

Retrospective study of effect of post-operative radiotherapy on control of cancer urinary bladder stage two and three

Ali Mohamed Ali, Ahmed M. Ameen, Shimaa Roshdy Abdelaal

Clinical Oncology Department, Faculty of Medicine, Sohag University

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Abstract:

Aim of the work: evaluate benefit of post-operative radiotherapy in stage two and three bladder cancer after radical cystectomy as regard LRC, OS, DFS, and MFS and evaluate toxicity profile.

Patients and Method: A retrospective study of sixty two patients with pathologically proven bladder cancer who presented to the clinical oncology department, sohag University hospital from januray 2010 to December 2014. All of them underwent RC or anterior pelvic exenteration followed by post-operative radiotherapy after surgery for 5000 cGy in 25 fractions, over 5 weeks using 2D technique. This study was conducted by hand search in the files and radiotherapy sheet of these patients.

Results: Sixty two eligible bladder cancer patients were included in our study; it includes 39 males (63%) and 23females (37%), with a male to female ratio of 1.7:1. The mean age was 58.15 years. Transitional cell carcinoma representing (61%) of cases while SCC representing (39%) of cases

Forty eight patients of our study developed acute and chronic toxicities (77%), Out of 62 eligible bladder cancer patients, 2 patients (3%) developed local recurrence, while 8 patients (13%) developed distant metastasis, The 2, 3 and 5yr OS of the whole cohort of patients are 66%, 64% and 53.5% respectively, The 2, 3 and 5yr MFS of whole cohort of patients was 90%, 84% and 80.5% respectively, The 2, 3 and 5yr LRC of whole cohort of patients was 95%, 95% and 95% respectively.

Conclusion: In our retrospective study, post-operative radiotherapy showed good OS, DFS, LRC and MFS rates that were in agreement with some previous studies. Due to the small number of patients, the relatively short follow up periods and the statistical bias linked to retrospective design of clinical studies, further prospective studies with longer follow up periods are warranted to better evaluate such an effect better with using new radiotherapy modalities such as CRT and IMRT.

Introduction:

Bladder cancer is the ninth most common cancer worldwide and is more common in developing countries (1). In Egypt, bladder cancer incidence is much higher than reported in western countries, bladder cancer contributed 6.94% of all cancer in Egypt according to results of the National Population-Based Registry Program of Egypt 2008–

2011, and males are more affected than females (2).

There are different histological subtypes of bladder cancer, For decades, SCC was considered the most common pathological subtype of cancer bladder in Egypt but this has changed greatly over the years, according to the NCI study in 2007, TCC predominated over SCC (3).

Radical cystectomy (RC) and pelvic lymphadenectomy with or without neoadjuvant chemotherapy still remains the gold standard treatment for muscle-invasive bladder cancer (4). Local regional recurrence following radical cystectomy for patients with muscle-invasive UBC is common, it accounts for approximately 75% of the failures of this treatment (5). A meta-analysis of randomized controlled trials with or without platinum-based chemotherapy following local therapy (usually RC) showed that 25.6% of patients with chemotherapy had locoregional recurrence as a first event with or without synchronous distant metastasis (6). Local disease control is a clinically relevant challenge in the management of muscle-invasive bladder carcinoma. In an attempt to increase locoregional control, the use of postoperative radiotherapy (PORT) was explored decades ago and demonstrated robust local control. Postoperative radiotherapy has the advantage of dealing with microscopic cells that are easier to sterilize (7). The radiation-induced late complications are the main limiting factor for the use of PORT after RC worldwide; however, the risk for radiation-induced complications can be minimized by novel radiotherapy techniques CRT or IMRT (8).

Aim of the work:

1. Evaluate benefits of post-operative radiotherapy in stage II & III bladder cancer after radical cystectomy as regard LRC, OS, DFS & DFFS.
2. Evaluate toxicity profile .

Materials and Methods:

Our study included 62 patients with pathologically proven bladder cancer who presented to the Oncology department, Sohag University Hospital,

from January 2010 till December 2014. Informed consent was taken from all cases whenever possible.

▼ Exclusion criteria:

Patients with end organ failure, patients with stage one or metastatic disease, patients with histological types other than (TCC, SCC, adenocarcinoma).

▼ Methods

All the patients were subjected to radical cystectomy or anterior pelvic exenteration with urinary diversion and referred to our department for post-operative radiotherapy. The patients underwent clinical examination, routine labs, CT chest, abdomen & pelvis. The patients were staged according to the American joint committee of cancer clinical staging system 2010. After being certain of no metastasis, the patients underwent simulation using our 2-D simulator machine to define volume to be treated. The patients were treated by 3 fields, one anterior and 2 lateral wedged fields aiming at delivering 50 GY /25 fractions /5 weeks to isocenter by our 6 MV linear accelerator. The volume to be treated for all patients was as follow :

- Upper border: between lumbar vertebra five and the first sacral vertebra .
- Lower border: at the inferior border of obturator foramen.
- Lateral border: 1.5 cm outside the bony pelvic brim.
- The anterior border of the lateral field lies just in front of the symphysis pubis.
- The posterior border at the junction of anterior one third and posterior two thirds of the rectal circumference or the junction of the first and second sacral vertebrae.

Follow up was done weekly during radiotherapy as regard evaluation of toxicity. The follow up visits after radiotherapy made every 3 months, during which patient underwent clinical examination, routine labs, radiological examination when indicated.

Assessment of outcomes of treatment was done by means of the following end points:

- Overall survival (OS): the period started from the date of diagnosis until patient death or time of last follow up.
- Disease free survival (DFS): the period started from the date of cystectomy until the first appearance of relapse (local, nodal or systemic) or the last date of follow up.
- Local control period: is the time started from the date of cystectomy until appearance of loco regional

Results:

Sixty two patients who were fulfilling our eligibility criteria were included in our study, the follow up period ranged between 30 to 60 months with median at 36 months. The patient's age range between (30years-75years) with mean age 58.15years.

Follow up of the patients was done in Sohag University Hospital, Health Insurance, Sohag Cancer Institute. Some patients couldn't be assessed except by telephone.

Sixty two eligible bladder cancer patients were included in our study; it includes 39 males (63%) and 23 females (37%), with a male to female ratio of 1.7:1. The mean age was 58.15 years. Twenty patients were smokers (32%), 3 patients had history of bilharziasis (5%), 9 patients were hypertensive (15%) and 6 patients were diabetic (10%) as shown in table (1).

Transitional cell carcinoma representing (61%) of cases while SCC representing (39%) of cases. High grade tumors (grade 3) representing 58% while low grade tumors representing 42%. The commonest pathological stage was pT3b which was reported in 47% of patients followed by pT2b counted in 23% of patients as shown in table (2)

Surgery in the form of radical cystectomy was performed for 50 patients constituting (81%) of all patients, Anterior pelvic exenteration was performed for 12 patients constituting (19%) of all patients. All patients received post-operative radiotherapy 50 GY in 25 fractions in 5 weeks with or without concurrent weekly chemotherapy. Thirty two (52%) of the patients received concurrent chemotherapy, 8 of them (25%) received carboplatin and 24 (75%) received cisplatin. Thirty five of the cases (56%) received their radiotherapy course in ≤ 40 days as shown in table (3).

recurrence, or time of last follow up in those who did not develop local recurrence.

- Metastasis free survival (MFS): the period from cystectomy until first appearance of dissemination or time of last follow up in those who did not develop distant metastasis.

Statistical analysis:

Data was analyzed using STATA intercooled version 12.1. Quantitative data was represented as mean, standard deviation, median and range. Qualitative data was presented as number and percentage. Survival analysis was done using Kaplan-Meier method and comparison between two survival curves was done using log-rank test. Graphs were produced by using Excel or STATA program. P value was considered significant if it was less than 0.05.

Forty eight patients of our study developed acute and chronic toxicities (77%), 41 patients (66%) developed acute intestinal toxicity, 3 patients (5%) developed late intestinal toxicity, 15 patients (24%) developed acute skin toxicity, 12 patients developed acute renal toxicity and 8 patients developed chronic renal toxicity as shown in table (4).

Out of 62 eligible bladder cancer patients, 2 patients (3%) developed local recurrence, while 8 patients (13%) developed distant metastasis, 4 of them (6% of total sample) developed bone metastasis, 3(5% of total sample) developed lung metastasis and only one (2% of total sample) developed liver metastasis as shown in table (5).

The 2,3 and 5yr OS of the whole cohort of patients are 66%,64% and53.5% respectively , on analyzing the impact of different clinico_ pathological factors as shown in table(6) we found that, age , biharzial infestation and pathological type significantly affected OS with P-value at 0.001, 0.01 and 0.04 respectively .

The 2, 3 and 5yr DFS of whole cohort of patients are 86%,83% and79% respectively, on analyzing the impact of different clinico_ pathological factors as shown in table(7), pathological type found significantly affected DFS(P-value 0.04).

The 2, 3 and 5yr LRC of whole cohort of patients was 95%,95% and 95% respectively , on analyzing impact of different clinico_ pathological factors as shown in table (9), no factor found significantly affected LRC.

The 2, 3 and 5yr MFS of whole cohort of patients was 90%,84% are 80.5% respectively , on analyzing impact of different clinico_ pathological factors as shown in table(8), no factor found significantly affected MFS.

Table (1): Patient's characteristics

Characteristics	Number	Percentage (%)
Age		
≤65 years	43	69.35
>65 years	19	30.65
Gender		
Females	23	37.10
Males	39	62.90
Smoking		
No	21	33.87
Yes	20	32.26
Unknown	21	33.87
Bilharziasis		
No	32	51.61
Yes	3	4.84
Unknown	27	43.55
Hypertension		
No	36	58.06
Yes	9	14.52
Unknown	17	27.42
DM		
No	42	67.74
Yes	6	9.68
Unknown	14	22.58

Table (2): disease characteristics of studied populations

Characteristics	Number	Percentage (%)
Surgical pathological type		
SCC	24	38.71
TCC	38	61.29
Surgical pathological grade		
Grade 1	5	8.06
Grade 2	21	33.87
Grade 3	36	58.06
T stage		
T2b	14	22.58
T3a	9	14.52
T3b	29	46.77
T4a	10	16.13

Table (3): treatment characteristics

Treatment given	Number	Percentage (%)
Surgery		
Anterior pelvic exenteration	12	19.35
Radical cystectomy	50	80.65
Diversion type		
Neo bladder	19	30.64
Uretero colic	11	17.75
Uretro cutaneous	32	51.61
Post-operative radiotherapy 50 CGY /25 fraction /5 weeks	62	100%
Concurrent chemotherapy		
No	30	48.39
yes	32	51.61
Type of used chemotherapy		
Weekly Carboplatin	8	25
Weekly cisplatin	24	75
Duration of radiotherapy/day		
≤40	35	56.45
>40	27	43.55

Table (4): Toxicity in studied populations

Characteristics	Number	Percentage (%)
Toxicity		
No	14	22.58
Yes	48	77.41
Acute intestinal toxicity		
No	21	33.87
Yes	41	66.13
Chronic intestinal toxicity		
Yes	3	4.83
No	59	95.16
Acute skin toxicity		
No	47	75.81
Yes	15	24.19
Chronic skin toxicity		
No	62	100
Acute urinary toxicity		
No	50	80.65
Yes	12	12.90
Chronic urinary toxicity		
No	54	87.1
Yes	8	12.9

Table (5): local recurrence and distant metastasis in studied population

Characteristics	Number	Percentage (%)
Local recurrence		
No	60	96.77
Yes	2	3.23
Distant metastasis		
No	54	87.10
Bone	4	6.45
Liver	1	1.61
Lung	3	4.84
Death		
No	36	58.06
Yes	26	41.94

Table (6): Overall survival of studied cases and its relation to different factors

Factors	Number	Cum survival at 2 yrs %	Cum survival at 3 yrs %	Cum survival at 5 yrs %	P-value
Whole group	62	66.09	64.25	53.41	
Age					
≤65 years	43	76.74	74.19	66.53	0.001
>65 years	19	42.11	42.11	22.46	
Gender					
Females	23	65.22	65.22	53.51	0.93
Males	39	66.57	63.67	52.90	
Smoking					
No	21	47.62	47.62	31.75	0.06
Yes	20	70.00	64.62	57.44	
Unknown	21	80.95	80.95	67.25	
Bilharziasis					
No	32	50.00	50.00	34.29	0.01
Yes	3	66.67	33.33	33.33	
Unknown	27	85.19	85.19	74.71	
Surgical pathological type					
SCC	24	53.85	48.95	37.30	0.04
TCC	38	73.68	73.68	63.77	
Surgical pathological grade					
Grade 1	5	100	100	100	0.23
Grade 2	21	57.14	57.14	50.79	
Grade 3	36	66.67	63.64	47.25	
T stage					
T2b	14	57.14	57.14	57.14	0.34
T3a	9	88.89	76.19	76.19	
T3b	29	55.17	55.17	45.14	
T4a	10	90.00	90.00	56.52	
Duration of radiotherapy/day					
≤40	35	62.86	59.86	49.37	0.45
>40	27	70.18	70.18	60.15	
Concurrent chemo therapy					
Yes	32				0.07
No	30				

Table (7): Diseasefree survival of studied cases and its relation to different factors

Factors	Number	Cum survival at 2 yrs %	Cum survival at 3 yrs %	Cum survival at 5 yrs %	P-value
Whole group	62	86.07	83.10	79.32	
Age					
≤65 years	43	91.65	87.66	82.79	0.12
>65 years	19	68.63	68.63	68.63	
Gender					
Females	23	85.52	85.52	77.75	0.78
Males	39	86.27	80.88	80.88	
Smoking					
No	21	82.54	68.78	68.78	0.32
Yes	20	87.50	87.50	87.50	
Unknown	21	89.16	89.16	81.73	
Bilharziasis					
No	32	84.08	74.73	74.73	0.25
Yes	3	50.00	50.00	50.00	
Unknown	27	91.83	91.83	86.09	
Surgical pathological type					
SCC	24	74.41	66.97	66.97	0.04
TCC	38	93.38	93.38	86.71	
Surgical pathological grade					
Grade 1	5	100	100	100	0.28
Grade 2	21	77.54	69.79	69.79	
Grade 3	36	88.26	88.26	78.45	
T stage					
T2b	14	77.78	62.22	62.22	0.74
T3a	9	87.50	87.50	87.50	
T3b	29	87.67	87.67	87.67	
T4a	10	90.00	90.00	67.50	
Duration of radiotherapy/day					
≤40	35	83.56	79.16	74.22	0.23
>40	27	89.72	89.72	89.72	

Table (8): distantmetastasis free survival of studied cases and its relation to different factors

Factors	Number	Cum survival at 2 yrs %	Cum survival at 3 yrs %	Cum survival at 5 yrs %	P-value
Whole group	62	89.95	84.44	80.60	
Age					
≤65 years	43	94.45	90.35	85.33	0.08
>65 years	19	76.69	65.73	65.73	
Gender					
Females	23	90.34	83.89	76.26	0.61
Males	39	89.51	83.92	83.92	
Smoking					
No	21	88.89	66.67	66.67	0.20
Yes	20	93.33	93.33	93.33	
Unknown	21	89.16	89.16	81.73	
Bilharziasis					
No	32	92.98	77.48	77.48	0.29
Yes	3	0.50	50.00	50.00	
Unknown	27	91.83	91.83	86.09	
Surgical pathological type					
SCC	24	84.44	70.15	70.15	0.10
TCC	38	93.38	93.38	86.71	
Surgical pathological grade					
Grade 1	5	100	100	100	0.42
Grade 2	21	82.54	74.29	74.29	
Grade 3	36	91.67	87.08	77.41	
T stage					
T2b	14	87.50	70.00	70.00	0.93
T3a	9	87.50	87.50	87.50	
T3b	29	91.71	85.16	85.16	
T4a	10	90.00	90.00	67.50	
Duration of radiotherapy/day					
≤40	35	86.84	78.53	73.62	0.12
>40	27	94.44	94.44	94.44	

Table (9) LRCof studied cases and its relation to different factors

Factors	Number	Cum survival at 2 yrs %	Cum survival at 3 yrs %	Cum survival at 5 yrs %	P-value
Whole group	62	95.30	95.30	95.30	
Age					
≤65 years	43	96.67	96.67	96.67	0.32
>65 years	19	90.00	90.00	90.00	
Gender					
Females	23	94.44	94.44	94.44	0.72
Males	39	95.83	95.83	95.83	
Smoking					
No	21	92.31	92.31	92.31	0.50
Yes	20	93.33	93.33	93.33	
Unknown	21	100	100	100	
Bilharziasis					
No	32	89.67	89.67	89.67	0.30
Yes	3	100	100	100	
Unknown	27	100	100	100	
Surgical pathological type					
SCC*	24	86.54	86.54	86.54	0.049
TCC	38	100	100	100	
Surgical pathological grade					
Grade 1	5	100	100	100	0.81
Grade 2	21	92.31	92.31	92.31	
Grade 3	36	96.30	96.30	96.30	
T stage					
T2b	14	85.71	85.71	85.71	0.62
T3a	9	100	100	100	
T3b	29	95.65	95.65	95.65	
T4a	10	100	100	100	
Duration of radiotherapy/day					
≤40					0.96
>40	35	96.00	96.00	96.00	
	27	94.74	94.74	94.74	

Discussion:

Bladder cancer is a common malignancy in Egypt; it is representing 6.94% of all cancers (2).

In this retrospective study, 62 patients with bladder cancer presented to the clinical oncology department in Sohag University Hospital, all underwent RC and received PORT. Several epidemiological and clinical factors were studied as well as prognostic factors influencing local tumor control, distant disease failure in addition to survival. Bladder cancer is typically diagnosed in older individuals; with a median age at time of diagnosis is 73. It is more common in males than in females with a 3:1 ratio (3).

In our study 69.35 % of patients were ≤ 65 years at time of diagnosis with mean age at 58.15 year. The male to female

ratio is (1.7:1). Younger age has better 5-ys OS that is 66.5% for patients ≤ 65 yr versus 22.5% for patient >65 yr (p- value 0.001), this may be due to comorbid disease association with older age as shown in table (6).

Transitional cell carcinoma was found more prevalent in our cohort of patients representing 61% versus squamous cell carcinoma that found in 39% of patients as seen in table (2), also association with bilharzial infestation was seen in small percent of our patients (4%). Such these findings also observed by other investigators such as Gouda I and colleagues who conducted a study on 9843 patients in NCI, Cairo Egypt and found that 65.8 % of patients were TCC and association with bilharzial

infestation was found in 55% in contrast to 82 % in older series. (3)

Postoperative radiotherapy led to marked reduction in the incidence of local recurrence and hence improved the disease-free survival in bladder cancer patients (7). Many Egyptian series had been performed to assess postoperative radiotherapy and its influence on survival. Well-conducted retrospective randomized series reported that postoperative radiotherapy improved disease free survival concerning different stages, different grades and lymph nodal status (12). The beneficial effect of PORT was proved in a large prospective randomized trial at NCI-Cairo, including 236 patients, for locally advanced bladder cancer patients. The 5 year LC rates were $87\% \pm 4\%$ and $93\% \pm 3\%$ for hyperfractionated (HF) and conventional (CF) PORT respectively compared to $50\% \pm 6\%$ for the cystectomy alone group. This effect was consistent across all tumor types, grades and pathologic stages whether or not the lymph nodes were involved. The 5-year LC rates for pT3a, pT3b, and pT4a were 96%, 91%, and 74% respectively (7). These results were confirmed in nonrandomized controlled Radiation Therapy Oncology Group (RTOG) trials, Cozzarini et al. (1999) and other Egyptian and non-Egyptian series for patients having TCC, SCC, and adenocarcinoma (12). Better DFS and LC rates with PORT were also reported by Reisinger et al. (1992) who found that, DFS rates ranged between 45% - 79% while LC rates ranged between 79% - 97% in patients received PORT (13).

In 2015, Nasr and colleagues conducted a study to reevaluate this protocol regarding its effect on prognosis and complications, the results were published in 2015 and showed high LC

rates at 93% similar to results described previously by Zaghoul et al. 1992. (12) Depending on these results, the routine work at NCI-Cairo was to give PORT for bladder cancer patients with T-stage \geq pT2b or node positive cases (12).

In our study 3-years LRC is 95 % for whole group, 3-years DFS is 83 % for whole group and 3-years OS is 64 % for whole group as shown in table (6, 7 and 9).

Synchronous chemo radiotherapy may have advantages over radiotherapy alone, only one randomized trial has compared these two approaches in bladder cancer which reported that addition of chemotherapy to standard-dose radiotherapy was associated with a relative reduction of 33% in the risk of loco regional recurrence with a reduction of almost 50% in invasive recurrences compared with radiotherapy alone, and resulted in good long-term bladder function. (14). In our study concurrent weekly chemotherapy has no impact on survival (p-value 0.07) as shown in table (6).

With reference to period of overall treatment, prolongation of overall period of delivery of postoperative radiotherapy reduces the local control rate for bladder cancer (18). In Zaghoul, et al 2002, 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 (17). But this is not reported in Safwat and Bond study that did not find a significant effect of unplanned treatment gap on the local control rate (19).

In our study, Those whose overall treatment periods were of 40 days or less had 2-yr LRC rate of 96% compared to 94.7% for those received treatment in

more than 40 days with P-value (0.96) as shown in table (9). This was also going with Safwat and Bond study that showed that the duration of treatment had no significant impact on local control.

The incidence of distant metastasis was low in early Egyptian bladder cancer series ranged between 2-5.8% (21). While in the recent reports systemic metastasis had as much higher incidence at 23%. (20). This change was probably due to the addition of adjuvant local measures either in the form of preoperative or postoperative radiotherapy that had led to better local control and subsequently a longer disease-free survival which allowed a greater number of distant metastasis to manifest and appear, The independent risk factors for distant metastasis and local control were: pelvic lymph node involvement ($p=0.005$), pathological stage ($p=0.004$) and histo pathological grade ($p=0.05$) (7).

In the present study distant metastasis occurred in 8 patients (13%). The 3-yr DFFS rate is 84.5 % that means that the cumulative distant metastases rate at 3-yr is 15.5%, an incidence similar to that reported earlier by Zaghoul 1996 as shown in table (7). Four of these reported distant metastasis were in bone (50%), three in the lung (37.5%), and one in the liver (12.5%) as shown in table (5).

Post-operative radiotherapy in bladder cancer remains unpopular owing to the fear of late intestinal complications. Warning results were published by Reisinger et al. (1992) as they reported 37% (15 out of 40 patients) rate of intestinal obstruction in patients who received PORT. Nine out of these 15 patients required surgery and three died (13). In contrast, Zaghoul et al. (1992) had 14 out of the 78 patients (18%)

treated with post-operative conformal radiotherapy (CRT) and four out of the 75 patients (5%) treated with hypo fractionated (HF) PORT, experienced chronic enteritis of different grades. Only three (4%) and four (5%) out of the CRT and HF patients, respectively, progressed to fistula that necessitated surgery (7). Similar complications were experienced by adenocarcinoma patients treated with PORT in a nonrandomized study comprising 192 patients after RC and pelvic lymphadenectomy (19). The difference in late sequelae between the latter two studies and that of Reisinger et al. (1992) was probably due to the larger volume of radiation used in the Reisinger et al. (1992) study (upper border at fourth Lumbar vertebrae) or the biologically higher dose reaching intestine as patients were given 500 CGy single dose preoperatively followed by 4000- 4500 CGy CF postoperatively, which led to severe late bowel complications. Also, Nasr et al. (2015) study documented ~71% (148 patients) suffered from small bowel reactions (diarrhea/abdominal colic) mostly of grade 1 and 2 intensity with 55% and 43% respectively. Bleeding per rectum was encountered in only 4 patients (3%). Grade 4 early bowel reactions were not experienced in any of the 208 patients. As for the late toxicity, 24% suffered late reactions; lower limb edema, scrotal swelling, ureteric stricture. Only 6 patients (3%) suffered from intestinal obstruction, in this study the figure was much less than that seen in Reisinger et al. (1992) study and claiming the continuous benefit of PORT with low complications that were seen in Zaghoul et al. (2006) study (12).

In our study 48 out of 62 patients (77.5%) developed toxicities, 41 patients (66%) had shown acute intestinal

toxicities (Increased frequency or change in quality of bowel habits / rectal discomfort), most of them grade 1 and 2 and did not need any surgical intervention, 15 patients (24%) developed acute skin toxicities (erythema / epilation / dry desquamation), most of them grade 1 and 2, only 3 patients (5%) with chronic intestinal toxicities as shown in table (4).

References

- 1-Torre LA, Bray F, et al (2015): Global cancer statistics, 2012. CA Cancer J Clin; 65:87.
- 2-Amal S. Ibrahim, Hussein M. Khaled, et al (2014): Journal of Cancer Epidemiology Volume 2014 (2014), Article ID 437971, 18 pages.
- 3-Gouda, I., Mokhtar, N., Bilal, D., et al (2007); Bilharziasis and Bladder Cancer: Journal of the Egyptian National Cancer Institute, 19, 158-162.
- 4-Bolenz, C, Ho, R, Nuss, G.R, et al (2010) ,BJU International, 106, 1324-1329.
- 5-Ghoneim MA, El-Mekresh MM, El-Baz MA, (1997): Radical cystectomy for carcinoma of bladder: Critical evaluation of the results of 1026 cases. J. Urol., 158: 393.
- 6-Abol-Enein, H., et al. (2005): Neoadjuvant Chemotherapy for Invasive Bladder Cancer. Cochrane Database of Systematic Reviews, Article ID: CD005246
- 7-Zaghloul MS, Awwad HK, (1992), Int J Radiat Oncol Biol Phys; 23: 511-7.
- 8-Madersbacher S, Schmidt J, Eberle JM, et al (2003): Long-term outcome of ileal conduit diversion. J Urol; 169: 985.
- 9-Reisinger SA, Mohiuddin M, et al (1992): Combined pre- and postoperative adjuvant radiation therapy for bladder cancer. Int J Radiat Oncol Biol Phys; 24: 463-8
- 10-Nicholas D. James, Syed A. Hussain, et al (2012) ,N Engl J Med 2012; 366:1477-1488.
- 11-Balci, U., Ozer, K., Gorgel, S.N., Sefik, E., et al (2013): World Journal of Urology, 31, 1177-1182.
- 12-De-Neve W., Lybeert M.L., et al (1995): Radiotherapy for 72 T3 carcinoma of the bladder: the influence of over all treatment time. Radiat Oncol; 36: 183-188.
- 13-Safwat A. and Bond S, et al (1999): Unplanned treatment gaps in post-operative, Radiotherapy of carcinoma in the bilharzial bladder, the results of an audit. J. Egypt Nat. Cancer Inst., 11: 271-277.
- 14-Zaghloul, M.S., Nouh, A., Nazmy, Zaghloul, A.S., et al (2006) ,Urologic Oncology: 24, 13-20 .
- 15-Zaghloul M.S, et al (1996): Distant metastasis from bilharzial bladder cancer. Cancer 77: 743-749
- 16-El-Sebai I, et al (1983): Bladder cancer, CRC Press, Vol., II: 163-197.