

Undermined by Altered Epidemiology: Changing Concepts in the Management of Bilharzial Urinary Bladder Carcinoma in Egyptian Population

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Abstract

Background: The objective is to validate the new clinicopathological features of urinary bladder carcinoma in the Egyptian population. These are caused by altered epidemiology, and proposed to have reflection on management.

Patients and methods: Timely contributions of leading Egyptian experts in bladder cancer in the last 4 decades were reviewed. Additionally, 102 patients were studied in 2 subsets A&B based on a preplanned treatment modality: cystectomy facing transurethral resection plus radiotherapy. Observation on gross and microscopic features and their reflection on treatment decision are recorded.

Results: An overview of studies published in the last 4 decades is given, demonstrating a striking change in the characteristic features of bladder carcinoma in Egypt, more obvious in 2007 and after. In the present work, 65% of patients had their tumors in a bilharzial bladder, while 35 % had their tumors in a non bilharzial bladder, where walls demonstrated the classical cystoscopic features of the disease. Group A patients were treated by cystectomy carrying 7.7 % perioperative mortality, whereas patients in group B received radiotherapy preceded by transurethral resection.

Conclusions: Bladder cancer in Egyptian patients has lost its peculiar features imposed by bilharzial cystitis, shifting towards traditional types suitable for organ preserving management.

Keywords: Bilharzial cystitis; Bladder carcinoma; Carcinoembryonic antigen; Cystectomy; Trimodality therapy

Introduction

The link between chronic bilharzial cystitis and urinary bladder carcinoma in Egyptians is well documented [1-3], but what was less known is the exact nature of that link. A milestone was achieved in 1987 when Saied and Khalil assigned distinct clinicopathological and biochemical features to this type of cancer, attributing it to local irritation by the parasite ova or to carcinogenesis induced by products of abnormal tryptophan metabolism [1,4-6]. Secondary infection was also strongly accused, as the infecting bacteria secrete β -glucuronidase enzyme catalyzing the liberation of carcinogenic nitrosamines from their precursors in urine increasing them by 3 fold [7,8]. Today this link is largely accepted, and specific features were made out to discriminate bilharzial cancer from genuine one developing in a healthy bladder [4,9,10]. The tumor affects younger age, relentlessly aggressive, slow in growth, and has the tendency to recur locally rather than to metastasize. Patients usually present late as their symptoms are similar to those of the pre-existing cystitis. The tumor is massive mostly of the fungating type, occupying the lateral, posterior or anterior walls more than the vault or trigone. The prostate, prostatic urethra and seminal vesicles were rarely involved (< 5%). The bladder mucosa frequently shows features of bilharzial cystitis, ranging from sandy patches to leukoplakia [10-12]. Histologically, the tumor was typically squamous cell carcinoma (SCC) showing cell nests & fibrosis with invasion of the underlying muscle layer. Infrequent transitional cell tumors (TCC) were characteristically multicentric due to submucosal lymphatic permeation, while implantation to intact or ulcerated mucosa causes extensive in situ lesions [5,6]. Regional lymph nodes involvement was uncommon [13-17], but bacteruria, pyuria, anemia and eosinophilia were invariably manifested [5,12,13]. Also there was a simultaneous

rise of both serum and urinary carcinoembryonic antigen (CEA) levels even in its premalignant phase, to normalize only after successful management [14-16]. Due to associated fibrosis, radiotherapy was of little benefit, used only as a neoadjuvant in operable cases [12,17-20]. Patients with organ confined tumors were best treated by cystectomy with urinary diversion offering the greatest prospect for cure with minimal locoregional recurrence. The 5-year survival rate approaches 33 % regardless of the histological type, being linked more to the disease stage and/or tumor grade [17,18]. Fortunately, recent epidemiologic studies indicate that bladder cancer prevalence in Egyptian population has declined dramatically in the last 2 decades, matching a similar drop in the incidence of the mother disease bilharziasis, thanks to the social and environmental developments in the country. This fall was briskly reflected on the embedded classical features of this domicile bladder tumor causing a striking change [21].

Patients and methods

The current research proposal has been reviewed and approved by the Ethics Committee of Cairo University Hospitals (CUHs), and

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the work was conducted from January 2011 through February 2013, Ccarcinoma of the bladder in Egypt is much more common in males than in females. This is particularly true for the post bilharzial type, where it affects men in rural areas where the water fresh water snail *Bolinus Truncatus* (the intermediate host) lives. incorporating 102 nonsmoking Egyptian subjects: 90 males and 12 females, having mean age 48 (range 40-65) years. All patients signed a written informed consent. Inclusion criterion was the presence of verified bladder carcinoma. Exclusion criteria were: presence of systemic metastases, diabetes mellitus, blood urea above 80mg/dl, creatinine above 2mg/dl, gross liver disease (or elevation of its enzymes), impaired coagulation factors and history of operations on the urinary tract for any reason. Cystoscopy (& biopsy), CT urogram, and chest x-ray were routinely carried out, while bone scan was limited to patients having raised alkaline phosphatase [22]. Subsequently patients were distributed over 2 groups based on the intended treatment modality: group A (Bilharzial bladder), 66 patients set aside for surgery and group B (Non Bilharzial bladder), 36 subjects were subjected to transurethral resection, then handled to the radiotherapist (TURBT). The indications for cystectomy (radical, total or partial) in group A patients were superficial tumors having large size, and large infiltrating ones placed at the bladder base [23]. At NAMROK nuclear medicine center of CUHs, radiotherapy was given to group B patients. The accelerated x- ray beams (energy 6-15 MV) were focused on the bladder, targeting the tumor area harboring radiosensitive microscopic residue, cautiously sparing the surrounding normal tissues. Doses delivered were 52.5-55 Gy in 20 daily fractions over 4 weeks. In basal tumors the prostatic urethra was included to minimize local recurrence. To boost the effect of radiotherapy, concomitant cisplatin radio sensitization was constantly given. BCG installations into the bladder followed radiotherapy in patients left with *in situ* lesions.

Results

Group A cases had their tumors occurring in a bilharzial bladder where walls demonstrated one or more of the classical cystoscopic features of the disease. Histologically, 36 cases were differentiated SCC and the remaining 30 were TCC. Group B cases had their tumors

in a non-bilharzial bladder, 30 of them were histological TCC and the remaining 6 were SCC. For group A patients: one stage radical cystectomy with rectal bladder was carried out for 39 males, total cystectomy for 3 cases holding a domal tumor, and partial cystectomy for the remaining 22cases. Group B patients received radiotherapy (Table 1).

Discussion

After many years of struggle, the incidence of bilharziasis in Egypt has dramatically dropped, particularly over the last 2 decades, and new infestation is now almost eliminated [1,24]. Concomitantly, a spectacular change in the epidemiology and makeup of the intimately bound bladder carcinoma was observed, acquiring a new look, that was fully described by contemporary researchers [1972- 2012] [21]. Moreover there is a significant increase in TCC from 20% to 66%, with a paradoxical decline in SCC from 73% to 25%, without remarkable differences in the tumor stage, grade or incidence of lymph node metastasis [21,23,25]. However, uncertainty was constantly present whether these new features represent an everlasting change in the inherent properties of the tumor requiring a change in treatment strategy, or stillness is required for some time? Results extracted from the present work demonstrated that this inclination is still manifest. The relative frequency of SCC in enrolled patients slump to 41.1% and TCC climbed to 58.9% (Table 2 and Figure 1), associated with a change in the cystoscopic gross features of the tumor to brands not commonly seen before; like the flat (*in situ*), superficial and the noninvasive papillary types. These varieties embrace a significant hint, and are well meaning: Egyptian urologists have to change their treatment guidelines, keeping untouched the 3 inventive objectives: cure, prevention of local, pelvic or systemic recurrence and preservation of both urinary & sexual functions. In the mean time reconsideration of the criteria of what was considered locally advanced tumors is mandatory: massive and fixed lesions are not exclusively a neoplasm, but an alloy of granulomatous, fibrous and neoplastic components. Labeling these tumors (in the past) as locally advanced was inaccurate and deprived patients from appropriate surgery in the proper time [4].

With time, results of surgery have even improved more and

Gr	Urinary Bladder	No	Bilharzial Imprint						Tumor Description													Treatment Modality	
			SP	C	BNS	St	Cg	p	Site					Gross					Microscopic			Surgey	Radio
									PW	AW	B	LW	V	U	P	F	FI	Is	TTC	SCC	invasion	66	
A	Bilharzial	66	42	9	6	3	3	6	30	12	12	6	6	36	6	21		3	30	36	42		
B	Nonbilharzial	36									12	12	12		12	3	9	12	30	6			
														Size (5-10 cm)					n=60 n=42			N=66 n=36	

Table 1: Carcinoma of the Urinary Bladder in Egyptian Population: Findings in the Present Series, Cairo, Egypt, 2011-2013, Kasr Al-Aini University Hospitals, From January 2011 Through February 2013, Total Number 102, Mean Age 48 Years, Sex: 90 males and 12 females.

Study	Year	Pt.No.	Cell Type			% SC
			SCC	TCC	Ad	
Khafagy et al [6]	1972	86	66	18	2	76.7
El-Boulkainy et al [9]	1972	229	All			100
Hussein et al [26]	1975	162	111	42	9	68.5
Ghoneim et al. [10]	1985	126	83	27	16	65.9
Saied & Khalil [4]	1987	22	all			100
Saied et al [14]	2007	43	22	21		51.2
Salem & Mhfouz [21]	2010	1932				25.0
Present Series	2013	102	42	60		41.1

Table 2: Carcinoma of the Urinary Bladder in Egyptian Population, Tracing of 8 Egyptian Studies in 4 Decades (1972 – 2013).Total Number 2702 Patients, Showing Decreasing Frequency of Squamous Cell Carcinoma in Contrast to Increasing Frequency of Transitional Cell Carcinoma.

more owing to advances in surgical techniques, availability of blood transfusion, major improvement in anesthesia, formulation of new antimicrobials and evolution of intensive care medicine [24,26,27].

Moreover, radiotherapy, the lone adequate alternative to operation, had a weak effect on such a tumor which is overwhelmingly SCC, with extensive local fibrosis [4,22,26,28,29] (Table 2). Unfortunately, both operation and radiotherapy were associated with a non negligible incidence of impotence and/or ejaculatory problems caused via different complex mechanisms. This can't be avoided by autonomic nerve preservation at surgery, or by their protection from fibrosis induced by radiation therapy [30].

Patients undergoing cystectomy must be willing to accept urine diversion or be rewarded by building up of an orthotopic neobladder. Recently, serious trials thinking about the development of a neo-urinary conduit seeded with autologous smooth muscle cells are going on, and may potentially eliminate the complications associated with the current schemes and greatly facilitate recovery from operation [31-34]. Despite the earlier traditional concept that considers cystectomy as the best and safest management technique in this country; many workers now feel uncertain of this. This uncertainty might explain the ongoing drop in practicing this operation from almost 100% in the sixties and seventies to 65% in this study, substituted by radiotherapy with equal treatment end-results regardless of the presence or absence of bilharziasis [8,9,22,35-42] (Figure 2).

Nowadays, cystectomy having a mortality less than 2%, is only designated for cases having muscle-invasive tumors, or those refractory to cystoscopic resection or involving the prostatic urethra, and also rationally for palliation of pain, bleeding, or intolerable frequency [29,30]. In the meantime, partial cystectomy, a procedure currently

gaining some acceptance, is a safe alternative to total cystectomy with no survival disadvantages particularly if potentiated by radiotherapy.

In fact, and regardless of the lack of consensus, and absence of controlled studies, we believe that a properly performed partial cystectomy (with negative resection margins) is adequate for a solitary tumor situated at a surgically amenable location in the bladder and having favorable pathologic features. The operation has additional undeniable merits: shorter operating time, absent need for urine diversion or bladder augmentation, and low postoperative morbidity & mortality [43]. It also requires less hospitalization and provides a better quality of life, with no stoma, incontinence or impotence. However, we always keep in mind that in none of the cases treated by this way, were explicit details given in modern literature regarding criteria of safety margins and lymph node dissection. At the same time, adequate definition of the exact surgical procedure in every case is not clear, lacking too, any appropriate quality control. Therefore, the question still to be answered is whether a further improvement can be obtained by adjuvant therapy or not? Indeed, home researchers are unquestionably conscious about the promising results of treating patients with a bimodality approach consisting of systemic chemotherapy followed by partial cystectomy, expecting to have a 16-33% lower risk patients dying of their disease due to locoregional recurrence opposed to surgery alone [24]. A third treatment option is radiotherapy alone, a modality avoided in the past in the absence of any prospective randomized trials comparing its results with cystectomy. Recently, this conflict has changed and a large sector of our patients at present, have received radiotherapy with curative intent.

Simultaneously there is a decline in patients treated by cystectomy alone, after too many years of unmatched first-rate reputation [44]. Fortunately novel irradiation techniques and new-generation drugs are currently being tested in an attempt to improve disease control interval,

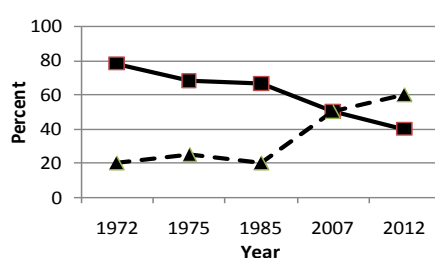


Figure 1: Carcinoma of the Urinary Bladder in Egyptian Population (40 Years Tracing: 1972-2012). The Formerly Predominant Squamous Cell Carcinoma Type (Line) is Lowering With Concomitant Rise in Transitional Cell Carcinoma Type (Dashed). Meeting Point at Year 2007, Overturned After and Clearly Noticeable at 2012.

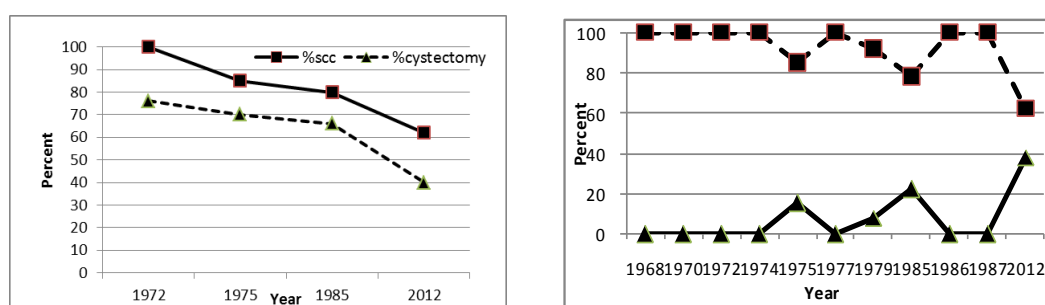


Figure 2: Carcinoma of the Urinary Bladder in Egyptian Population (44 Years Tracing: 1968-2012).

- a) The Decreasing Frequency of Squamous Cell Type (scc), Coincided With a Parallel Decrease in Frequency of Performing Cystectomy as a Primary Treatment .
 b) The Decrease in Performing Cystectomy (Dashed) Coincided With A Concomitant Increase in Using Radiotherapy (Line).

one of them is to combine radiotherapy with intravesical installation of chemo or immunotherapy [45,46]. At the same time, radiotherapists today are more enthusiastic, and care to administer a large treatment volume to involve generous margins, working against organ motion [47]. In fact Fellin and his colleagues in 1997 reviewed their patients having TCC and found only half of them responded adequately to cisplatin sensitized radiotherapy, while non responders (34%) were candidates of immediate cystectomy with no treatment-related deaths in both categories [42]. Conversely, the results of the present work clearly point to better results if radiotherapy and minor surgery were combined. This Triple- sequence therapy (TURBT, radiation, and systemic chemotherapy), is particularly appropriate for patients not willing to do surgery, or unable to do it due to comorbidities. It carries a lower 5-year survival rate compared to cystectomy, embracing at the same time the advantage of slipping back to radical surgery if recurrence occurs at anytime [43]. This recurrence is sometimes so difficult to treat, calling for stronger methods for surveillance and prevention. An easy, cost effective and up-to-date method is the thrice per year monitoring of urinary CEA level for at least 2 years supported by annual cystoscopy. Two consecutive elevations after successful management reflect the likelihood of recurrence, correlating at the same time with the recurring tumor volume. Following its introduction, urinary CEA determination soon became the gold standard for detecting recurrence particularly for the postbilharzial type, and should remain the primary modality used [14].

Conclusion

Egyptian urologists have to follow new guidelines for treatment of domicile bladder carcinoma. The disease is shifting more and more towards the western types, and turned suitable for organ preserving management policy. Triple sequence therapy may be offered as a safe and reasonable alternative to patients not willing to do cystectomy [48].

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