changes in the urothelium in these endemic regions. Also, the decline of squamous cell carcinoma in this study may be linked to lower prevalence of squamous metaplasia (5.6%). This explanation may be supported by previous findings reported and linked the increased BCA risk in Egyptian patients to other risk factors as tobacco smoking or other occupations [55,64]. Also, several investigators mentioned smoking and other occupational exposure are carcinogens of biggest risk factors to develop BCA. So, reduction of occupational carcinogens is the preventative programs of BCA with reduction of mortality and morbidity and total cost therapy of this tumor [16,65,66].

Thirty (16.7%) out of all cases showed tumor invasion in muscularis propria and 45 cases (25%) revealed invasion in muscularis mucosae. All the cases of squamous cell carcinoma showed invasion to muscularis propria. In the opposite side the remaining 105 cases (58.3%) were free from tumor deposits. Additionally 10 (5.4%) out of all the cases revealed an associated carcinoma in situ, squamous metaplasia was detected in 10 (5.6%), and glandular metaplasia in 6 cases (3.3%). These findings are in agreement with other studies that mentioned majority of patients with squamous cell carcinoma who underwent for partial or radical cystectomies demonstrated invasion in the perivesical fat (pT3) and beyond [67,68]. A study explained presence or absence of muscularis propria invasion is the crossroad of radical versus conservative management of patients with BCA [40]. As well as previous researches reported in 22% of cases, the deeply situated compact hyperplastic muscularis mucosae muscle bundles may have similarity to muscularis propria and confused with the later in TURB and may leading to upstaging [40,69,70].

Conclusion

Bladder cancer shows a wide range of geographical variation. Also, according to the WHO classification of urothelial neoplasms, accurate diagnosis and categorization of BCA are mandatory, as PUNLMP group carry low rate of recurrence and progression to invasive cancer, low grade urothelial cell carcinoma also carries the same previous feature with slight increase, whereas the high grade urothelial cell carcinoma is characterized by more rate of recurrence and malignant features so, of need to special therapeutic attention.

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