Review

Bladder cancer and schistosomiasis

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Abstract Schistosoma-associated bladder cancer was believed, for several decades, to be a completely unique entity of disease, different from urothelial cancer. This was probably due to its distinct clinicopathologic and demographic features that varied from those of urothelial entity. The carcinogenesis is an extremely complex process resulting from the accumulation of many genetic and epigenetic changes leading to alterations in the cell proliferation regulation process. In bladder cancer, many of these carcinogenic cascades were not fully documented or somewhat conflicting. Inspite of the efforts performed, much is still needed to explore the presence or absence of the carcinogenic difference with a different etiology. The control of schistosomiasis in certain countries and the subsequent decrease in the intensity of infestation showed changing of features approaching that of urothelial tumors. However the schistosoma-associated bladder cancer presented in more advanced stages than schistosoma-non associated urothelial cancer. More recently, data are gathered that, upon applying the same treatment protocol and management care, stage by stage comparison of the treatment end-results were found to be similar in bladder cancer patients with a different etiology. All treatment options; including radical cystectomy with or without adjuvant or neoadjuvant chemo- or radiotherapy or trimodality bladder preserving treatment seem to lead to similar end-results regardless of etiologic factor(s) implicated in bladder cancer development.

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Schistosomiasis Hematobium and its relation to bladder cancer

Introduction

Bladder cancer is an important worldwide health problem with a global estimate of 386,300 new cases and 150,200 deaths in the year 2008. The majority of bladder cancer occurs in males and there is a 14-fold variation in incidence internationally. The highest incidence rates are found in the countries of Europe, North America, and Northern Africa [1]. It is estimated that one in 26 males and one in 87 females in USA will develop bladder cancer during their life time [2]. Smoking and occupational exposure are the major risk factors in Western countries, while chronic infection with Schistosoma Hematobium (SH) in developing countries, particularly in Africa and the Middle East, accounts for the main total burden [3].

Superficial (non-muscle invasive) category represents the majority of bladder cancer population while around 20–40% of the patients will present with or subsequently develop invasive cancer. Bladder cancer is morphologically heterogeneous; more than 90% of bladder cancer cases are urothelial (UC, transitional cell, TCC) carcinoma, whereas primary squamous cell carcinoma (SCC), adenosquamous, small cell carcinoma and other rare tumors are less common [4]. Urothelial cell carcinoma may present in a mixed form with other malignant components including squamous differentiation (present in 20–60% of bladder cancer cases), adenosquamous or glandular differentiation (10%), sarcomatoid (7%), micropapillary (3.7%) and lymphoepithelioma-like carcinoma. In many developing countries, life expectancy is much lower than in western countries, which may lead to a lower BC incidence (not age-specific incidence) in these developing countries [2]. Bladder cancer is associated with substantial morbidity and mortality. History of Tobacco smoking not only increases the incidence of BC, but also it can increase the tumor grade, its size and the tumor number [5]. Chronic schistosomal cystitis was related for a long period to the development of BC in areas endemic for schistosomiasis like Egypt. In these areas, risk factors are many, including exposure to schistosomiasis, increased smoking rate and exposure to many carcinogenic chemicals [6].

There was an increasing incidence of bladder cancer, in spite of the reduction in smoking in the United States, this suggests that other environmental factors may be playing an increasing role in the development of this cancer. Contrarily, there was a 5.14% decrease in the death rate due to bladder cancer in USA, between 1990 and 2007 [2], due to the success in management.

Bladder cancer formation

Urothelial tumor is characterized by its multifocality. The modern carcinogenesis model suggests that malignancy represents clonal expansion of one or a few cancer stem cells that proliferate through asymmetric differentiation and can diversify into heterogeneous cancer cell lineages. Following cell division, one daughter cell retains the capacity to divide again and the other daughter cell possesses genetic plasticity, allowing phenotypic variation in the offspring. When tumors arise from Chromosomal Somatic Changes (CSC) of progenitor cells, a specific set of genomics, epigenomic and/or microenvironment niche alterations is essential for continued clonal expansion. Therefore, each CSC and its pro/zaxgency possess a unique set of genetic, epigenetic and phenotypic features. Genetic alterations of stromal somatic cells assist CSCs in the niche to promote cancer development and progression [7].

Schistosomiasis Hematobium and its relation to bladder cancer

According to the World Health Organization (WHO), schistosomiasis infect 200 million people and is endemic in as much as 76 tropical developing countries. Schistosomes are parasitic blood flukes, which have a mammalian host and an intermediate invertebrate host: fresh water snails [8,9]. There are four human schistosomes: S. haematobium, Schistosoma Mansoni, Schistosoma Japonicum, Schistosoma Mekongi. S. Haematobium (SH) is the one associated with bladder cancer. The SH, like other schistosomes is dioecious as the adult female lives in-copulo in the gynecophoral canal of the male; and lives in the venules of the human urinary bladder. Eggs laid in the urinary bladder produce irritation and tissue fibrosis, that may contribute to the development of human carcinogenicity [10].

All schistosoma infections follow direct contact with fresh water that harbors free-swimming larval forms of the parasite known as cercariae. Cercariae penetrate the skin. The cercariae shed their bifurcated tails, and the resulting schistosomula enter capillaries and lymphatic vessels en route to the lungs. The worms migrate to the portal venous system, where they mature and unite. Worms then migrate to the vesical plexus and veins
draining the ureters. Egg production starts few weeks after infection and continues for 3–5 years. Eggs pass from the blood vessels lumen into adjacent tissues, and then through the bladder mucosa to shed in the urine. The life cycle is completed when the eggs hatch; releasing miracidia that, in turn, infect specific fresh water snails (Bulinus species). After two generations—primary and then daughter sporocysts, within the snail, cercariae are released [11].

Schistosomiasis was first linked to urinary bladder cancer by Furgesson in Egypt in 1911 [12]. The incidence of urinary bladder cancer in the Middle East and Africa is greater in areas with high rather than low SH prevalence. The overall prevalence of SH infection in Egypt was 37–48% that decreased due to the antibilharzial campaign to 3% [13]. The urinary bladder cancer previously accounted for about 31% of the total incidence of cancers in Egypt that subsequently decreased to 12% in recent years [14]. There are several factors that may contribute to the oncological potential of schistosomiasis infection. The ova deposited in the bladder provoke an intense inflammatory reaction, associated with the production of oxygen-derived free radicals, which may induce genetic mutations or promote the production of carcinogenic compounds (such as N-nitrosamines and polycyclic aromatic hydrocarbons) [15,16], leading to malignant transformation. It is known that schistosomiasis is often accompanied by chronic bacterial super-infection, which may in itself predispose to squamous cell (SC) neoplasia [17]. Bacteria that usually accompany schistosomiasis can promote the formation of N-nitrosamines. International Agency for Research on Cancer (IARC) found that the intensity of infection is determined by urinary egg counts and compounded by smoking, and the combination was strongly considered. Positive association between bladder cancer and SH infection was detected, with odd ratios ranging from 2 to 14 [18].

Pathology of schistosomiasis and SA-BC

The pathological findings of schistosomiasis are mainly due to inflammatory and immunological responses to egg deposition. Granulomatous areas form around the eggs and induce an exudative cellular response consisting of lymphocytes, polymorphonuclear leukocytes and eosinophil. The peri-oval granulomas, fibrosis and muscular hypertrophy are detected histologically. In the urinary bladder, masses of large granulomatous inflammatory polyps containing eggs are found at urinary bladder walls. Polyps may ulcerate and slough, producing hematuria. Bladder ulcers, sandy patches, irregularly thickened or atrophic bladder mucosa, fibrosis and granulomas containing calcified or disintegrated eggs were also seen [19]. The response to egg deposition could lead to calcification of the urinary bladder, infection, stone formation and mucosal proliferation [20].

Carcinogenesis of chronic schistosomal infection

Efforts have been made to study the specific genes involved in the induction of SA-BC. Cell exposed to SH cell total antigen (worm extract) was found to divide faster than those not exposed to the antigen and died much less, probably due to the increased level of bcl2 [21]. Murine urothelium exposed to SH total antigen showed dysplasia, low grade intra-urothelial neoplasm, non-invasive malignant flat lesions in 70% of the tested mice. Bladder carcinoma harbors gene mutations that constitutively activate the receptors tyrosine kinase Ras pathway [22]. Botelho et al. [23] suggested that the parasite extract has carcinogenic ability possibly through oncogenic mutation of Kras gene.

Among the most common genetic changes in bladder cancer is the loss of heterozygosity (LOH) on chromosomes 9p and 9q, which is found regardless of tumor grade and stage [24,25]. No line of demarcation between schistosomiasis-associated and non schistosomiasis-associated bladder cancer was detected in terms of LOH of microsatellite markers on chromosome 9. This suggests that data obtained from SA-BC can be extrapolated to bladder cancer induced by other etiologic mechanism [26]. Bladder cancer is a very heterogeneous disease cytogenetically, which suggests that the pathogenesis of the disease may not be consistent for every case. The overexpression of the BCL-2 gene in SA-BC patients was found to be up-regulated in squamous but not transitional cell cancers. Therefore, this BCL-2 overexpression is consistent with the predominance of SCC in SA-BC. Mutations of TP53 were detected in 73% of tumors, BCL-2 expression in 32% and abnormalities of both TP53 and BCL-2 in 13% [27].

Furthermore, cyclooxygenase-2 is overexpressed in SA-BC. The cyclooxygenase-2 role in the complex multi-stage process of SA-BC carcinogenesis was proposed: pro-inflammatory cytokines such as interleukin-1, tumor growth factor-B and tumor necrosis factor-alpha. H-RAS, deletion of p16 and p15, increased epidermal growth factor receptor, c-erb-2 and tumor necrosis factor-alpha are additional mutation reported. These changes increase tumorigenicity by decreasing cell apoptosis and/or creating immunosuppression. Prostaglandin products of cyclooxygenase-2 cause tumor progression and eventual metastasis by down-regulating adhesion molecules, increasing the degradation of extracellular matrix and increasing angiogenesis [28].

Schistosoma-associated bladder cancer (SA-BC)

The association between SA-BC and SH was initially established through case-controlled studies and through the close correlation of the incidence of bladder cancer with the prevalence of SH within different geographic areas. The association was based on the frequent association of tumors with the presence of parasitic eggs and egg-induced granulomatous pathology involving bladder tissues. However, there is yet, no clearly defined cellular mechanisms linking SH infestation with bladder cancer formation.

SA-BC was known by characteristic pathology (i.e. squamous carcinoma, transitional cell carcinoma, or adenocarcinoma, rather than predominantly transitional) and cellular and molecular biology that may differ from non-schistosoma-associated bladder cancer (NSA-BC). The cytogenetic and molecular genetic abnormalities were scarcely studied in SA-BC. Some compared DNA copy number changes in SA-BC and NSA-BC [5,6,29,30]. Muscheck et al. [5] demonstrated deletion similarities in Schistosoma-associated transitional cell carcinoma (SA-TCC) and Schistosoma-associated squamous cell carcinoma (SA-SCC), compared to what has been previously reported by Kallioniemi et al. [6] on SNA-TCC and Tsutsumi et al. [29] on SNA-SCC. Armengol et al. [30] in pools
of tissue arising from patients having similar pathological subtypes revealed recurrent primary changes that prevail in each subtype. The pooled specimens of SA-BC tumors showed no schistosomiasis specific changes, compared with pools of NSA tumors. The comparison between SA-TCC and SNA-TCC and that between SA-SCC and SNA-SCC were similar. DNA copy number profiles of urinary bladder SA adenocarcinoma revealed similarities to those of SA-TCC and SA-SCC [32]. Detailed individual gene analysis revealed a set of genes with the same copy number changes in all bladder carcinomas, including both SA and SNA tumors. There were no major cytogenetic differences among different urinary bladder epithelial tumors, regardless of the suspected predisposed carcinogen [31]. Abnormalities in chromosomes 1, 3, 5, 7, 9 and 17 are the most frequently involved chromosomes in urothelial bladder cancer [33]. In a recent study Aly et al. [35] using FISH technique proved changes in SA-BC. This was previously detected using CGH technique in SA-BC together with aberrations in chromosomes 3, 4, 5, 6 and 11 [4,34]. It was found that the most commonly found chromosomal deletions in all stages in SA and SNA-BC involves deletions in chromosome 9 [24,25,35], resulting in the loss of three gene encoding proteins that activate the Rb and P53 tumor suppressor pathways. Furthermore, chromosome 9 harbors the TSCI tumor suppressor that down-regulates the antiapoptotic Akt/mTOR pathway [36]. Therefore, deletions on one chromosome may have a crucial influence on the initial steps in tumor development. Furthermore, these mutations may overactivate the fibroblast growth factor receptor 3 protein, which likely directs bladder cells to grow and divide abnormally leading to the formation of bladder tumor [35]. This suggested that cytogenetic profiles of chemical- and Schistosoma-induced carcinoma are largely similar [5,30,31]. The decreased intensity of schistosomal infestation in Egypt led to a changing pattern of the clinicoepidemiologic features of SA-BC. The reported clinicoepidemiologic differences between SA-BC and SNA-BC are now continuously minimizing and the features of SA-BC are slowly approaching those of SNA-BC as reported by Koraitim et al. [37] and Zaghloul et al. [38]. If these changes continue, SA-BC is expected to become identical in features to that of western countries SNA-BC [4,38,39].

Prognostic influence of chromosomal aberrations

The prognostic value of these aberrations was not totally clear. One study denoted a prognostic value for chromosome 4 abnormalities [35]. However, the whole genome analyses showed that low stage low grade tumors generally show fewer changes than higher stages and grades. Furthermore, several genomic alterations were shown to be highly specific for more aggressive tumors. Morphologically normal urothelium in bladder cancer patients frequently show the same type of genomic alterations as the tumor itself. This makes an issue of to what extent information on genomic changes will produce reliable prognostic information [35].

Clinical presentation

Clinical presentations in SA-BC and SNA-BC are similar with few minor differences. Hematuria, dysuria and necroturia are the main symptoms in both situations. However, SA-BC patients usually had previous history of such symptoms as a result of simple schistosomal cystitis and this may be the reason of their relatively late presentation. The early stages (Pa, Pis, P1) were fewer in SA-BC than those in SNA-BC (urothelial and non-urothelial). The pelvic nodal involvement was nearly similar in SA-BC (range: 16.7–25.5%), urothelial SNA-BC:

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patients #</th>
<th>PT1</th>
<th>PT2</th>
<th>PT3</th>
<th>PT4</th>
<th>Nodal Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNA-BC (Pure Urothelial Carcinoma)</td>
<td>Cheng et al. [46]</td>
<td>218</td>
<td>—</td>
<td>50</td>
<td>28</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Stein et al. [60]</td>
<td>1054</td>
<td>74</td>
<td>81,68</td>
<td>47</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Medersbacher et al. [100]</td>
<td>507</td>
<td>76</td>
<td>62</td>
<td>40</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Takahashi et al. [63]</td>
<td>466</td>
<td>81</td>
<td>74</td>
<td>47</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Dhar et al. [91]</td>
<td>385</td>
<td>—</td>
<td>63</td>
<td>19</td>
<td>NM</td>
</tr>
<tr>
<td></td>
<td>Ho et al. [101]</td>
<td>148</td>
<td>77</td>
<td>68</td>
<td>65</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Manoharan et al. [92]</td>
<td>432</td>
<td>79</td>
<td>60</td>
<td>43</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Abdollah et al. [93]</td>
<td>11697</td>
<td>80</td>
<td>—</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Lughezzani et al. [94]</td>
<td>11260</td>
<td>61</td>
<td>57</td>
<td>49</td>
<td>47</td>
</tr>
<tr>
<td>SNA-BC (Urothelial &amp; Non-urothelial)</td>
<td>Nishiyama et al. [95]</td>
<td>1113</td>
<td>82</td>
<td>84,69</td>
<td>59</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Niu et al. [96]</td>
<td>356</td>
<td>—</td>
<td>73,44</td>
<td>22</td>
<td>0</td>
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<tr>
<td></td>
<td>Gupta et al. [48]</td>
<td>502</td>
<td>90</td>
<td>78</td>
<td>70,58</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Abdollah et al. [93]</td>
<td>614</td>
<td>75</td>
<td>—</td>
<td>53.7</td>
<td>53.7</td>
</tr>
<tr>
<td>SNA-BC (Urothelial &amp; Non-urothelial)</td>
<td>Ghoneim et al. [52]</td>
<td>1026</td>
<td>73</td>
<td>66</td>
<td>47,31</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>El Mekresh et al. [97]</td>
<td>185</td>
<td>83</td>
<td>—</td>
<td>41</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Khaled et al. [98]</td>
<td>180</td>
<td>55</td>
<td>—</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Zaghloul et al. [73]</td>
<td>192</td>
<td>100</td>
<td>100,47</td>
<td>40</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Zaghloul et al. [99]</td>
<td>216</td>
<td>100</td>
<td>51</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Ghoneim et al. [53]</td>
<td>2720</td>
<td>82</td>
<td>75,53</td>
<td>40</td>
<td>30</td>
</tr>
</tbody>
</table>

* = a/b, NM = not mentioned.
BC (range: 16.3–45%) and non-urothelial SNA-BC (21.8–23%). The clinicopathologic differences between SA-BC and SNA-BC were previously summarized as: late presentation, younger median age and a higher percentage of squamous cell carcinoma [40]. Distant metastases are similar in SA-BC and SNA-BC including the different histopathological variants. In a study that included 357 SA-BC patients, the 5-year incidence of distant metastasis was 23%. The 5-year actuarial incidence of distant metastasis varied according to the tumor cell type. Squamous cell carcinoma led to a distant metastasis incidence rate of 15% at 5 years compared to 39% for TCC and 58% for adenocarcinoma. Although the difference was statistically significant on univariate analysis it was not statistically significant when multivariate analysis was applied [41]. Similarly, the incidence of distant metastasis in urothelial cancer ranged from 12% to 35% [42,43].

Loco-regional recurrence with or without distant metastasis was found in 5–31% of the patients treated with RC, depending on their pathological and clinical features [44]. Factors associated with local recurrence are mostly the same as those determining distant metastasis, namely pathologic tumor stage, grade and regional nodal involvement together with the lymphadenectomy extent. Rates of local recurrence were reported in SNA-BC as 6, 18 and 51% in patients with stage pT1, pT2 and pT3, respectively [44]. Another SNA-BC study showed that the 5-year local recurrence rate reached 11, 23 and 31% for stages II, III and IV, respectively [45]. In a third study, the 10-year local recurrence rate was reported to be 25% for pT3, 51% for pT4 and 49% in node-positive patients [46]. Volkmer et al. [47] showed that the 10-year recurrence rate was 48.6%. Out of the relapsed 41% developed local recurrence and 324 (73%) had distant metastasis at the time of first relapse [47]. On the other hand, Gupta et al. reported 29% (145/502) who underwent RC developed recurrence [48]. Of these, 40 (27.6%) patients developed local pelvic recurrence and 105 (72.4%) developed distant metastasis. Similar results of loco-regional recurrences were repeatedly reported in SA-BC [49–53].

Treatment of non-muscle invasive bladder cancer

Non-muscle-invasive bladder cancer comprised Ta (confined to the mucosa) T1 (invades the lamina propria) as well as flat high grade tumors that are confined to the mucosa Tis or CIS). The molecular biology techniques and clinical experience demonstrated the highly malignant, invasive potential of Tis and T1 lesions. Therefore, the term non-muscle invasive or superficial bladder cancer is suboptimal description [54]. Complete and correct TURBT (contains the complete tumor plus a part of the underlying bladder wall), is essential for treatment [55]. Random biopsies from normal-looking mucosa should be performed in patients with positive urinary cytology and absence of visible tumor. A second TUR should be considered when the initial resection is incomplete [56]. Adjuvant treatment depends upon risk group classification (low, intermediate and high). This risk classification determines progression, motality and recurrence rates. There is strong evidence that one immediate intravesical chemotherapy instillation significantly reduces the risk of recurrence in TaT1 tumors. Mitomycin C, epirubicin and doxorubicin showed beneficial effect and none of them is superior to the others [54]. The choice between further chemotherapy or immunotherapy (BCG) instillation depends largely on risk status. For intermediate and high-risk tumors adjuvant BCG proved to be superior to chemotherapy for tumor recurrence prevention [57]. Although this treatment type is very popular in urothelial cancer, it is less popular in SA-BC and non-urothelial SNA-BC. This may be due to the prevalence of many precancerous or cancerous lesions in the bladder mucosa, and the fewer number of non-invasive stages in these patients [58].

The European Association of Urology (EAU) [54] advocated cystectomy for multiple recurrent high-grade tumors, BCG treatment failures, high-grade T1 and high-grade tumors with concurrent CIS. Delay of cystectomy in these patients might lead to decreased disease-specific survival [54]. Ali-EL-Dien et al. [59] confirmed the value of this recommendation in 204 urothelial cancer patients including SA-BC and NSA-BC.

Treatment of muscle-invasive bladder cancer

Radical cystectomy

Muscle-invasive bladder cancer is mostly treated with radical cystectomy in many parts of the world. Radical cystectomy procedure includes removal of the bladder, seminal vesicles and prostate together with perivesical fat and peritoneal coverage, in addition to the varying level of pelvic lymphadenectomy in male patients. In females, it includes removal of the bladder, its perivesical fat and peritoneal coverage, urethra, uterus, ovary and anterior wall of the vagina (anterior pelvic exenteration) [52,53,60]. Reviewing recent literature of treatment end-results of different bladder cancer categories; showed that applying the same treatment yielded nearly the same level of results in the same pathological stage [51,61]. The 5-year overall survival rates were similar in SA-BC, pure urothelial and combined urothelial and non-urothelial SNA-BC types. The results were slightly higher in Stein et al. [60] (NSA-BC) and Zaghloul et al. [51] (SA-BC) probably due to adding neo-adjuvant or adjuvant radiotherapy and /or chemotherapy in more than one third of their patients (see Table 1). The same conclusion applies for a comparison of disease-free survival, overall survival, or local control rates for radical cystectomy or even in adjuvant and neoadjuvant radiotherapy types of treatment for SA-BC and SNA-BC [51,61]. The treatment end-results of radical cystectomy was not affected by the association with schistosomiasis, nor tumor cell type (urothelial or non-urothelial) in most published literature [51,60,62]. These results were constant for both SA-BC (ranged from 47% to 83%), and SNA-BC (ranged from 50% to 84%) and significantly worse when reporting upon locally advanced tumors (PT3N0M0, PT4aN0M0 or Any N). These worse results were experienced by both SA-BC and SNA-BC patients [51,60,62,63]. In spite of the old belief that aberrant differentiation leads to worse results, yet many authors reported similar results of these variants to UC when comparing stage to stage. Rogers et al. [64] reported a 5-year progression-free survival rate of 60 ± 2% after radical cystectomy for UC and 55 ± 11% for SCC. This difference was not statistically significant. Patients with UC or SCC had statistically significant higher progression-free survival rates than non-UC non-SCC patients including those having adenocarcinoma. A second study containing a considerable number of adenocarcinoma...
patients was conducted using 17 Surveillance, Epidemiology and End Results (SEER), showed no difference of statistical significance in adenocarcinoma patients who underwent RC than their UC counterparts. A third study using a similar SEER database demonstrated that SCC was more aggressive than urothelial cancer after adjusting for common prognostic factors, such as stage and grade [65]. Scosyrev et al. [65] concluded that SCC was an independent predictor of mortality among patients with stages III and IV disease, and among patients with stages I and II disease who did not undergo cystectomy as part of their treatment. Therefore, squamous histology per se was not associated with increased mortality among patients with stages I and II disease when treated with cystectomy. Furthermore, Ploeg et al. [66] studied all invasive bladder cancer cases treated in The Netherlands during a 12 year period. They concluded that the relative survival of muscle-invasive adenocarcinoma patients was equal to that of UC patients. For stages II and III disease, adenocarcinoma patients had even better outcome. Muscle-invasive SCC patients showed worse survival regardless of stage. In SA-BC, Ghoneim et al. [53] demonstrated that SCC (1345 patients) had 10 year overall survival rate (OS) of 53% compared to 48% for pure UC (705 patients) and 51% for adenocarcinoma (262 patients). Those patients who had UC with squamous or adenomatous metaplasia (286 patients) showed a lower 10-year OS of 43%. The lowest 10-year OS was experienced by those patients who had undifferentiated pathology (122 patients) having 10-year OS of 34. It is clear from this large-number single institution study that the OS of SCC, UC and adenocarcinoma were similar and having the same profile as that of SNA-BC. The multivariate analysis proved that tumor cell type is not an independent working factor determining the OS. Many authors cautiously concluded that RC treatment end-results were not affected by tumor histology or etiology but affected by other prognostic factors like stage, grade, nodal involvement, lymphovascular invasion, angiogenesis, P53, P21, Retinoblastoma genes (Rb) and other biological factors. These prognostic and predictor factors were shown in many SA-BC and SNA-BC studies [53,61,65,66].

Preoperative and postoperative radiotherapy

The rationale of preoperative radiotherapy is to prevent intraoperative seeding of tumor cells in the operative field and to sterilize microscopic residue in the perivesical tissues. In the English literature, only six randomized trials addressed the issue of preoperative radiotherapy to RC. Two of these 6 studies were on SA-BC patients [67,68]. Only one [67] out of the 6 trials showed the benefit of preoperative radiotherapy. Most of the other 5 studies revealed that the effect was restricted to high stage and high grade tumors, with no difference in early cases. Meta-analysis of these randomized studies showed a corrected odd ratio of 0.94, indicating absence of benefit for adding preoperative radiotherapy to RC [69].

Postoperative radiotherapy (PORT) has the advantage of dealing with microscopic cells that are easier to sterilize. It allows better identification of the group of patients that may benefit from such adjuvant therapy. One large prospective randomized trial proved the benefit of PORT in locally advanced SA-BC. The 5-year disease-free survival (DFS) rate was 49 and 44% for PORT conventional (CF) and hyperfractionated (HF), respectively compared with 25% for cystectomy alone patients [50]. This effect was constant across all tumor cell type, all muscle-invasive stages and grades in SA-BC. Nearly identical results were replicated in a non-randomized prospective controlled Radiation Therapy Oncology Group (RTOG) trial on SNA-BC [70]. The results of the 2 studies proved to be nearly identical when compared stage by stage [39]. The only difference was that the RTOG trial reported high GIT late complication rate [70]. Intestinal obstruction was reported in 37% (15 out of 40 patients) after PORT. Nine out of these 15 patients required surgery and 3 died. On the contrary, Zaghloul et al. [50] reported 5% and 18% of all grades of late GIT complications for the HF and CF respectively. Only 4% and 5% out of the HF and CF group respectively necessitated surgical interference. Similarly, low levels of late GIT complications were experienced by other retrospective studies reported on SA-BC and SNA-BC [71–73]. This difference between the late GIT complications was related to the difference in radiation volume in different studies and not to association with schistosomiasis [61].

In a prospective randomized trial, Abdel Moneim et al. [74] compared preoperative and postoperative radiotherapy in SA-BC. They administered the same dose of 50 Gy in 5 weeks to both groups. The study reported both similar treatment end-results and similar late complication rates for the pre-and postoperative radiotherapy. The EAU expected that with the availability of recent radiotherapy equipment and techniques allowing for more precise targeting and less damage to the surrounding normal tissues. The EUA and others invite a serious revisit to the option of pre and post-operative radiotherapy [58,74–76].

Neoadjuvant and adjuvant chemotherapy

Neoadjuvant and adjuvant chemotherapy have been utilized in bladder cancer, in an attempt to improve the outcome for patients with high risk muscle-invasive disease. Several meta-analysis indicated that patients who underwent neoadjuvant chemotherapy with methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) prior to cystectomy have a 5.0–6.5% survival advantage over those who underwent surgery alone [77,78]. However, some investigators continue to argue that this neoadjuvant advantage is small and chemotherapy might be better targeted to those at the highest risk of relapse after surgery. Many elderly patients or those having comorbidities will not tolerate MVAC chemotherapy. Therefore, many investigators tried adjuvant chemotherapy in supposing more favorable situation. In reality, adjuvant chemotherapy yielded a modest, statistically significant improvement in the survival of SNA-BC patients over cystectomy alone [79,80].

The Egyptian bladder cancer cooperative group compared neoadjuvant chemotherapy using a more tolerable gemcitabine–cisplatin regimen to cystectomy alone in 109 SA-BC patients. The one-year survival rate was 54% for the cystectomy alone patients compared to 69% for the neoadjuvant chemotherapy patients [81]. However, this difference did not rank to the level of significance.

Bladder preservation trimodality treatment

Since the 1980s, many centers investigated the bladder preservation strategy as an alternative to radical cystectomy. The rationale of this strategy depends on 3 goals: eradication of
the local disease, elimination of potential micrometastasis and maintenance of the best possible quality of life (QoL) through organ preservation [82]. Variable treatment protocols were carried out by different investigators. However, they all comprised 3 essential procedures. The first main procedure is maximal TURBT, to be followed by the second procedure: neoadjuvant chemotherapy or radiochemotherapy and followed by cystoscopic assessment. The third procedure is either consolidation radiochemotherapy for the complete responders or cystectomy. Cystoscopic assessment will segregate the complete responder (CR) for bladder-conserving management and those showing less than CR to undergo salvage cystectomy [83]. The 5-year OS rates ranged between 39% and 58% and the 5-year survival with native bladder preservation ranged from 36% to 43% [83–88]. Sabab et al. [89] reported similar results for UC (SA-BC and SNA-BC) in Egypt using a trimodality treatment. Complete remission was achieved in 79% of cases after initial radiochemotherapy using gemcitabine-cisplatin regimen. The 5-year OS rate for patients with initial CR was 68% which is comparable to that obtained in SNA-BC in the western countries treated with the same modality. Sabab et al. [74] emphasized that the association with schistosomiasis had no significant impact on the results of therapy for their patient. Similarly, Aboziada et al. [90] reached to the same conclusion though in a relatively smaller number of patients and shorter follow up.

Conclusions

With the continuous advancement in health care in schistosoma-endemic areas, the management of SA-BC followed, to a great extent, the recommendations for urothelial tumors. The application of evidence-based recommendations in the management of bladder cancer regardless of its etiology may improve the treatment end-results including the quality of life. The availability of a large number of patients will allow the determination of a recommended risk-adapted therapy that minimizes the under- or over-treatment for such patients.

References


