

Original Article **Pathologic Pattern of Invasive Bladder Carcinoma: Impact of Bilharziasis**

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ABSTRACT

Objective: To describe the pathologic pattern of invasive bladder carcinoma in cystectomy specimens in relation to bilharziasis.

Patients and Methods: Between April 2002 and October 2006, 148 consecutive patients with invasive bladder cancer were subjected to radical cystectomy and orthotopic sigmoid bladder substitution at Al-Azhar Urology Department, Cairo, Egypt. A retrospective computerized database analysis of the pathologic features of the cystectomy specimens was done focusing on the impact of bilharziasis on the pathology of bladder carcinoma. The tumor cell type, stage, grade and gross features in addition to lymph node involvement were particularly noted.

Results: Bilharzial bladder pathology (lesions or ova) was present in 105 (70.9%) of 148 cystectomy specimens. Tumor histology included transitional cell carcinoma (TCC) in 84 (56.7%), squamous cell carcinoma (SCC) in 51 (34.5%), adenocarcinoma in 9 (6.1%) and anaplastic tumor in 4 (2.7%) of these specimens. Most tumors associated with bilharziasis were bulky and appeared fungating or ulcerative. The pathologic tumor stage was pT2 in 23%, pT3 in 70.9% and pT4a involving the prostate or seminal vesicles in 6.1%. None of these pT4a tumors were SCC. The tumor grade was described as low grade in 72 (48.6%) and high grade in 76 (51.4%) specimens. Regional lymph node involvement was detected in 31 (20.9%) specimens irrespective of bilharzial infestation.

Conclusion: Invasive bladder carcinoma associated with bilharzial pathology is mainly stage pT3, low-grade SCC and commonly appears as an ulcerative, bulky, fungating or verrucous mass. On the other hand, bladder carcinoma not associated with bilharziasis is mainly high-grade TCC and commonly appears as nodular or fungating lesions. Positive surgical margin and lymph node involvement are unrelated to bilharzial infestation.

Keywords : Bladder carcinoma, bilharziasis, squamous cell carcinoma, transitional cell carcinoma.

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INTRODUCTION

Worldwide, bladder cancer is the second most common genitourinary malignancy after prostate cancer in men. In a population-based study on all incident cancers in the province of Gharbiah, Egypt, published in 2007, the incidence of bladder carcinoma was reported to be 9.4%¹. Urinary bladder cancer is the commonest cancer among males in Egypt due to its etiological relationship to urinary bilharziasis. This association

with bilharziasis was first reported by Makar² who described the various lesions occurring in the bilharzial bladder and concluded that squamous cell carcinoma (SCC) was a sequel of urinary bilharzial infestation in Egypt. In a series of 304 Egyptian patients with bladder cancer published in 1972, SCC was encountered in 66.7%, transitional cell carcinoma (TCC) in 23.4%, adenocarcinoma in 8.1% and anaplastic carcinoma in 1.8% of the cas-



Fig. 1: Photomicrograph of well-differentiated squamous cell carcinoma forming keratinized cell nests associated with bilharzial ova (H & E x 400).

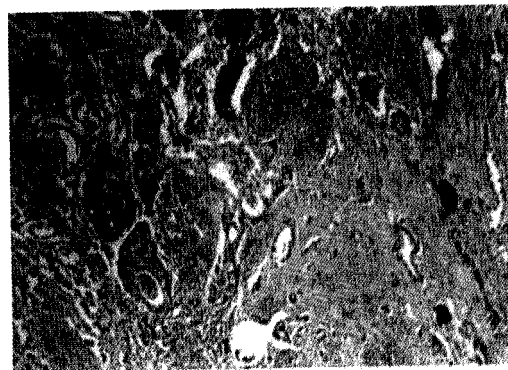


Fig. 2: Photomicrograph showing clusters of high-grade transitional cell carcinoma invading bladder muscles associated with scattered calcified bilharzial ova (H & E x 100).

es.³ In 1977, Mousa studied the relation between bladder cancer and bilharziasis in 100 patients and found SCC in 63.3% of bilharzial compared to 20% of non-bilharzial cases⁴. Other studies^{5,6} confirmed the preponderance of SCC in patients with invasive bladder carcinoma associated with bilharziasis.

The present study was carried out in order to examine the pathologic pattern of invasive bladder carcinoma in relation to bilharzial pathology.

PATIENTS AND METHODS

Between April 2002 and October 2006, 148 consecutive patients with invasive bladder cancer were scheduled for radical cystectomy and orthotopic sigmoid bladder substitution at Al-Azhar Urology Department, Cairo, Egypt. The mean patient age was 51.9 ± 2 (range 28-79) years with a male-to-female ratio of 5.4:1 (125 males and 23 females). Radical cystectomy entailed en-bloc removal of the bladder, the lower ureters and all pelvic lymph nodes, in addition to the prostate and seminal vesicles in males and the uterus and adenexa in females. Histopathological examination focused on the presence of bilharzial pathology, tumor cell type, grade, stage and gross features. Pelvic lymphadenectomy of the obturator, internal, external and common iliac nodes was routinely done. All removed regional lymph nodes (7-20 in number) were examined for malignant depo-

sits. In 6 patients lymphadenectomy was performed during previous partial cystectomy for malignancy. A recurrent confined bladder carcinoma without pelvic extension in these cases was managed by salvage surgery. Both Student's t-test and Chi-square test were used for statistical analysis.

RESULTS

The tumor cell type was TCC in 84 (56.7%), SCC in 51 (34.5%), adenocarcinoma in 9 (6.1%) and anaplastic tumor in 4 (2.7%) cystectomy specimens.

Bilharzial bladder pathology (lesions or ova) was present in 105 (70.9%) specimens (Table 1). These included 50 (98%) of the 51 SCC specimens (Fig. 1) and 55 (56.7%) of the 97 non-SCC specimens. This difference in tumor cell type in relation to bilharzial association is statistically significant ($P < 0.005$). Furthermore, bilharzial pathology was found in 77.8% and 57.1% of the adenocarcinoma and TCC (Fig. 2) specimens, respectively, while none of the 4 anaplastic tumors harbored bilharzial infestation (Table 1).

A low tumor grade was found in 72 (48.6%), while a high tumor grade was seen in 76 (51.4%) cases (Table 2). There was no relation between tumor grade and bilharzial infestation; high grade was

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Table 1: Tumor cell type of invasive bladder carcinoma in relation to associated bilharzial pathology.

Tumor Type	Associated Bilharziasis						Total		P value
	Present		Absent		Undefined		No.	%	
	No.	%	No.	%	No.	%	No.	%	
TCC	48	32.4%	33	22.3%	3	2%	84	56.7%	<0.07
SCC	50	33.8%	1	0.7%	0	0	51	34.5%	<0.005
Adenocarcinoma	7	4.7%	2	1.4%	0	0	9	6.1%	<0.03
Anaplastic	0	0	4	2.7%	0	0	4	2.7%	---
Total	105	70.9%	40	27.1%	3	2%	148	100%	----

TCC = transitional cell carcinoma, SCC = squamous cell carcinoma

Table 2: Tumor grade in relation to cell type in 148 cystectomy specimens.

Tumor Grade	Tumor Type								Total		P value
	TCC		SCC		Adenocarcinoma		Anaplastic		No.	%	
	No.	%	No.	%	No.	%	No.	%	No.	%	
Low	26	31%	36	70.6%	8	88.9%	2	50%	72	48.6%	< 0.005
High	58	69%	15	29.4%	1	11.1%	2	50%	76	51.4%	< 0.005
Total	84	56.7%	51	34.5%	9	6.1%	4	2.7%	148	100%	--

detected in 50.5% and low grade in 49.5% of 105 cystectomy specimens associated with bilharzial pathology ($P>0.05$). Similarly, low-grade tumors were found in 46.5% and high-grade tumors in 53.5% of the remaining 43 cystectomy specimens without bilharzial pathology ($P>0.05$). A particular feature was the prevalence of high-grade tumors of the TCC cell type, as 69% of TCC were of high grade compared to 29.4% of SCC specimens ($P<0.05$).

The pathologic tumor stage included 23% with stage pT2 and 70.9% stage pT3, while pT4a was detected in 6.1% (Table 3). The pT3 stage was encountered significantly more often than other stages ($P<0.005$). SCC was mainly of pT3 stage (80.4%), while 66.7% of TCC were pT3 ($P>0.05$).

Fungating and nodular (Fig.3) tumor gross features were described in 48 (32.4%) and 35 (23.6%) of 148 cystectomy specimens, respectively, while ulcerative tumors were found in 52 (35.2%), infiltrative tumors in 11 (7.4%) and verrucous tumors in 2 (1.4%) specimens. Nodular gross tumor morphology was significantly documented in TCC when compared to SCC ($P<0.05$) (Table 4).

Regarding the surgical margins, a positive margin was present in 2.7% each of the specimens with and without bilharzial pathology, while a negative margin was noted in 101 (96.2%) of 105 specimens with bilharzial pathology ($P<0.005$) (Table 5).

Free surgical margins were noted in all specimens with SCC, while 5.4% of the

Table 3: Tumor stage in 148 cystectomy specimens in relation to cell type.

Tumor Stage	Tumor Type								Total		P value
	TCC		SCC		Adenocarcinoma		Anaplastic		No	%	
	No	%	No	%	No	%	No	%			
pT2	21	14.2%	9	6.1%	2	1.4%	2	1.4%	34	23%	<0.05
pT3	56	37.8%	41	27.7%	6	4.0%	2	1.4%	105	70.9%	<0.005
pT4a	7	4.7%	1	0.7%	1	0.7%	0	0	9	6.1%	--
Total	84	56.7%	51	34.5%	9	6.1%	4	2.7%	148	100%	--



Fig. 3: Post-operative specimen of radical cystectomy showing nodular growth of the dome while the verumontanum is shown at the distal tip of the prostatic urethra.

TCC specimens showed a positive surgical margin. Data analysis confirmed a negative correlation between surgical margin and the tumor gross features (Table 5). The tumor was invading adjacent resectable organs in 11 cases (T4a), of them 9 infiltrating the prostate while 2 invaded the seminal vesicles.

The mean number of retrieved lymph nodes was 13±2 (range 10-20) in 107 (72.3%) cystectomy specimens, and 7-9 lymph nodes in 35 (23.6%) specimens. Lymph node examination was not possible in 6 (4.1%) specimens due to previous lymphadenectomy prior to cystectomy. Lymph node involvement was detected in 31 (20.9%) cystectomy specimens, while negative lymph node

metastases were confirmed in 111 (75%). Lymph node involvement was unrelated to the associated bilharziasis but related to the tumor cell type. Positive nodes contained TCC in 84% (26 of 31 cases) with a statistically significant difference ($P<0.05$) when compared to SCC. Furthermore, no relation between lymph node involvement and the other tumor features was noted (Table 3).

Significant bacteriuria was found in all urine cultures taken from cases with SCC associated with bilharzial pathology and in 62.5% of non-squamous cell bladder carcinoma.

DISCUSSION

Bladder carcinoma is one of the most common malignancies treated by urologists. Worldwide, most bladder cancers are TCC (>90%), while SCC and adenocarcinoma are rare types⁶.

In the present study the mean age was 51.9 years which is comparable to that reported by other authors^{5,7}. In contrast, in a study of 33 cases with SCC done by Riadh et al. the mean patient age was 59 years⁸, which may, however, be attributed to the selection of cases (SCC only).

Also the male-to-female ratio found in our patient group (5.4:1) is similar to that reported in other studies^{3,6,7,9,10}.

Table 4: Tumor gross features in relation to tumor cell type

Tumor Morphology	Tumor Cell Type								Total (%)		P value
	TCC		SCC		Adenocarcinoma		Anaplastic		No	%	
	No	%	No	%	No	%	No	%			
Ulcerative	30	20.2%	20	13.6%	2	1.4%	0	0	52	35.2%	<0.08
Fungating	20	13.6%	24	16.1%	3	2.0%	1	0.7%	48	32.4%	<0.08
Nodular	25	16.8%	5	3.5%	3	2.0%	2	1.4%	35	23.6%	<0.07
Infiltrative	9	6.1%	0	0	1	0.7%	1	0.7%	11	7.4%	--
Verrucous	0	0	2	1.4%	0	0	0	0	2	1.4%	--
Total	84	56.7%	51	34.5%	9	6.1%	4	2.7%	148	100	--

Table 5: Positive surgical margins in relation to bilharziasis and tumor cell type and gross features

Parameter	Free margins		Positive margins		Total		P-value
	No	%	No	%	No	%	
Associated bilharziasis:							
Present	101	68.2%	4	2.7%	105	71%	<0.005
Absent	36	24.3%	4	2.7%	40	27%	
Undefined	2	1.4%	1	0.7%	3	2%	
Tumor cell type							
TCC	76	51.3%	8	5.4%	84	56.7%	<0.005
SCC	51	34.5%	0	0	51	34.5%	
Adenocarcinoma	8	5.4%	1	0.7%	9	6.1%	
Anaplastic carcinoma	4	2.7%	0	0	4	2.7%	
Gross features							
Ulcerative	50	33.8%	2	1.4%	52	35.2%	>0.05
Fungating	44	29.7%	4	2.7%	48	32.4%	
Nodular	33	22.3%	2	1.4%	35	23.6%	
Infiltrating	10	6.7%	1	0.7%	11	7.4%	
Verrucous	2	1.4%	0	0	2	1.4%	

In the past, the type of bladder carcinoma observed in Egypt was mainly SCC with a frequency distribution of 53%-75% as reported by various authors^{2,3,4,9,11}. In the present study, SCC was detected in 34.5% of the cystectomy specimens compared to 56.3% of TCC. This preponderance of TCC was also confirmed by a recent, population-based study conducted in the province of Gharbiah, Egypt, where TCC was described in 67% and SCC in 22% of the patients¹. The difference between this study and ours might be due to the geographic location. In the present study, the patients came from various areas of upper and lower Egypt, while in the population-

based study the patients were from Gharbiah only.

In this study, pT2 bladder carcinoma was present in 23%, pT3 in 70.9% and pT4a in 6.1% of the cystectomy specimens. Similarly, Lagwinski et al. reported pT2 tumors in 31%, pT3 in 60% and T4a in 7%¹⁰, while in the study of Herr et al. less than half the patients had tumors of stages pT3 and pT4¹². Also in the Gharbiah study, superficial and local bladder carcinoma was detected in 48%, regional in 37% and metastatic in 15%.¹ This difference may be due to the fact that the

Table 6: Lymph node involvement in relation to bilharziasis, tumor cell type and gross features.

Parameter	Inapplicable		Positive		Negative		Total		P-value
	No	%	No	%	No	%	No	%	
Associated bilharziasis:									
Present	5	3.4%	18	12.2%	82	55.4%	105	71%	>0.05
Absent	1	0.7%	12	8.1%	27	18.2%	40	27%	>0.05
Undefined	0		1	0.7%	2	1.4%	3	2%	--
Tumor cell type									
TCC	3	2.0%	26	17.5%	55	37.2%	84	56.7%	<0.05
SCC	1	0.7%	3	2.0%	47	31.7%	51	34.5%	>0.05
Adenocarcinoma	1	0.7%	2	1.4%	6	4.1%	9	6.1%	--
Anaplastic carcinoma	1	0.7%	0	0	3	2.0%	4	2.7%	--
Gross features									
Ulcerative	2	1.4%	9	6.1%	41	27.7%	52	35.2%	>0.05
Fungating	1	0.7%	10	6.7%	37	25.0%	48	32.4%	>0.05
Nodular	3	2.0%	9	6.1%	23	15.5%	35	23.6%	>0.05
Infiltrating	0	0	3	2.0%	8	5.4%	11	7.4%	--
Verrucous	0	0	0	0	2	1.4%	2	1.4%	--

latter two studies included superficial bladder carcinoma.

In the present study, bladder carcinoma was well differentiated in 48.6% and poorly differentiated in 51.4% of the cystectomy specimens. No difference was found between high and low tumor grade in the 105 cystectomy specimens associated with bilharzial pathology. Also no difference was found between low and high grade in 43 cystectomy specimens without any bilharzial pathology. Most of the TCC cystectomy specimens (69%) were of high grade, while most of the SCC specimens (70.6%) were of low grade. In the Gharbiah study, grade I-II was diagnosed in 57.2% and grade III-IV in 42.8% of all cases¹. Also, Lagwinski et al.¹⁰ reported moderately, poorly and well differentiated tumors in 64%, 29% and 7%, respectively.

In this study, positive surgical margins were documented in 11 (7.4%) of 148 cystectomy specimens; this is similar to the

results of Herr et al. who proposed optimum standards that include overall 10% positive surgical margins and 15% in specimens with pT3 and pT4 tumors.¹²

Lagwinski et al. studied 45 SCC cystectomy specimens and found exophytic and nodular tumors in 43% of the specimens, while ulcerated tumors were described in 42%.¹⁰ In the present study, fungating and nodular tumor gross features were described in 56.1% of the specimens and ulcerative, infiltrative and verrucous tumors in 35.1%, 7.4% and 1.4%, respectively. This difference is related to the fact that the study of Lagwinski et al. included SCC cystectomy specimens only.¹⁰

Herr et al. proposed an optimum number of dissected lymph nodes in cystectomy specimens of between 10 and 14.¹² In our series the number of retrieved lymph nodes was 10-20 in 72.3% and 7-9 in 23.6%. Lymph node involvement was detected in 20.9% of all cystectomy specimens which is comparable to the results of Herr et al.¹²

Bilharzial pathology was present in 71% of all cystectomy specimens and in 98% of the SCC specimens in our study. Similarly, Mousa found that 100% of his cases with SCC were associated with bilharziasis.⁴ Urinary tract bacterial infection was detected in all our cases with SCC and in 62.5% of non-squamous cell bladder carcinoma.

El-Bolkainy concluded that bladder carcinogenesis was mostly related to bacterial and viral infections associated with bilharzial infestation.¹¹ Urinary bacteria secrete the β -glucuronidase enzyme that clears conjugated carcinogens and produce carcinogenic nitrosamines from their precursors in the urine¹³. Many studies were conducted to evaluate the role of the human papilloma virus (HPV) in bladder cancer, but the authors found no significant role of HPV in the development of bladder SCC^{14,15}.

Eissa et al. compared the use of nuclear matrix protein, fibronectin, urinary bladder cancer antigen and urine cytology for early detection of bladder cancer and concluded that NMP22 and urine cytology had the highest specificity; they recommended the use of a combination of both to increase the sensitivity from 44% to 95.3%. They found a higher sensitivity of these markers in bilharzial compared to non-bilharzial bladder cancer which will make them useful for the screening of patients with urinary bilharziasis for early detection of carcinoma in the future¹⁶.

The reported change in the type of bladder carcinoma in Egypt may indicate the importance of anti-bilharzial oral therapy and possibly the frequent use of proper antibiotic therapy for the treatment of bacterial urinary tract infection associated with the bilharzial bladder. The increased frequency of TCC in Egypt may also be explained by other risk factors, such as smoking. Future studies aimed at finding other precipitating factors (carcinogens) other than or in addition to bilharziasis and secondary bacterial infection would be of great value.

In conclusion, muscle invasive bladder carcinoma in association with bilharzial

lesions is mainly of low grade SCC and commonly appears in the form of fungating, ulcerated or verrucous bulky pT3 lesions. Bladder carcinoma not associated with bilharziasis is mainly high-grade TCC and grossly nodular or fungating. Positive surgical margin and lymph node involvement is unrelated to bilharzial infestation. There has been a significant change in the tumor type of bladder carcinoma in Egypt in the last few years. TCC is seen twice as frequently as SCC in spite of the high prevalence of associated bilharziasis.

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