

Bilharziasis and Bladder Cancer: A Time Trend Analysis of 9843 Patients

IMAN GOUDA, M.D.*; NADIA MOKHTAR, M.D.*; DALIA BILAL, M.D.**;
TAREK EL-BOLKAINY, M.D.* and M. NABIL EL-BOLKAINY, M.D.*

The Departments of Pathology and Biostatistics & Cancer Epidemiology**, National Cancer Institute, Cairo University.*

ABSTRACT

Objective: To explore any changes in bladder carcinoma during 37 years period, in regard to: its frequency, bilharzia association, histological profile and demographic data.

Patients and Methods: This is a retrospective study on 9843 patients treated at the National Cancer Institute (NCI), Cairo University, during the years 1970-2007. Three groups were selected: series (A) included 3212 patients during 1970-1974, series (B) 3988 patients during 1985-1989 and series (C) 2643 patients during 2003-2007. For statistical analysis, data of series (A), (B) and (C) were compared to determine the significance of difference (p value 0.005).

Results: A significant decline of the relative frequency of bladder cancer was observed from 27.63% in the old series to 11.7% in the recent series. Bilharzia association dropped from 82.4% to 55.3%. There was a significant rise of transitional cell carcinomas from 16.0% to 65.8%, becoming at present the most common tumor type, with a significant decrease in squamous cell carcinomas from 75.9% to 28.4%. There was an increase in the median age of patients from 47.4 years to 60.5 years and a decrease of male: female (M/F) ratio from 5.4 to 3.3.

Conclusions: The decline in the relative frequency of bladder cancer is associated with a decline in bilharzia egg positivity in the specimen and is probably related to better control of bilharziasis in the rural population in Egypt. This was accompanied by a change in the histological profile of tumors, with significant predominance of transitional cell carcinoma and an increase in the age of patients, a pattern rather similar to that in western reports.

Key Words: Bladder carcinoma – Bilharziasis – Pathology.

Correspondence: Dr Iman Gouda, Department of Pathology, National Cancer Institute, Cairo University, imangouda@nci.edu.eg

INTRODUCTION

Bilharziasis is a parasitic disease that dates back to ancient times. Thus, bilharzial eggs were identified in Egyptian mummies (1200 B.C.) and the main symptom, hematuria, was recorded in the oldest papyrus of Kahum, 1900 B.C. [1]. In 1852, Theodor Bilharz, a German pathologist working in Cairo, discovered the worms in the portal circulation and was the first to describe the associated cystitis. Ferguson in 1911 was the first to report on the high frequency of bladder cancer in Egypt and to suggest an etiologic relation with urinary bilharziasis [2]. The high frequency of bladder cancer was confirmed by early reports of the NCI registry (1977) in which that tumor contributed 27.6% of all cancers [3]. However, so far, no epidemiologic studies are available to clarify the exact relation of bilharziasis to bladder cancer, whether it is etiologic or just a mere association.

During the past five decades, valuable contributions have been made by several Egyptian investigators on the bilharzia-associated bladder cancer. This included: the urologic aspects of the disease by Makar [4], surgical treatment by El-Sebai [5] and Ghoneim [6] and pathologic features by El-Bolkainy and associates [7,8,9]. The bilharzia-associated bladder cancer presents distinctive clinico-pathological features, quite different from that reported from Europe and North America. Thus, it affects patients at a much younger age (mean 46.7 years) with males predominating over females 5.6 times [7]. Squamous cell carcinoma is the most common histological type (76.6%) since it arises on top of

squamous metaplasia resulting from chronic bilharzial cystitis [7,10]. Finally, the majority of tumors present at an advanced stage, 95.3% of cases are muscle invasive > T1 [6], hence radical cystectomy is the main line of treatment.

The initial strategy adopted in Egypt to combat bilharziasis started in 1920 and involved intravenous injections of patients by antimony compounds and control of snails by molluscicides. But, since these efforts were usually of limited nature, both in time and place, they had a slight impact on the prevalence rate of the disease as determined by survey of rural populations for bilharzias eggs in urine [11,12]. Conversely, the introduction of more effective oral antibilharzial drugs into Egypt (metrifonate in 1977 and praziquantel in 1985) resulted in a significant decline in the prevalence rate of urinary bilharziasis in two surveys reported in 2002 [13,14]. Also, in a time trend analysis of a pathology series of bladder cancer over a period of 30 years (1962-1992), a significant decline of the intensity of bilharzial infestation was reported [15]. However, a possible change in the frequency of bladder cancer during this period was not determined in that study.

The objective of the present study is to explore a possible change in the relative frequency of bladder cancer over a period of 37 years. Moreover, changes in the frequency of bilharzia association, histological profile of carcinomas and demographic data of patients are also investigated.

PATIENTS AND METHODS

The present retrospective study was based on 9843 patients with bladder carcinoma treated at the NCI, Cairo Univ., during the period 1970 to 2007. The NCI is the largest multidisciplinary cancer center in Egypt (about 500 beds) to which patients are referred from different provinces of Egypt. About 52.6% of patients are referred from Cairo and Giza, 29.6% from lower Egypt, 14.6% from middle Egypt and 3.2% from upper Egypt. This reference rate from different areas of Egypt did not significantly change during the period of the study.

The pathologic material of the study included 3052 cases of biopsies and 6791 resection specimens. Histopathological typing of carcinomas

was made following the World Health Organization (WHO) classification of tumors [16]. Thus, transitional cell carcinomas with squamous metaplasia were classified under transitional cell carcinoma. Also, verrucous carcinomas were included in the squamous cell carcinoma group. Previously unclassified carcinomas were reviewed to establish the exact histological type. For the evaluation of bilharzia association, specimens containing bilharzia eggs, in bladder, ureters, prostate, or seminal vesicles, were considered egg-positive and their frequency determined relative to the total specimens examined.

For time trend analysis, patients were grouped into 3 series, namely: series (A) including 3212 patients treated during the years 1970-1974, series (B) of 3988 patients treated during 1985-1989 and series (C) of 2643 patients treated during 2003-2007. For statistical analysis, data of series A, B and C were compared by testing any significant difference between proportions using the chi square test [17] and *p* value was considered significant at the 0.05 level.

RESULTS

A significant decline in the relative frequency of bladder cancer was observed when series A and C were compared, with a drop from 27.63% in the old series to 11.7% in the recent series (Table 1). The drop in frequency was most marked after the year 2003 (Fig. 1). The decline in the frequency of bladder cancer was associated with a decrease of bilharzial association in the specimens with a drop of egg-positive specimens from 82.4% in series A to 55.2% in series C (Table 2 and Fig. 1).

There was a significant decline in the frequency of squamous cell carcinoma (from 75.9% in series A to 28.4% in series C) and an increase of transitional cell carcinoma (from 16.0% in series A to 65.8% in series C), ultimately becoming more frequent than squamous cell carcinoma (Fig. 2), with insignificant change in the other histological types during the period of the study. In the old series, squamous cell carcinoma predominated over transitional cell carcinoma with a ratio of 4.7. The histological type predominance was reversed in series C

with a transitional cell carcinoma/squamous cell carcinoma ratio of 2.3. The change in the relative frequency of histological types of bladder carcinoma remained significant when only the resection specimens were analyzed after excluding the biopsies (Table 2).

Significant changes in the demographic data of bladder cancer patients were also observed during the past 37 years. The median age of patients increased from 47.4 years in the old series to 60.5 in recent series and male predominance decreased from 5.4 to 3.3 (Table 3).

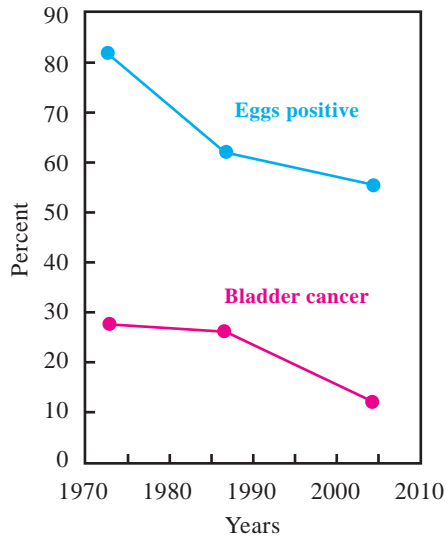


Fig. (1): The decline in the relative frequency of both bladder carcinoma and its bilharzial association during 37 years (1970-2007).

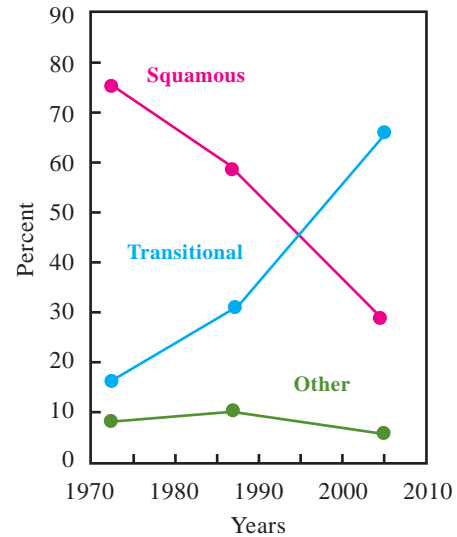


Fig. (2): The change in the relative frequency of histological types of bladder carcinoma during 37 years (1970-2007).

Table (1): The decline in the frequency of bladder carcinoma during 37 years, 9843 patients.

Series (period)	All cancers (No. of cases)	Bladder carcinoma	
		No.	%
A (1970-1974)*	11,626	3212	27.63
B (1985-1989)*	15,112	3988	26.39
C (2003-2007)*	22,580	2463	11.70
Total	49,318	9843	19.96

* The difference between the series was statistically significant ($p=0.012$).

Table (2): Pathologic time trend analysis of bladder carcinoma in resection specimens, 6791 patients.

Parameter	Series (period)			p-value*
	A (1970-1974)*	B (1985-1989)*	C (2003-2007)*	
Bilharzia eggs +ve (%)	82.4	61.7	55.3	$p<0.001$
Carcinoma type (%):				$p<0.001$
Transitional	16.0	24.1	60.3	
Squamous	75.9	66.0	33.0	
Others	8.1	9.9	6.7	
No. of cases	3212	2080	1499	

* The statistical significance of difference between the series.

Table (3): Demographic time trend analysis of bladder carcinoma, 9843 patients.

Parameter	Series (period)		
	A (1970-1974)*	B (1985-1989)*	C (2003-2007)*
Median age	47.4	54.5	60.5
M/F ratio	5.4	3.7	3.3
No. of cases	3212	3988	2643

DISCUSSION

In the present report, a significant decline in the relative frequency of bladder cancer (from 27.6% to 11.7%) was observed in the past 37 years by analysis of 9843 patients at the Department of Pathology, NCI, Cairo University. Our recent figure of 11.7% is comparable to a recent figure of 9.4% reported from Gharbia Cancer Registry, which covers 3.4 million population in the South of Nile Delta [18]. The above mentioned Egyptian figures are still higher than a recently published frequency rate of 4.6% from U.S.A. [19]. However, if the current decline in the frequency of bladder cancer continues with the same rate, it will probably reach the Western figure in the future, in about 10 years.

Our investigation demonstrated a decline in the frequency of bilharzia egg positivity in the specimens during the same period of the study. A similar finding was previously reported showing a decline in the severity of bilharzial infestation by time trend analysis of 878 patients with bladder carcinoma [15]. This change is most probably the result of better control of bilharziasis in Egypt following the use of oral antibilharzial drugs.

An even more dramatic reduction in the prevalence of *Schistosoma haematobium* in rural Egyptian population is evident by comparing the reports of different surveys to identify eggs in urine samples. The first country-wide survey, published by Scott in 1937 [11], demonstrated high prevalence rates (60% in Nile Delta, 89% in Fayoum and 25% in Upper Egypt). Miller in 1976 [12] reported a decrease in prevalence (30% in Nile Delta, 27% in Beni-Suef, and 6% in Upper Egypt). El-Khoby and associates in 2000 [13,14] reported a significant reduction in prevalence (0.45% in Nile Delta, 13.7% in Fayoum and 7.8% in Upper Egypt). This

significant reduction in the prevalence of *S. haematobium* (particularly in lower and middle Egypt) was probably the result of the use of effective oral antibilharzial drugs in therapy, namely: metrifonate in 1977 and praziquantil in 1985 [13].

A marked change in the histological profile of carcinomas was also observed in the present study, namely: a decline in the frequency of squamous cell carcinoma and increase of transitional cell carcinoma. This is probably due to a decrease of squamous metaplasia of urothelium as a result of decline in both the incidence and intensity of bilharzial infestation. A similar finding was previously reported by Koraitim and associates [15], but in that report squamous cell carcinoma was still more frequent than transitional cell type (54% versus 35%), whereas, in the present study, transitional cell carcinoma predominated over squamous cell carcinoma (65.8% versus 28.4%).

The demographic changes observed in the present series included: an increase of age of patients and a decrease of male predominance. These findings are in agreement with a previous report from Egypt [15]. The increase of age of patients is probably the result of aging of Egyptian population, as well as, the decline of bilharziasis which is known to cause bladder cancer at a young age. The reduction of M/F ratio from 5.4 to 3.3 is probably also due to the control of bilharziasis during the past two decades, hence, the male Egyptian farmers who are the main candidates of infestation are getting less infected by the disease. The present male predominance ratio in our study (3.3) is close to a ratio of 2.9 recently reported from U.S.A. [19].

The exact relation of bladder cancer in Egypt to bilharziasis has been a subject of long debate. Statistical association between two variables does not establish a cause and effect etiologic relation. Strict logical criteria must be fulfilled to confirm causality [17], namely: strong association, site specificity, temporal relation and an available molecular model to explain carcinogenesis. The strong association is demonstrated in the present study by the concomitant decline in the frequency of both bilharzia eggs and bladder carcinoma. Moreover, in a previous screening study in rural Egyptian population [9], bladder carcinomas were only detected in farmers infested with bilharziasis. Site specific-

ity of this relation is also evident, since patients infested with both urinary and intestinal bilharziasis only develop bladder and not colonic carcinoma. Temporal relation implies that the change in the cause must precede the change in the effect. This is also evident in our investigation, since the decline of bilharzial prevalence in rural population occurred after 1990 [13,14], whereas the decline in the frequency of bladder cancer was observed after 2003 in the present study.

Finally, two reasonable biological models are available to explain carcinogenesis, both involving the associated bacterial infection rather than the parasite. Thus, bacteria may produce carcinogenic nitrosamines from their precursors in urine [20]. The second model proposes that free radicals produced by inflammation will directly affect DNA causing gene mutation [21]. The above discussion, of our observations as well as others, supports an etiologic relation of bilharzial cystitis and bladder cancer.

In conclusion, the decline in both the relative frequency of bladder carcinoma, as well as bilharzia association is probably the result of better control of bilharziasis in rural Egyptian population with the use of effective oral anti-bilharzial drugs. This change is associated with predominance of transitional cell carcinoma over the squamous cell type, an increase of the age of the patients and a decrease of male predominance. If these changes continue with the same rate, bladder cancer in Egypt will become identical in features to that of Western countries in the near future.

REFERENCES

- 1- Badr M. Schistosomiasis in Ancient Egypt. In El-Bolkainy and Chu, editors. Detection of bladder cancer associated with schistosomiasis, NCI, Cairo, Alahram Press. 1981, p. 1-8.
- 2- Ferguson AR. Associated bilharziasis and primary malignant disease of the urinary bladder with observation series of forty cases. *J Path Bacteriol*, 16: 76-94.
- 3- El-Sebai I. Bilharziasis and bladder cancer. *CA J for Clin*. 1977, 27: 100-6.
- 4- Makar N. Urologic aspects of bilharziasis in Egypt. SOP Press, Cairo. 1955, 1-52.
- 5- El-Sebai I. Cancer of bladder in Egypt. *Kasr El-Aini J Surg*. 1961, 2: 183-241.
- 6- Ghoneim MA, El-Mekresh MM, El-Baz MA, El-Attar IA, Ashamallah A. Radical cystectomy for carcinoma of the bladder: Critical evaluation of the results of 1, 026 cases. *J Urol*. 1997, 158: 393-9.
- 7- El-Bolkainy MN, Mokhtar NM, Ghoneim MA, Hussein MH. The impact of schistosomiasis on the pathology of bladder carcinoma. *Cancer*. 1981, 48: 2643-8.
- 8- El-Bolkainy MN, Chu EW (eds). Detection of bladder cancer associated with schistosomiasis. NCI, Al-Ahram Press. 1981.
- 9- El-Bolkainy MN, Chu EW, Ghoneim MA, Ibrahim AS. Cytologic detection of bladder cancer in a rural Egyptian population infested with schistosomiasis. *Acta Cytol*. 1982, 23: 303-10.
- 10- Khafagy MN, El-Bolkainy MN, Mansour MA. Carcinoma of the bilharzial urinary bladder, a study of the associated mucosal lesions in 86 cases. *Cancer*. 1972, 50: 150-9.
- 11- Scott JA. The incidence and distribution of human schistosomiasis in Egypt. *Am J Hyg*. 1937, 25: 566-614.
- 12- Miller FD, Hussein M, Mancy KH, Hilbert MS, Monto AS, Barakat RMR. An epidemiological study of schistosoma haematobium and *S. mansoni* infection in 35 rural Egyptian villages. *Trop Geogr Med*. 1976, 45: 355-65.
- 13- Abdel-Wahab MF, Esmat G, Ramzy I, Narooz S, Medhat E, et al. The epidemiology of schistosomiasis in Egypt: Fayoum Governorate. *Am J Trop Med Hyg*. 2000, 62: 55-64.
- 14- El-Khoby T, Galal N, Fenwick A, Barakat R, El-Hawey A, et al. The epidemiology of schistosomiasis in Egypt: Summary findings in nine Governorates. *Am J Trop Med Hyg*. 2000, 62: 88-99.
- 15- Koraitim MM, Metwalli NE, Atta MA, El-Sadr AA. Changing age incidence and pathological types of schistosoma-associated bladder carcinoma. *J Urol*. 1995, 154: 1714-6.
- 16- Eble JN, Sauter G. Pathology and genetics of tumors of the urinary system and male genital organs, World Health Organisation classification of tumors. Lyon, IARC Press. 2004, p. 93-134.
- 17- Riffenburgh RH. Statistics in medicine. 2nd edit. Elsevier Academic Press, Boston. 2006, p142, 264.
- 18- Ibrahim AS, Ismail K, Abdel Bar I, Hussein H, Hablas A, Ramadan M. Cancer profile in Gharbia-Egypt, GPCR Tanta, Ministry of Health and Population. 2002, p. 38.
- 19- Jemal A, Murray T, Ward E, Samuels A, Ram C. Cancer statistics. *CA Cancer J Clin*. 2005, 55: 10-30.
- 20- El-Merzabani MM, El-Aaser AA, Zakhary NI. A study on the etiological factors of bilharzial bladder cancer in Egypt: Nitrosamines and their precursors in urine. *Europ. J Cancer*. 1979, 15: 287-91.
- 21- Warren W, Biggs PI, El-Baz M, Ghoneim MA, Stratton MR, Venitt S. Mutations in the p53 gene in schistosomal bladder cancer. *Carcinogenesis*. 1995, 16: 1181-9.