

## Post Operative Radiotherapy in Bladder Cancer

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### ABSTRACT

**Purpose:** To investigate the effect of adjuvant postoperative radiotherapy after radical cystectomy on the disease free survival, local control and distant metastases of bladder cancer patients.

**Patients and Methods:** Eighty-nine patients with bladder cancer presented to El-Minia Oncology Center between July 1998 to March 2001 were treated by radical cystectomy or anterior pelvic exenteration plus postoperative radiotherapy.

**Results:** The most commonly encountered pathological subtype in this study was squamous cell carcinoma 49.4% while transitional cell carcinoma was reported in 34.8% of cases. The commonest pathological stage was P3, which was encountered in 41.6% of patients followed by P2b 29.2% and P4a 10% (UICC, 1997).

Pathological pelvic lymph node involvement was reported in 22.5% of patients of the present study. The 3-year disease free survival in the whole group was 64±10% while the 3-year local control rate was 78.6±9%. The 3-year disease free survival rates for squamous cell carcinoma was 73±14% and 53±15% for transitional cell carcinoma. The disease free survival was 66±13% for P2b carcinoma and 83±7% for stage P3. Patients having the pathological stage P4a had a 2-year disease free survival rates of 75±21%.

The 2-year disease free survival rate was 83.3% for lymph node negative patients and 57±15% for lymph node positive patients.

**Conclusions:** These results emphasized the high rate of disease-free survival and local control rates obtained by adding postoperative radiotherapy to cystectomized patients. The value of post-operative radiotherapy was illustrated in all tumor types and all tested stages.

**Key Words:** Bladder cancer - Postoperative radiotherapy - Disease-free survival - Local control - Distant metastasis.

### INTRODUCTION

Bladder Cancer constitutes 4% of all cancer in United States, and represents 30% of all can-

cer cases treated at Egyptian National Cancer Institute [27]. Faculty of Medicine Cairo University hospitals reported a lower frequency of 10% [7].

The relative frequency of histological subtypes of bladder carcinoma depends on the clinical setting. About 90% of bladder carcinoma reported from the West is transitional cell type, [26]. In large series reported from Egypt, squamous cell carcinoma accounted for 59-73% of bilharzial bladder cases [6,16,31].

Radical cystectomy is the treatment of choice for carcinoma in bilharzial bladder [10]. Local recurrence accounts for approximately 75% of the failures of this treatment [9,15].

Postoperative radiotherapy led to a marked reduction in the incidence of local recurrence by around 40%. This reduction was reflected on the disease free survival. In a large prospective randomized study, postoperative radiotherapy could reduce local recurrence and improve the disease-free survival [32]. However, postoperative radiotherapy did not affect the incidence of distant metastasis. The 5-year cumulative metastatic rate was estimated to be 23%, which did not differ much with adjuvant radiotherapy [30].

This retrospective study was performed to evaluate the disease-free survival rate of bladder cancer patients who received postoperative radiotherapy as an adjuvant treatment to radical cystectomy. The effect of postoperative radiotherapy upon different categories was also tested.

## MATERIAL AND METHODS

This retrospective study included 89 patients with bladder cancer presented to radiotherapy department of El-Minia Oncology Center during the period of July 1998 to March 2001.

*Pre-treatment evaluation:* clinical examination and work up of the patients include laboratory: complete blood picture, serum and creatinine liver function tests. Radiological: chest x-ray, abdomenopelvic CT and bone scan prior to surgical intervention.

The patients were staged according to UICC staging system (1997). Surgical procedures included radical cystectomy (74 patients) or anterior pelvic exenteration (15 patients) followed by post-operative radiotherapy with curative intent.

### *Radiotherapy:*

All patients received postoperative radiotherapy to the pelvis aiming at: 50 Gy/25 fraction/5 weeks using linear accelerator 6MV Photon at 100cm SAD.

The upper border of the target volume was at L5 -S1, while the lower border at the lower margin of the obturator foramen. In case of prostatic involvement the lower border of the field was shifted to a level below the ischeal tuberosities, the lateral border were 1.5 cm lateral to the pelvic brim, the anterior border was at the anterior border of the symphysis pubis, the posterior border included the anterior one third of the rectum.

*The treatment of the patients was carried out in 2 phases:*

*Phase I:* 30 Gy / 15 fraction / 3 weeks (2 parallel opposing fields).

*Phase II:* 20 Gy / 10 fraction / 2 weeks (3 fields, anterior and 2 lateral fields) to spare the posterior rectal wall.

*Post-treatment evaluation:* All patients were regularly followed up at bimonthly basis. Every six months patients were evaluated by: chest x-ray, abdomenopelvic CT and/or isotopic bone scan. These investigations were also performed when clinical situation necessitated.

All patients were followed up for a period ranged from 6 to 70 months with a median of 25 months.

### *Statistical evaluation:*

The survival estimates were calculated using kaplan -Meier methods [19].

The comparison between the survival curves of the different groups was performed using the log-rank (LR) test [23].

All reported *p*-values are two sided *p*-value of  $\leq 0.05$  was considered significant.

## RESULTS

The age of the patients ranged between 30-79 years. The peak age incidence was in the sixth and seventh decades, with the mean age  $56.24 \pm 11$  years.

Patients whose age were below 40 years constituted 6.7% and those above 70 years constitutes 4.5% as illustrated in table (1). Male to female ratio in the study was 3.9:1

Surgery in the form of radical cystectomy was performed for 71 male and 3 female patients (total 74 patients) constituting 83.2% of all patients.

Anterior pelvic exenteration was performed for 15 female patients, representing 16.8% of the whole population.

The most commonly encountered pathological subtype in the study was squamous cell carcinoma representing 49.5% while transitional cell carcinoma was reported in 34.8% of cases, adenocarcinoma was represented in only 9% of the study (Table 2).

Tumour was pathologically staged according to the TNM staging system (UICC 1997). The commonest pathological stage was P3 {tumours invade perivesical fat, either microscopically (a) or macroscopically (b)} which was reported in 41.6% of patients, followed by P2b (tumour invade deep muscle layer) counted in 29.2% of patients. P4a (tumour invade surrounding respectable structure i.e. prostate, vagina, uterus) represented 10% of cases.

Thirteen patients were operated upon outside El Minia Oncology Center and their specimens were not examined in a systemic way (14.6%). Therefore their exact stage were not known (Table 3).

Lymph nodes were infiltrated in 22.5% of cases. Needless to say that 13 patients (14.6%)

were not examined systematically to detect lymph node involvement.

Around sixty percent of the patients in the present study received their postoperative radiotherapy treatment in an overall period of <40 days. The other 40% had prolonged overall treatment periods (Table 5).

*Treatment results:*

The relapsed patients represent 18% of patients of the study, while 82% were free.

Local recurrence was experienced in 7 patients of this study while distant metastasis occurred in the remaining 9 patients. (Table 4).

Distant metastasis were detected mostly in the bone (56% of the patients) followed by the lung (22%=2 patients). The liver and brain were the site of distant metastasis in the remaining 2 patients.

*Survival results:*

The 3 - year disease free survival (DFS) rate in the whole group of the study was 64±10 %. Fig. (1).

On the other hand the 3-year disease free survival rate was 73±14% for squamous cell carcinoma and 53±15% for transitional cell carcinoma. Fig. (2) and Table (6) (p=0.08).

The 2-year disease free survival rate was 83±7 % for lymph node negative patients and 57±15% for lymph node positive patients. This difference was statistically significant at a level of 0.05. Fig. (3).

The 3-year local control rate for the whole study group was 78.6±9%. Fig. (4).

The 3-year distant metastasis-free survival for all study group was 82±7%. Fig. (5).

No difference was noticed in the different pathological stages, as the 2-year disease free survival for P2b patients was 66±13%, while those with P3 pathological stage had 83±7% disease free survival. Patients having the pathological stage P4a had a 2-year disease free survival rates of 75±21%. Fig. (6) and Table (6).

The 2 year disease free survival rate in patients who had received their treatment in an overall period of ≤ 40 days was 77.6±8% while it was 46.8±16% for the patients who had an overall period more than 40 days. This differ-

ence was statistically significant at a level of 0.05.

*Radiation complications and side effects:*

Seven patients (8%) suffered from nausea (grade 1 radiation sickness) while 12 patients (13%) had transient vomiting (grade2 radiation thickness) and only 4 patients (4%) had persistent vomiting that required treatment (grade 3). Sixty patients (67%) had diarrhea as a manifestation of early small bowel reactions. It was less than 2 days duration (grade 1) in 35 patients (39%) and it was tolerable but more than 2 days duration (grade 2) in 22 patients (25%). Only 3 patients (3%) experienced grade 3 severe diarrhea requiring simple medication. Tensmus (early rectal reactions) was experienced by 46 patients (52%). All patients had rectal reactions as grade 1.

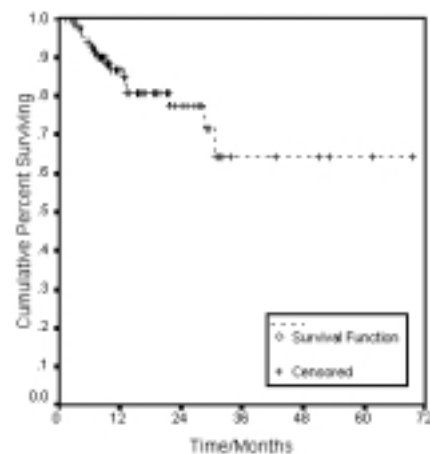


Fig. (1): Disease free survival for the 89 bladder cancer patients.

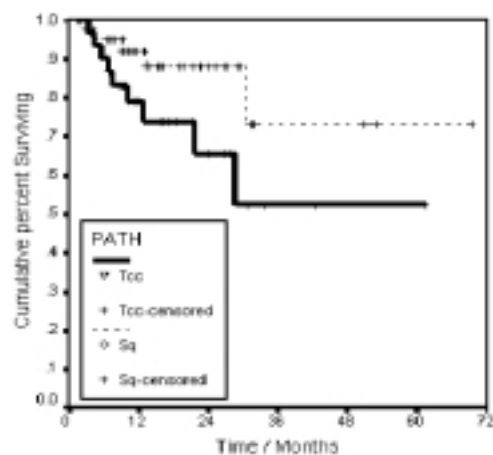


Fig. (2): Disease free survival according to the pathological types in 89 patients with bladder cancer.

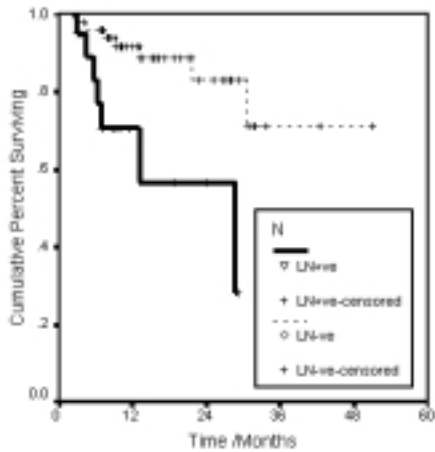


Fig. (3): Disease free survival for different lymph node status.

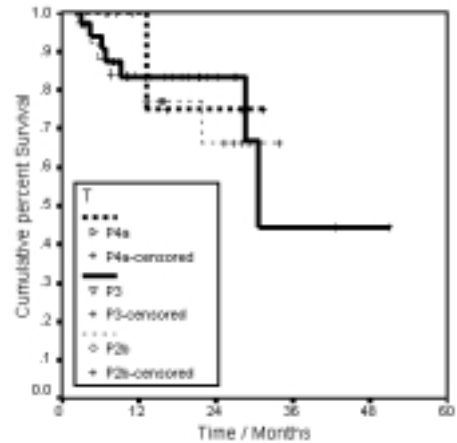


Fig. (6): Disease free survival for different pathological stages.

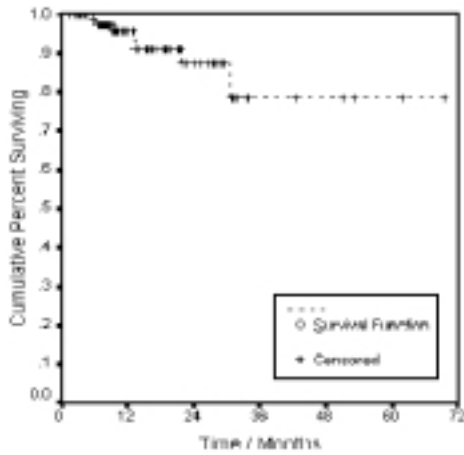


Fig. (4): Local control rate for the whole group of 89 bladder cancer patients.

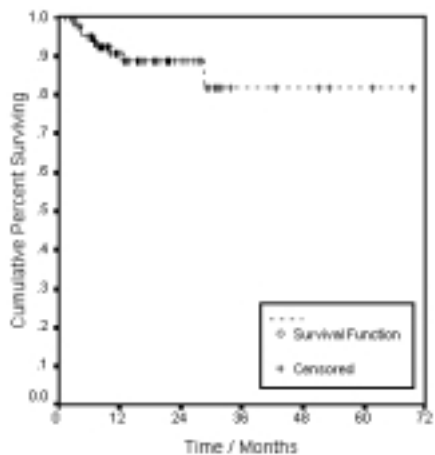


Fig. (5): Distant metastasis disease free survival for the whole group of patients.

Table (1): Age distribution of 89 patients with operable bladder cancer.

Age	No. of patient	%
30 - 39 y	6	6.7
40 - 49 y	19	21.3
50 - 59 y	25	28.1
60 - 69 y	35	39.3
70 - 79 y	4	4.5

Table (2): Pathological subtypes of 89 patients with operable bladder cancer.

Path. Subtype	No. of patient	%
Sq. C. Ca	44	49.5
T.C. Ca.	31	34.8
Adenocarcinoma.	8	9
Unknown	6	6.7

Table (3): Pathological stage of 89 patients with operable bladder cancer.

Pathological stage	No. of patient	%
P2a	4	4.5
P2b	26	29.2
P3	37	41.6
P4a	9	10.1
Unknown	13	14.6

Table (4): Local and Systemic relapse in bladder cancer patients after postoperative radiotherapy.

Type of relapse	No. of patient	%
Local	7	43.75
Systemic	9	56.25

Table (5): Distribution of patients according to their post-operative radiotherapy overall period.

Over all period	No. of patients	%
20 ≤	8	9
40 ≤	45	50.6
60 ≤	23	25.8
80 ≤	13	14.6

Table (6): Three-year disease-free survival rates (DFS) in different categories of bladder cancer patients.

Category	3-y DFS	p Value
All patients	64±10%	—
<i>Stage:</i>		
P2b	66±13	0.25
P3	83±7	
P4a	75±21*	
<i>Pathological types:</i>		
Squamous	73±14	0.08
Transitional	53±15	
<i>Nodal status:</i>		
Positive	83±8*	0.05
Negative	57±15*	

\* 2-year disease-free survival

## DISCUSSION

Bladder cancer is the most common form of cancer encountered in Egyptian males. It represents 30% of all cancer cases treated at the National Cancer Institute, Cairo [27]. In the western countries the peak age incidence is at the 7th decade with an average age of 65 years [1]. In the present study, the age of the patients ranged between 30-79 years with a mean age of 56.2±11. The peak age incidence was at the sixth and seventh decades. The relative younger age of Egyptian patients correlate with the age structure in Egyptian population and the corresponding short life expectancy. Early exposure to bilharzial infestation may also play a role [9].

Males made up 79.8% of the study population with a M:F ratio 3.9:1 which is comparable to that reported in most Egyptian series [9,15,16,30,31,32]. The high M:F ratio was explained by a higher exposure to bilharziasis among males working as farmers [9]. In western countries M:F ratio ranged between 2:1 to 3:1 [1].

The high frequency of squamous cell carcinoma was one of the main distinctive features of carcinoma in the bilharzial bladder and has been noted for a long time in different reports

from Egypt [5,10]. Many Egyptian series reported a higher incidence of squamous cell carcinoma (66-77%) [9,13,15,20,31]. Lately, the frequency of squamous cell carcinoma had decreased to 46.8% as reported by El-Debawy [8], which coincided perfectly with the present study (49.5%).

This decline in the relative frequency of squamous cell carcinoma was associated with the decline in the prevalence of bilharziasis in Egypt along the years [7,13].

In a population-based regional cancer registry performed in El-Minia, Egypt the age-standardized bladder cancer incidence rate was 17.8 in 100,000 male population [33], while it was 24.4 in 100,000 in a similar registry performed in Gharbia, Egypt [17].

This high prevalence of squamous cell type contrasted sharply with the relative frequency of true squamous cell carcinoma in western world, which varied between 3-7% [18] and transitional cell carcinoma, which constituted about 90% of all bladder carcinoma [28].

Most of patients presented in an advanced stage. Using the UICC pathological staging system (1997) the relative frequency of P2a, P2b, P3, P4a were 4.5%, 29.2%, 41.6%, 10% respectively. This pattern is similar to that reported by El-Bolkainy et al. [5], Zaghloul et al. [30,31,32] that 81-86% of the operated upon patients have stages P3-P4 disease.

This delayed presentation and advanced stages were probably due to the fact that the symptoms of bladder cancer overlap with that of simple chronic bilharzial cystitis that farmers used to have and it usually take some time before the patients appreciate a definite change in symptoms that needs medical attention [9].

While in western countries 75-85% of bladder cancer are superficial (Ta-T1) and 15-25% have incidence of muscle invasion [3,21].

Although, most of the patients presented in advanced stage, yet the reported incidence of nodal involvement in the present study was 22.5%.

This incidence was similar to the 21-24% incidence reported by Zaghloul et al. [32], El-Debawy, [8] and Ghoneim et al. [15] in patients having P3 and P4 tumors.

Postoperative radiotherapy led to marked reduction in the incidence of local recurrence and hence improved the disease-free survival in bladder cancer patients [31,32].

The main reason for the unpopularity of postoperative radiotherapy is the wide spread belief that irradiation of small bowel is a major dose limiting factor as the volume to be irradiated may be significantly large, to cover the whole operative field. Large loops of small intestine and colon are included in the radiation field [32]. Since more space became available for accommodation of more loops of intestine after surgery, more loops were exposed to irradiation during postoperative radiotherapy. Moreover, Adhesions that can develop after surgery may fix these loops and tend to expose the same gut segment throughout most or all the course of treatment resulting in serious bowel damage [28,32].

Many Egyptian series had been performed to assess postoperative radiotherapy and its influence on survival. Well-conducted prospective randomized series reported that postoperative radiotherapy improved disease free survival concerning different stages, different grades and lymph nodal status.

The present study reported 3-years disease free survival of  $64\pm 10\%$  which is comparable to what had been reported before by Zaghoul et al. [31] that the 2-years disease free survival for the post operative radiotherapy groups was  $65\pm 6\%$  compared to  $33\pm 6\%$  for cystectomy alone group.

Zaghoul et al. [32] reported that the 5 year disease free survival was  $47\pm 6\%$  for patients who received postoperative radiotherapy (153 patient) compared to  $25\pm 5\%$  for patients treated with cystectomy only (83 patient). Reisinger et al. [24] reported that the 5-year disease free survival rate was 67% for patients received a similar dose of postoperative radiotherapy (with 5 Gy single preoperative dose at the day of the operation). El-Debawy [8] reported that the 4-year disease free survival rate was  $75.8\%\pm 4\%$ .

The incidence of distant metastasis was low in early Egyptian bladder cancer series ranged between 2-5.8%. [11,14] while in the recent reports systemic metastasis had as much higher incidence as 23% [30].

This change was probably due to the addi-

tion of adjuvant local measures either in the form of preoperative or postoperative radiotherapy that had lead to better local control and subsequently a longer disease free survival which allowed a greater number of distant metastasis to manifest and appear [32].

In the present study distant metastasis occurred in 9 patients (10%). The 3-year distant metastases free survival rate was  $82\pm 7\%$  that means that the cumulative distant metastases rate at 3-years was 18%, an incidence much similar to that reported earlier by Zaghoul [30]. Five of these reported distant metastasis were in bone (55.6%), two in the lung (22.2%), one in the liver (11.1%), and one in the brain (11.1%).

This result agreed with Zaghoul [30], that 70% of reported metastasis were skeletal, followed by lung 24%, nodal sites outside the pelvis were reported in 8%, liver in 6% of distant metastasis, the remaining 6% of distant metastatic patients had brain deposits.

The independent risk factors for distant metastasis and local control were: Pelvic lymph node involvement ( $p=0.005$ ), pathological stage ( $p=0.004$ ) and histopathological grade ( $p=0.05$ ) [32].

For each advancement of stage there was a significant reduction in the probability of survival in bladder cancer patients treated with radical cystectomy. The 5 year disease free survival rate amounted to 73% in P1 tumour, 65% in P2 tumour, 43% in P3a tumour, 31% in P3b tumour and 9% in P4 tumour [26]. However, in the present study no difference was noticed in the various muscle-invasive pathological stages as the 3-year disease free survival for P2b patients was  $66\pm 13\%$ , while those with P3 pathological stage had  $83\pm 7\%$  disease free survival. Patients having the pathological stage P4a had a 2year disease free survival rates of  $75\pm 21\%$ . This may be mainly attributed to the addition of postoperative radiotherapy to all patients that ameliorated, to a great extent, the effect of advancement of stage on local recurrence and hence on disease free survival.

In the present study the 2-year disease free survival according to lymph node status was 83.3% for lymph node negative patients and  $57\pm 15\%$  for lymph node positive patients.

There was no statistical significant difference between different pathological subtypes;

as the 3-year disease free survival rate was  $73\pm 14\%$  for squamous cell carcinoma while it was  $53\pm 15\%$  for transitional cell carcinoma. This finding was agreed upon in different series containing mixed pathology bladder cancer [5,9,11,13,14,15,30,31,32].

Furthermore, Frazier et al. [12] reviewed 531 patients and concluded that pathological stage, grade, nodal involvement and age at surgery were significant factors influencing cancer - specific survival. However tumor histological type was not associated with survival differences [12,15].

In the present study the 3-year local control rate was  $78.6\pm 9\%$  while the 5-year local control rate reported by Zaghloul et al. [32] was  $93\pm 3\%$  for conventional postoperative radiotherapy. This is probably due to prolongation of the overall period for delivery of postoperative radiotherapy as more than 40% of the patients received there treatment in an overall period more than 40 days. Those whose overall treatment periods were of 40 days or less had 2 year DFS of  $77.6\pm 8\%$  compared to  $46.8\pm 16\%$  for those received treatment in more than 40 days. This coordinate with De-Neve et al. [4] that prolongation of overall period of delivery of postoperative radiotherapy reduce the local control rate for bladder cancer. Also, prolongation of the prescribed treatment for a variety of reasons has been shown to reduce local control rate for different types of carcinoma; the cervix, lung, head and neck and breast [2,22,29].

This is not in accordance with Safwat and Bond. [25], who did not find a significant effect of unplanned treatment gap on the local control rate.

We can conclude that the present study, though non-randomized, still show a benefit of postoperative radiotherapy in bladder cancer through improving the local control that was reflected in the disease free survival. The present study results coincided with the published data for patients treated with the same type of treatment and emphasized the importance of adding postoperative radiotherapy to cystectomized patient in order to improve the disease free survival of muscle-invasive bladder cancer patients.

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