

Primary Adenocarcinoma of the Urinary Bladder: Risk Factors and Value of Postoperative Radiotherapy

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ABSTRACT

Objective: To evaluate the clinical presentation and treatment outcome of primary adenocarcinoma of the urinary bladder, to determine the significant prognostic factors and to evaluate the value of postoperative radiotherapy as an adjuvant treatment.

Patients and methods: Out of 2787 cystectomized patients, 142 had adenocarcinoma of the urinary bladder with a relative frequency of 5.1%. Most of these patients (67.6%) presented in late stages (P₃ + P₄, UICC 1997). The incidence of pelvic lymph nodes involvement was 23.2%. Mucinous adenocarcinoma was reported in 21 patients (14.8%), papillary in 16 patients (11.3%), signet ring in 10 patients (7%), while not otherwise specified (NOS) was reported in 95 patients (66.9%) in the cystectomy specimens.

Results: Mucinous and signet-ring histological subtypes showed increased frequency of high stages and high grades and more nodal involvement than the papillary and NOS. All patients were treated with radical cystectomy and pelvic lymphadenectomy with (46 patients) or without (96 patients) postoperative radiotherapy (PORT). The 5-year disease-free survival (DFS) rate was 46.6±5.0% for all adenocarcinoma patients. Postoperative radiotherapy improved the DFS, though it did not reach to the level of significance ($p = 0.06$). The 5-year DFS rate for PORT group was 56.7±7.5% compared to 38.2±6.1% for cystectomy alone group. The difference was more apparent ($p = 0.01$) when we compared patients whom PORT was indicated (P_{2b}, P₃, P_{4a}) as cystectomy alone in such patients attained 24.2±9.0% 5-year DFS rate. PORT improved local recurrence significantly as the 5-year local control rate dropped markedly from 97±2.8% for PORT to 55.9±7.4% for cystectomy alone patients. Distant metastases were the leading cause of death in PORT group probably due to the short survival after local recurrence.

Conclusion: Within the limitations provided by retrospective studies, we can conclude that PORT improved the DFS through its effect on local control. The DFS independent prognostic variables were: tumor stage, PORT, nodal involvement and adenocarcinoma subclassification.

Key Words: Urinary bladder neoplasm - Adenocarcinoma - Adjuvant radiotherapy - Prognostic factors.

INTRODUCTION

Adenocarcinoma of the urinary bladder is classified according to its origin into 3 categories: primary, urachal and metastatic [1]. The reported incidence of primary adenocarcinoma was 0.5-2% [2]. However, it is more frequently encountered in areas where bilharziasis is endemic. This incidence ranged between 5-11.4% [3-6]. Metaplastic changes of potentially unstable urethelium were considered as the causative factor for development of adenocarcinoma of the urinary bladder [7]. It was proposed that the metaplastic potential of the urethelium has two distinct patterns [8]. Progressive invagination of hyperplastic epithelial buds into the lamina propria (Von Brunn's nests) leads to the formation of cystitis cystica. Subsequently, metaplasia of the urethelial lining of these cysts to columnar mucin-producing cells results in the production of cystitis glandular, which is a premalignant lesion [9]. Moreover, cuboidal or columnar metaplasia of the surface epithelium can occur with no downward invagination. Chronic vesical irritation and infection were mentioned as predisposing factors for these changes [7,8]. This may explain the higher incidence of these tumours among patients with bilharzial cystitis.

The pathological characteristics, clinical behaviors and response to different lines of treatment were not clearly identified, mostly due to its rare incidence and the lack of universal standardized treatment. Recently a report upon 185 primary adenocarcinoma patients treated

with radical cystectomy and pelvic lymphadenectomy was published [6]. The majority (76%) of their patients were in early stages (P₁ and P₂, UICC 1997). The 5 year DFS rate for such patients was excellent (83%) while patients with advanced stages (P₃ & P₄) experienced a statistically significant lower survival rate (41%).

Postoperative radiotherapy as an adjuvant therapy proved to improve the DFS through improvement of the local control of relatively advanced stages P_{2b}, P₃ and P_{4a} [4,10].

The aim of this study was to report upon a large series of primary adenocarcinoma of the bladder, their clinicopathologic characteristics and their treatment end results. All our patients were treated with radical cystectomy and bilateral pelvic lymphadenectomy with or without adjuvant postoperative radiotherapy. Testing the effect of adjuvant postoperative radiotherapy in such patients was feasible and of great value as adenocarcinoma is known to be radioresistant.

PATIENTS AND METHODS

Two thousand seven hundred and eighty seven bladder cancer patients were subjected to radical cystectomy and pelvic lymphadenectomy during the period from January 1994 till June 2001 at National Cancer Institute (NCI) Cairo University and Minia Oncology Center (MOC) (October 1998 till June 2001). The files of the patients were reviewed and those who had the pathology of primary adenocarcinoma of the bladder were thoroughly examined. Out of the total number of 2787 cystectomized patients 142 (5.1%) had adenocarcinoma. The pathological specimens were reviewed and sub classified according to Grignon et al. [11]. They divided vesical adenocarcinoma into 5 histologic subtypes: enteric (papillary) when the architectural and cytologic features resembled those of the typical colonic adenocarcinoma, mucinous when the tumor was characterized by single cells or nests of cells floating in lakes of extracellular mucin, signet-ring, when the tumor was composed of single signet-ring cells diffusely permeating the tissues, adenocarcinoma not otherwise specified (NOS), when the pattern did not fit into any of these previously mentioned categories and mixed, when the tumor showed 2 or more patterns with no single pattern accounting for more than 75% of the materials.

Detailed characteristics, treatment and follow up of these 142 patients were thoroughly looked at as they were the main concern of this report.

Radical cystectomy and pelvic lymphadenectomy were performed in 93 males and anterior pelvic excenteration with pelvic lymphadenectomy was the treatment in 49 females according to El-Sebai [12]. Out of the 142 patients only 46 patients (32.4%) received postoperative radiotherapy using 6 MV photon giving 50 Gy/5 weeks/25 fractions using 3 fields (one anterior and 2 posterolateral) technique. The target volume included the entire true pelvis and extending upward from the upper border of the first sacral vertebra to the lower border of both obturator foramina. The lateral borders of the radiotherapy fields were one cm lateral to the pelvic brim. The anterior border including half of the symphysis pubis and the posterior border included the anterior 1/3 of the rectal wall [4,10]. Patients were regularly followed up and examined to detect signs and site of treatment failure, depending upon clinical findings, radiological or histopathological evidence, whenever possible. Follow up period ranged between 0-78 months with a median of 34 months.

Statistical analysis:

Comparison between different percentages and frequencies were performed using the standard student *t*-test, *f*-test and χ^2 . The 5 year disease free survival rates, local control rates and distant metastasis free (DMF) rates were measured using the Kaplan-Meier product limit method [13]. The disease free survival period was defined as the period from the date of radical cystectomy to the date of occurrence of any relapse either local or distant. Patients who died of any other cause were considered failure at time of death. Local control period was defined as the period from radical cystectomy to the date of occurrence of local recurrence. Any other event, either distant metastasis, uraemia or death due to accidental disease was considered as censored. The period of freedom from distant metastasis was defined as that from the date of surgery to the detection of the first distant metastasis or the date of evaluation. Log rank test was used for comparison between survival curves [14]. Cox multivariate analysis was performed to determine the independent prognostic variables that affected the DFS. Interactions between variables were taken in

consideration in determining the independent factors [15].

RESULTS

This is a retrospective analysis of 142 urinary bladder adenocarcinoma patients who underwent radical cystectomy or anterior pelvic exenteration and pelvic lymphadenectomy with (46 patients) or without (96 patients) postoperative radiotherapy. Male to female ratio was 1.9:1. Their age ranged from 28 to 72 years old with a mean of 49.3 ± 9.6 and a median of 50 years.

Eight patients died postoperatively, within 30 days, leading to a postoperative mortality rate of 5.6%. Most of the patients (68 patients = 47.9%) belonged to the category PT₃ followed by those belonging to PT₂ (41 patients). Two thirds of the patients (n=94) had grade II tumours while grade I and III were documented in 20 and 28 patients, respectively. Pelvic nodal involvement was found in 33 patients giving a nodal involvement rate of 23.2% (Table 1).

Mucinous adenocarcinoma was reported in 21 patients (14.8%), signet ring in 10 patients (7.0%), papillary in 16 patients (11.3%), while 95 patients (66.9%) had the pathology not otherwise specified (NOS). The distribution of patients among the different histopathological subtypes of bladder adenocarcinoma did not show differences of statistical significance.

However, when the patients characteristics were compared according to the treatment adopted, either cystectomy alone (96 patients) or cystectomy with PORT (46 patients). Postoperative radiotherapy group had more advanced stages (P₃ + P₄), higher histological grade (GIII) and increased rate of pelvic lymph nodal involvement (44.4% vs 17.5%), respectively (Table 2). These differences were statistically significant.

Disease-free survival (DFS):

The 5-year DFS rate of all 142 adenocarcinoma patients was $46.6 \pm 5.0\%$. There was no difference in survival rates between males and females (43.0 vs 49.3%, respectively). The 5-year DFS rate decreased with the advancement of the level of tumor infiltration as all P₁ patients (5 patients) survived free of disease while the 5-y DFS rate decreased from 55.1% for P₂ till 35.4% for stage P₄. It is worth noting that stage

P_{2a} patients (n=7) enjoyed a 100% 5-y DFS rate while those with P_{2b} stage (34 patients) had a survival rate of $43.5 \pm 10.6\%$. The histological grade affected much the DFS as G3 patients had a dismal rate of 28.0% while those with G1 and G2 had a DFS rate of 42.1 and 58.5%, respectively. Nodal involvement had a major negative effect on DFS leading to a 5-year DFS rate of 26.9%, compared to 50.5% for those with no involvement. Papillary and NOS subtypes of the adenocarcinoma patients had a statistically significant higher 5-year DFS rate (67.5 and 46.4% respectively) than that for patients with the mucinous and signet-ring histological subtypes (19.8 and 20%, respectively) (Table 3). The difference among these DFS was statistically significant ($p = 0.05$).

Local control and distant metastasis-free (DMF) rates:

The 5-year local control rate was 70% with no difference between males and females (71.5 versus 67.4% respectively). The pathological stage had some influence on local control rate though it did not reach the level of significance ($p = 0.06$). The local control rate decreased from 100% for P₁ & P_{2a} to 66.6% for stages P_{2b} + 3 + 4_a patients. A further decrease to 40% was noticed for patients having stage P_{4b}. However, the histopathological grade did not influence the 5-year local control rates as they were 59.2, 71.7 and 71.3% for grades I, II and III, respectively. The local control rates were not affected by the metastatic involvement of the pelvic lymph nodes (70.4% for negative involvement and 69.9% for positive involvement). The same no effect of the pathological subtypes on the local control was also noticed. However, the papillary and NOS had higher local control rates (75% and 74.1%, respectively) than the mucinous and signet ring (42.5% and 66.7% respectively). The differences were not statistically significant (Table 4). On the other hand, the DMF rate for the 142 patients was 74.7% with no difference between males and females (74.3 and 75.5%, respectively). The DMF rates were affected by the stage, though did not reach to the level of significance ($p = 0.07$). The grade of the tumor affected the 5-year DMF rates significantly ($p < 0.001$). Moreover, both the involvement of pelvic lymph nodes and the pathological subtypes affected the DMF rates significantly ($p < 0.001$ and < 0.001 respectively) (Table 4).

Effect of PORT on DFS:

Table (6) shows the comparison of the 5-year DFS for patients who underwent radical cystectomy alone and those who received PORT as an adjuvant to surgery. It illustrated that PORT led to a higher DFS rate ($46.7 \pm 7.5\%$) than cystectomy alone ($38.2 \pm 6.1\%$). This difference did not reach to the level of significant ($p = 0.06$). However, this difference was higher when we restrict the comparison to those whom PORT supposed to be indicated (stages P_{2b}, 3 and 4_a). The exclusion of the early stages P₁ and P_{2a} and late stages where PORT did not suppose to improve DFS, led to 5 year DFS rate of $24.2 \pm 9.0\%$ for cystectomy alone. The improvement in DFS was consistent in patients with low and intermediate tumor grades (G1 and G2) and in those whose pelvic lymph nodes were involved or not. Postoperative radiotherapy could not improve the DFS in high grade tumors (G3), nor in patients with the mucinous and signet ring histopathological subtypes. Though PORT could improve the DFS rate of papillary and NOS subtypes from 66.7 and 45.6% for cystectomy alone group to 100 and 60.2% for

PORT group, this difference did not rank to the level of statistical significance ($p = 0.26$ and 0.28 respectively).

Causes of treatment failure:

Table (6) shows the different causes of failure for the 2 therapeutic groups, cystectomy and PORT. The leading cause of failure in the cystectomy group was local recurrence (34%) followed by distant metastasis (8%) and post-operative mortality. On the other hand the main cause of death in PORT was distant metastasis (33%) while local recurrence decreased to only (2%).

Multivariate analysis:

Cox multivariate analysis [15] was performed to identify the independent working prognostic factors determining the disease-free survival. Tumour stage, adjuvant PORT, pelvic nodal involvement and pathological subtypes were the 4 independent prognostic variables (p -value = 0.0006, 0.0025, 0.0067 and 0.0471 respectively). The pathological grade was not a prognostic factor as it was dependent upon other prognostic variables (Table 7).

Table (1): The clinicopathological characteristics of patients with adenocarcinoma of the urinary bladder.

Category	All patients (142)	Mucinous (21)	Signet-ring (10)	Papillary (16)	NOS (95)
Mean age \pm SD	49.3 \pm 9.6	51.2 \pm 9.6	50.3 \pm 9.2	50.0 \pm 9.3	49.2 \pm 9.6
Male : female ratio	1.9:1	9.5:1	0.4:1	3:1	1.6:1
<i>Stage:</i>					
P1	5 (3%)	1 (5%)	0	2 (13%)	2 (2%)
P2	41 (29%)	3 (14%)	2 (20%)	6 (37%)	30 (32%)
P2a	7				
P2b	34				
P3	68 (48%)	14 (67%)	7 (70%)	4 (25%)	43 (45%)
P4	28 (20%)	3 (14%)	1 (10%)	4 (25%)	20 (21%)
P4a	23				
P4b	5				
<i>Grade:</i>					
I	20 (14%)	4 (19%)	4 (40%)	2 (12.5%)	9 (9%)
II	94 (66%)	12 (57%)	1 (10%)	12 (75%)	70 (74%)
III	28 (20%)	5 (24%)	5 (50%)	2 (12.5%)	16 (17%)
<i>Nodal involvement:</i>					
Positive	33 (23%)	7 (33%)	3 (30%)	3 (19%)	20 (21%)
Negative	109 (77%)	14 (67%)	7 (70%)	13 (81%)	75 (79%)
<i>Treatment:</i>					
Cystectomy alone	96 (68%)	15 (71%)	5 (50%)	12 (75%)	64 (67%)
PORT	46 (32%)	6 (29%)	5 (50%)	4 (25%)	31 (33%)

Table (2): Patients characteristics according to treatment groups.

	Cystectomy (96)	PORT (46)	<i>p</i> value
Mean age ± SD	49.8±9.6	48.9±10.2	–
Male : Female	1.7:1	2.3:1	–
<i>Stage:</i>			
P1	5 (5%)	0	0.05
P2a	7 (7%)	0	
P2b	24 (25%)	10 (22%)	
P3	44 (46%)	24 (52%)	
P4a	10 (11%)	12 (26%)	
P4b	6 (6%)	0	
<i>Grade:</i>			
I	13 (13%)	6 (13%)	0.05
II	69 (72%)	26 (57%)	
III	14 (15%)	14 (30%)	
<i>Nodal involvement:</i>			
Positive	12 (12.5%)	21 (46%)	0.001
Negative	84 (87.5%)	14 (54%)	
<i>Histological subtype:</i>			
Mucinous	15 (16%)	6 (13%)	0.34
Signet-ring	5 (5%)	5 (11%)	
Papillary	12 (12%)	4 (9%)	
NOS	64 (67%)	31 (67%)	

Table (4): Five-year local control and distant metastasis-free (DMF) rates in different patients' subgroups.

Variable	Local control % ±SE	<i>p</i> -value	DMF % ±SE	<i>p</i> -value
All patients	70.0±4.6	–	74.7±4.9	–
<i>Sex:</i>				
Male	71.5±5.9	0.506	74.3±6.4	0.681
Female	67.4±7.4		75.5±7.3	
<i>Stage:</i>				
P1 + P2a	100	0.06	100	0.07
P2b+P3+P4a	71.5±5.4		63.1±9.7	
P4b	40.0±26.3		50.0±35.4	
<i>Grade:</i>				
I	59.2±11.9	0.262	78.4±11.2	0.0003
II	71.7±5.8		80.7±5.9	
III	71.3±10.5		48.0±11.9	
<i>LN:</i>				
Negative	70.4±5.2	0.729	82.3±5.0	0.0003
Positive	69.9±9.1		47.8±11.5	
<i>Subtypes:</i>				
Papillary	75.0±10.8	0.604	100	0.007
Mucinous	42.5±19.1		50.5±21.8	
Signet-ring	66.6±15.7		16.2±14.6	
NOS	74.1±15.6		79.6±5.4	

Table (3): Five-year disease free survival rates in different subgroups.

	No. of patients	5-y DFS ± SD	<i>p</i> -value
All patients	142	46.6±5.0	–
<i>Sex:</i>			
Male	93	43.0±6.4	0.339
Female	49	49.3±8.4	
<i>Stage:</i>			
P1	5	100	0.049
P2a	7	100	
P2b	34	43.5±9.1	
P3	68	38.4±6.4	
P4a	23	47.8±10.4	
P4b	5	Zero	
<i>Grade:</i>			
I	19	42.1±11.3	0.014
II	95	58.5±6.1	
III	28	28.0±6.2	
<i>Nodal involvement:</i>			
Negative	109	50.5±5.8	0.012
Positive	33	26.9±8.2	
<i>Histological subtype:</i>			
Mucinous	21	19.8±10.9	0.05
Signet-ring	10	20.0±12.6	
Papillary	12	67.5±12.1	
NOS	95	46.4±5.5	

Table (5): Comparison between actuarial 5-year disease-free survival rates in cystectomy and PORT groups according to different risk factors.

	Cystectomy (n = 96)	PORT (n = 46)	<i>p</i> -value
All patients	38.2±6.1	56.7±7.5	0.066
<i>Stage:</i>			
P1	100	–	–
P2a	100	–	–
P2b	17.3±12.7	57.3±16.1	0.21
P3	19.6±8.5	60.3±10.2	0.04
P4a	40.6±15.5	50.0±14.4	0.50
P4b	Zero	–	–
P2b+3+4a	24.2±9.0	56.7±7.5	0.01
<i>Grade:</i>			
I	30.7±12.6	66.7±19.3	0.19
II	40.1±7.3	69.2±9.0	0.02
III	40.0±12.7	10.8±10.0	0.34
<i>Nodal involvement:</i>			
Negative	41.1±6.6	75.2±8.8	0.02
Positive	15.0±12.7	35.6±10.7	0.01
<i>Subtypes:</i>			
Papillary	66.7±7.9	100	0.26
Mucinous	11.4±9.8	64.8±19.5	0.31
Signet-ring	20.0±17.9	Zero	0.84
NOS	45.6±6.8	60.2±9.1	0.28

Table (6): Causes of failure in both therapeutic groups (cystectomy & PORT).

Cause	Cystectomy	PORT	<i>p</i> value
	Number (%)	Number (%)	
Local recurrence	33* (34)	1 (2)	0.001
Distant metastasis	8* (8)	15 (33)	0.001
Postoperative death	8 (8)	–	–
Uremia	1 (1)	0	0.94
Intercurrent disease	2 (2)	1 (2)	0.94
Unknown	3 (3)	2 (4)	0.92

4 patients experienced both local recurrence and distant metastasis.

DISCUSSION

Primary adenocarcinomas are uncommon tumors of the urinary bladder. This category accounted for 0.5-2% of all bladder malignancies [2,16]. However, it is the most commonly reported malignancy of the exstrophic bladder [17], enterocystoplasty [18]. In areas where bilharziasis are endemic, the incidence of adenocarcinoma is higher ranging from 5-11.4% [4-6]. It is believed that these tumours result from metaplastic changes of potentially unstable urothelium [7]. The urothelium in the bladder infested with bilharziasis that of extrophic bladder or after enterocystoplasty is more likely to be unstable and more liable to metaplasia.

Grignon et al., classification [11] was adopted in the present study. Mucinous adenocarcinoma was found in 14.8%, signet-ring in 7%, papillary in 11.3% and NOS in 66.9% of cases. Signet-ring and mucinous adenocarcinoma had higher percentage of advanced stages (P₃ + P₄), high grades (G III) and more incidence of pelvic lymph nodal involvement than that in papillary and NOS, however, these differences did not rank up to the level of statistical significance. This was probably due to the relatively small number of patients in the different categories apart from NOS. Signet-ring adenocarcinoma, being frequently diagnosed in advanced stage, its survival rate was reported to be poor [19]. The present study could compare the 5-year DFS of signet-ring and mucinous adenocarcinoma to the other 2 categories (papillary and NOS). Mucinous (19.8%) and signet-ring (20%) 5-year DFS compared to 67.5% for papillary and 46.4% for NOS (*p* = 0.05).

The clinicopathological features of adenocarcinoma patients shown in the present study

Table (7): Multivariate analysis for the disease-free survival.

Variable	$\beta \pm SE$	<i>p</i>
Stage	0.333±0.097	0.0006
PORT	-0.925±0.306	0.0025
Nodal involvement	0.828±0.305	0.0067
Adeno subtype	0.248±0.12	0.0471
Grade	0.028±0.2235	0.906

did not differ much from that of the other Egyptian studies of mixed pathology bladder cancer. The mean age and male predominance were similar [3,4,10]. The pathological stage and grade distributions were also similar to that reported in the same Egyptian studies concerning all histological subtypes; transitional, squamous and adenocarcinoma. Pelvic nodal involvement was reported in 23.2% of the patients that coincided with the series arising from bilharzial endemic areas. However, adenocarcinoma patients in the present study presented in higher stages than that reported in El-Mekresh et al. [6] as P₃ and P₄ patients represented 67.6% of the whole population compared to 13% in El-Mekresh series. They reported 16% nodal involvement. This difference in presentation and nodal involvement could be understood in view of the earlier presentation of patients in their center. This earlier presentation was also noticed in another study of 1026 bladder cancer patients (including all tumour cell types) treated at the same center [5].

The 5-year DFS rate for the 142 adenocarcinoma patients was 46.6±5% which correlated with the results of other large adenocarcinoma series. Ghoneim et al. [5] reported a 5-year overall survival rate of 46.4±9.6%, while El-Mekresh et al. [6] reported an overall survival rate of 55±4.3%. It is worth mentioning that the patients in the present study had more advanced stages, higher grades and higher incidence of pelvic lymph node involvement.

The pathological stage affected markedly the 5-year DFS as the rate decreased from 100% in P₁ to 35.4±9% in P₄ stage (*p* = 0.049). The 5-year DFS was affected also by the histopathological grade (*p* = 0.011) and the pelvic nodal involvement (*p* = 0.012). These results were

previously confirmed in the adenocarcinoma series [6] and in transitional cell carcinoma [20] and in mixed pathology series [4,5].

Though radical cystectomy remained along the years, the treatment of choice for bladder cancer, including adenocarcinoma, yet local recurrence accounted for the majority of the causes of failure. Postoperative radiotherapy (PORT) improved the local control rate in mixed pathology series that contained adenocarcinoma patients [4,10]. This improvement of local control led to a considerable improvement in DFS. Although adenocarcinoma has been known to be radioresistant, yet postoperative radiotherapy was successful in decreasing local recurrence markedly in adenocarcinoma of the breast. The rarity of primary adenocarcinoma of urinary bladder made controlled randomized trials extremely difficult, even in areas where bilharziasis is endemic. The relatively large number collected in the present study, that included 32% who received PORT, allowed testing the value of adjuvant PORT in primary adenocarcinoma of the bladder. The group of patients who received PORT had a statistically significant higher stages ($P_3 + P_4$), higher incidence of both GIII tumours and pelvic lymph nodes involvement. In spite of this distribution bias against PORT group, the 5-year DFS of PORT group was higher than cystectomy alone group (56.7% vs 38.2%). The statistical significance was not reached ($p = 0.066$). When the comparison was restricted to patients belonging to the stages P_{2b} , P_3 and P_{4a} the difference in the 5-year DFS curves increased and it was significant at a level of 0.01 (this difference remained statistically significant even after exclusion of postoperative mortalities). This difference was constant in G I + II tumors and in lymph node negative and positive patients. Moreover, PORT improved the DFS in papillary and NOS subgroups though did not rank to the level of statistical significance ($p = 0.09$) (Table 4). Local failure was much lower in PORT group than cystectomy alone group (2% vs 34%) while the distant metastasis was higher in PORT (33% vs 8%). The other causes of failure were equally distributed among the 2 groups (Table 6). This was reflected on local control rates as that of PORT were much higher (97.2%) than in cystectomy group (55.9%). Multivariate analysis eliminated the effects of distribution bias and the interactions between the working variables. Out of 5 variables found

to be effective in the univariate analysis, tumor grade proved by multivariate analysis to be not an independent factor. Its effect was dependent upon the other factors. Tumor stage, adjuvant PORT, pelvic nodal involvement and adenocarcinoma subtypes proved to be independent risk factors for DFS in different probability values (from 0.0006 to 0.047). El-Mekresh et al. [6] found that tumor stage, grade and lymph nodal involvement were the only three independent risk factors for patients treated with radical cystectomy. However, El-Sobky et al. [21] denied any prognostic significance for tumor stage, grade and DNA profile and restricted the prognostic significance to tumour angiogenesis tested by mean vascular density. Their study was reporting upon 55 patients only that probably did not contain enough numbers in each subgroup to illustrate the significance of different variables.

On conclusion, as adenocarcinoma of the urinary bladder was examined more closely and thoroughly using a considerable number of patients, it seemed to be similar to other types of muscle invasive bladder cancer (squamous cell carcinoma and probably transitional cell carcinoma) in behavior after radical cystectomy. The use of adjuvant PORT could improve the DFS through improvement of local control. Distant metastasis is still a major problem especially in more aggressive subtypes of adenocarcinoma (mucinous and signet-ring). This suggests the strong need of adding effective chemotherapy.

REFERENCES

- 1- Wheeler J.D. and Hill W.T.: Adenocarcinoma involving the urinary bladder. *Cancer* 1954, 7: 468-76.
- 2- Thomas D.C., Ward A.M. and Williams J.L.: A study of 52 cases of adenocarcinoma of the bladder. *Br. J. Urol.* 1971, 43: 4-15.
- 3- El-Bolkainy M.N., Mokhtar N.M., Ghoneim M.A. and Hussein M.H.: The impact of schistosomiasis on the pathology of bladder carcinoma. *Cancer* 1981, 48: 2643-8.
- 4- Zaghloul M.S., Awwad H.K., Omar S., Soliman O. and El-Attar I.: Postoperative radiotherapy of carcinoma in bilharzial bladder. Improved disease-free survival through improving local control. *Int. J. Rad. Oncol. Biol. Phys.* 1992, 22: 511-17.
- 5- Ghoneim M.A., El-Mekresh M.M., El-Baz M.A., El-Attar I. and Ashamallah A.: Radical cystectomy for carcinoma of the bladder: Critical evaluation of the results in 1026 cases. *J. Urol.* 1997, 158: 393-9.

- 6- El-Mekresh M.M., El-Baz M.A., Abol Eniein H. and Ghoneim M.A.: Primary adenocarcinoma of the urinary bladder. A report of 185 cases. *Br. J. Urol.* 1998, 82: 206-12.
- 7- Allen T.D. and Henderson B.W.: Adenocarcinoma of the bladder. *J. Urol.* 1965, 93: 50-6.
- 8- Mostofi F.K.: Potentialities of bladder epithelium. *J. Urol.* 1954, 71: 705-14.
- 9- Kittridge W.E., Coliott A.J. and Morgan C.: Adenocarcinoma of the bladder associated with cystitis glandularis. A case report. *J. Urol.* 1964, 91: 145-50.
- 10- Zaghloul M.S., Awwad H.K., Soliman O., Omar S., El-Badawy S., Barsoum M., et al.: Postoperative radiotherapy of carcinoma in bilharzial bladder using a three-fractions per day regimen. *Radioth. Oncol.* 1986, 6: 257-65.
- 11- Grignon D.J., Ro J.Y., Ayala A.G., Johnson D.E., Ordonez N.G.: Primary adenocarcinoma of the urinary bladder. *Cancer* 1991, 67: 2165-72.
- 12- El-Sebai I.: Cancer of the bilharzial bladder in Egypt. *Kasr El Aini J. Surg.* 1961, 2: 183-24.
- 13- Kaplan E.L., Meier P.: Non-parametric estimation from incomplete observations. *J. Am. Stat. Assoc.* 1972, 53: 457-65.
- 14- Peto R., Pike M.S., Armitage P., Brestow N., Cox D.R., Howard S., et al.: Design and analysis of randomized clinical trials requesting prolonged observation of each patient. II. Analysis and examples. *Br. J. Cancer* 1977, 35: 1-39.
- 15- Cox D.R.: Regression methods and life tables. *J. R. Stat. Soc.* 1972, 34: 187-220.
- 16- Bennet J.K., Whealy J.K. and Walton K.N.: Ten years experience with adenocarcinoma of the bladder. *J. Urol.* 1984, 131: 262-3.
- 17- Clup D.A.: The histology of extrophied bladder. *J. Urol.* 1964, 91: 538-48.
- 18- Filmer R.B. and Spencer J.R.: Malignancies in bladder augmentations and intestinal conduits. *J. Urol.* 1990, 143: 671-8.
- 19- Holmang S., Bordghede G. and Johansson S.L.: Primary signet-ring cell carcinoma of the bladder: a report on 10 cases. *Scand. J. Urol. Nephrol.* 1997, 31: 145-8.
- 20- Stein J.P., Lieskovsky G., Cote R., Groshen S., Feng A., Boyd S., et al.: Radical cystectomy in treatment of invasive bladder cancer: Long term results in 1054 patients. *JCO* 2001, 19: 666-75.
- 21- El-Sobky E., Gomha M., El-Baz M., Abol Enien H. and Shaaban A.A.: Prognostic significance of tumour angiogenesis in schistosoma associated adenocarcinoma of the urinary bladder. *Br. J. Urol.* 2002, 89: 126-32.