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 urethera 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...
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 in situ lesions. 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 normal tissues. Doses delivered were 52.5-55 Gy in 20 daily fractions (in situ), (in situ superfical 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
more owing to advances in surgical techniques, availability of blood transfusion, major improvement in anesthia, 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 radiotherapy [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 potenitated 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,
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 splitting 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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