Research Article

The impact of post operative radiotherapy in treatment of stage II and III and IVA bladder cancer

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Abstract

Introduction: Bladder cancer (BC) is a common type of cancer and ranks the ninth most common cancer worldwide but more prevalent in the developing countries. In Egypt, it represents 6.94% of all cancer according to results of the National Population-Based Registry Program of Egypt 2008–2011, with predominance in males more than females. The major risk factors for BC particularly transional cell carcinoma (TCC) are smoking & occupational exposures but the main risk factor for squamous cell carcinoma (SCC) in developing countries is bilharzial infestation. Radical cystectomy (RC) and pelvic lymphdenectomy with or without neoadjuvant chemotherapy still remains the gold standard treatment for muscle-invasive bladder cancer. Due to the relatively high incidence of loco regional recurrence, the use of postoperative radiotherapy (PORT) was explored decades ago and demonstrated robust local control. **The Aim of the work** is to evaluate the outcome of PORT in stage II, III and IVA bladder cancer after RC on the level of overall survival (OS), local failure free survival (LFFS) and, distant failure free survival (DFFS) and to evaluate toxicity profile. **Patients and methods:** We retrospectively analyzed the registered data in the files of patients with BC treated in The Department of Clinical Oncology, Sohag Faulty of Medicine, Sohag University between January 2010 till December 2014 who fulfilled the eligibility criteria. Sixty two patients were collected and analyzed. **Results:** The median follow up period was 36 m. The 2, 3 and 5yr OS of the whole cohort of patients are 66%, 64% and 53.5% respectively. The 2, 3 and 5yr LFFS are 90%, 84% and, 80.5% with similar figures for DFFS. Age, and pathological type significantly affected OS with P-value at 0.001and 0.04 respectively. Radiotherapy associated acute intestinal toxicities developed in 41 (66%) patients and 3 patients (5%) suffered from late intestinal toxicities. **Conclusions:** PORT showed good OS, LFFS and, DFFS rates that were in agreement with some antecedent studies. Further prospective studies with longer follow up periods are warranted.

Key words: bladder cancer, post operative radiotherapy.

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Introduction

Amongst all cancers, BC ranks the ninth most common cancer worldwide. Around 429,800 new cases diagnosed in 2012 representing 3% from the total new cases. [1]

A large variation of incidence was reported in the literature, the highest incidence was reported in Southern Europe and North America while lowest rates reported in Estern Europe, Western Africa and, Asian countries.[2]

In Egypt, BC is a common malignancy accounting for about 6.94% of all cancers.[3]

Cigarette smoking is a strong risk factor for BC in both sexes and is estimated to be implicated in around 50% of tumors.[4]

The carcinogenic chemicals in the smoke like B-naphthylamine and polycyclic aromatic hydrocarbons are excreted in urine and exert their carcinogenic effect on the whole urinary tract.[5] Heavy smokers (≥ 30 pack-years) are more prone to develop high-grade, muscle invasive tumors compared with non-smokers.[6]

Occupational exposure to carcinogens like aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydro-carbons comes next to smoking as a risk factor for BC, associated with about 20% of cases, this type of exposure occurs mainly in industrial areas processing paint, dyes, metals, and petroleum products.[7]

Contamination of drinking water with arsenic is associated with double risk of BC.[8]
Bladder cancer could arise as a consequence of exposure to ionizing radiation. There is a significant increased risk after at least five years following irradiation, 15% after more than five years, and 34% after 10 years.[9]
Chronic cystitis that is based on recurrent infection with a parasitic trematode which is endemic in some parts of northern Africa, predispose individuals to bladder tumorigenesis, mainly SCC.[10]

It is hypothesized that various growth patterns of various urothelial tumors may resulted from various abnormal molecular pathways. Generally speaking, alterations in chromosome 9 are implicated in early development of urothelial neoplasia. Loss of heterozygosity in this chromosome is frequently seen in BC. Tuberous sclerosis gene (TSC1), a tumor suppressor gene controlling the mammalian target of rapamycin pathway (mTOR). It presents on chromosome 9 and mutations in TSC1 are found in a large percentage of BC suggesting an important role for this gene in urothelial neoplasia. In case of low-grade papillary urothelial carcinoma, different mutations in genes associated with mitogen activated protein kinase (MAPK) pathway and phosphorinositide 3-kinase (PI3K) pathways are frequently seen including mutations in HRAS, and fibroblast growth factor receptor 3 (FGFR3).[11,12]

Mutations in FGFR3 are identified in non invasive papillary tumors at a much higher rate than in flat CIS or in invasive tumors, suggesting that its presence may be a favorable prognostic factor.[13,14]
Also associated with low-grade noninvasive carcinoma and recurrence free survival are some mutations in PIK3CA[15,16]. In contrast, high-grade flat and invasive lesions are featured by mutations in the tumor suppressor gene TP53 and genes downstream of it like, p16, p21, p27, cyclin D1, cyclin D3, and retinoblastoma gene (RB).[17]

Complete physical examination including pelvic examination should be performed. Full urologic evaluation of the entire urinary tract is indicated including cysto urethroscopy, urine cytology, and also, evaluation of the upper urinary tract, since urothelial malignancies can be found multifocal.[18]

CT scans of chest, abdomen, and pelvis should be done with and without contrast. CT may demonstrate extra vesical extension, nodal involvement, visceral, pulmonary, osseous metastasis, and tumor involvement or obstruction of the upper urinary tract.[19]. MRI is as reliable as CT for demonstrating invasive and locally advanced disease. It could be superior than CT in assessment of tumors at the base and dome of the bladder, to detect superficial, multiple lesions, extravesical extension, and surrounding organ invasion.[20]

TNM system is the standard staging system for BC. It is based on pathologic studies of cystectomy specimens.[21] Patients with muscle invasive disease are at high risk of recurrence and metastasis with transurethral resection of bladder tumor (TURBT) alone so they need further definitive treatment. Radical cystectomy (RC) remains the standard of care for high risk patients like T4a, CIS, multifocal tumors, incomplete TURBT and, hydronephrosis.[22]

Although RC is considered the standard therapy in such patients, considerable interest in bladder preservation has led to the use of external beam radiotherapy as an alternative, especially in patients less fit for RC. However, radical radiotherapy is associated with a relatively high rate of incomplete response or local recurrence (up to 50%).[23], and synchronous chemotherapy may have advantages over radiotherapy alone.[24-27]

So in selected patients, trimodality bladder preserving treatment with maximal TURPT followed by concurrent chemoradiotherapy could be followed since similar survival rates to RC are reported.[22] Based on results of meta analysis of 11 randomised trials included 3005 patients, the use of cisplatin-based neoadjuvant chemotherapy is associated with a 5% absolute increase in 5-year OS and a 9% absolute increase in 5-

year disease-free survival (DFS) compared with RC alone.[28]

This survival benefit encourages the use of platinum based combination chemotherapy before RC or definitive radiotherapy. Also, for adjuvant chemotherapy, an updated meta-analysis of 9 randomised trials including 945 patients found an OS benefit [hazard ratio: 0.77 (0.59–0.99) at 95% CI & P = 0.049] and DFS benefit (Hazard ratio: 0.66 (0.45–0.91) at 95% CI & P = 0.014) among those who received cisplatin-based adjuvant chemotherapy. The DFS benefit was more apparent with positive lymph node involvement. Usually from 3 to 4 cycles of chemotherapy with either methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) or gemcitabine and cisplatin (GC) are given. The three-drug regimen gemcitabine, cisplatin, and paclitaxel could also be considered in selected patients. [29]

Concerning radiotherapy, the main advantage of PORT is the availability of pathologic staging. This allows the administration of adjuvant irradiation only to those patients who have a high probability of tumor recurrence following radical cystectomy.[30] Many Egyptian series had performed to assess the influence of PORT on survival. Well conducted prospective randomized series reported that PORT lead to marked reduction in the incidence of local recurrence and hence improved the disease-free survival in BC in different stages, grades, and lymph node status.[31] These trials also helped establish the role of adjuvant radiotherapy as the standard of care for locally advanced disease in Egypt.[32]

The Aim of this retrospective work is to evaluate the benefits of post operative radiotherapy in stage II, III and IVA BC after RC on the level of OS, LFFS and DFFS also to evaluate toxicity profile.

Patients and methods

This retrospective study was conducted by hand search in the medical files and radiotherapy sheets of patients treated in Souhag Faculty of Medicine, Department of Clinical Oncology from January 2010 till December 2014 who were treated with RC and PORT.

Patients

The eligibility criteria include patients treated in Department of Clinical Oncology, Souhag Faculty of Medicine, either male or female aged between 18 -75 yr, with BC histological subtypes including TCC, SCC and, adenocarcinoma (ADC) of any grade with no history of prior pelvic irradiation, no organ failure and with median follow up period at least 6 ms.

Patients with stage I and IV B, those with metastasis, histological subtypes other than that mentioned above, also patients with history of previous cancer and those with no recorded follow up data were excluded from analysis.

Ethical approval was taken from the scientific ethics committee. The medical records of these patients were reviewed by the panel. All patients treated with RC with urinary diversion and referred to our department for PORT underwent clinical examination, routine labs, CT chest, abdomen and pelvis, performance status was evaluated using WHO scaling system and TNM stage of their cancers were categorized according to AJCC/TNM system that is given in tables 1 and 2 respectively.

Table (1): TNM classification of urinary bladder cancer.

Primary tumor (T)	
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Urothelial carcinoma in situ: "Flat tumor"
T1	Tumor invades lamina propria (subepithelial connective tissue)
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical soft tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Extravesical tumor
T4a	Extravesical tumor invades directly into prostatic stroma, uterus, vagina
T4b	Extravesical tumor invades pelvic wall, abdominal wall
Regional lymph nodes (N)	
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Distant metastasis limited to lymph nodes beyond the common iliacs
M1b	Non-lymph-node distant metastases

Table (2): American joint committee on cancer / TNM staging system for bladder cancer

Prognostic stage groups			
When T is...	**And N is...**	**And M is...**	**Then the stage group is...**
Ta	N0	M0	0a
Tis	N0	M0	0is
T1	N0	M0	I
T2a	N0	M0	II
T2b	N0	M0	II
T3a, T3b, T4a	N0	M0	IIIA
T1-T4a	N1	M0	IIIA
T1-T4a	N2, N3	M0	IIIB
T4b	Any N	M0	IVA
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB

Radiotherapy method

Upon confirmation of absence of distant metastasis the patients underwent simulation using our 2-D simulator machine to define the volume to be treated that were encompassing the pelvic lymph nodes and the bladder bed. The patients were treated by 3 fields, one anterior and 2 lateral wedged fields aiming at delivering 50 GY /25 fraction /5 weeks to the isocenter by our 6 MeV linear accelerator. The boundaries of treatment fields were extending from the interspace between the 5^{th} lumbar vertebra and the 1^{st} sacral one to the inferior border of the obturator foramena, while laterally it stops at 1.5 cm outside the bony pelvic brim. For the lateral fields, the upper and lower borders were the same as mentioned above but the anterior border was usually just in front of the symphysis pubis and the posterior one set at the junction of the first and second sacral vertebrae. The patients underwent planning and treatment in supine position with knee support and upper arms over the chest.

Toxicity assessment

During the course of radiotherapy and in the follow up period following irradiation, the patients underwent regular check up for assessment of treatment related toxicities using the Common Terminology Criteria for Adverse Events (CTCAE) version 3. Acute toxicities are considered when symptoms develop during radiotherapy and within 3 ms from its start and chronic toxicities are considered when symptoms persist after 3 ms from the start of radiotherapy or develop 3 ms or later from the start of radiotherapy.

Assessment of outcome

The primary objective of this study included the OS, LFFS, DFFS as indicators of the influence of PORT on treatment outcome. These indicators were defined as the period from the date of diagnosis until patient's death or time of last follow up for OS, the period from the end of radiotherapy until the date of appearance of first local or distant relapse or the date of last follow up for LFFS and DFFS respectively.

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.

Table 3: CTCAE V.3

GIT side effects	Grade	Clinical description
Diarrhea	G1	<4times per day over base line.
	G2	From 4 to 6 times per day over base line; I.V fluids indicated < 24 hours.
	G3	> 7 times per day over base line; incontinence; I.V fluids indicated > 24 hours.
	G4	Life threatening consequences
Proctitis	G1	Rectal discomfort, intervention is not indicated.
	G2	Intervention is indicated but symptoms do not interfere with ADL.
	G3	Stool incontinence or other symptoms interfering with ADL.
	G4	Life threatening consequences (e.g. perforation).
Bleeding per rectum	G1	Mild, requires iron supplements.
	G2	Symptomatic, requires medical intervention.
	G3	Requires intervention by transfusion, radiotherapy, . or surgery.
	G4	Life threatening condition.
vomiting	G1	1episode in 24 hours.
	G2	2-5episodes in 24 hours; i.v fluids indicated <24 hours.
	G3	> 6 episodes in 24 hours; i.v fluids or TPN indicated > 24 hours.
	G4	Life threatening consequences.
Urinary tract side effects	grade	Clinical description
Increase frequency of micturation	G1	Polyurea / nycturea up to 2 x normal.
	G2	More than 2x normal but < 1per hour.
	G3	>1per hour; urgency, catheter indicated .
Cystitis	G1	Asymptomatic
	G2	Frequency with dysurea , macroscopic haematurea.
	G3	Transfusion, i.v pain medications, bladder irrigations Indicated.
	G4	Severe bleeding that necessitate intervention.
hematuria	G1	Mild, requires iron supplements.
	G2	Symptomatic, requires medical intervention.
	G3	Requires intervention by transfusion, radiotherapy, or surgery.
	G4	Life threatening condition.

Results

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

The patient's and disease's characteristics were mentioned in table 4 and 5 respectively. Symptoms of the disease at presentation included hematuria (74%), dysuria (46%), frequency (3%), retention (3%), pelvic pain (2%), interrupted stream of urine (1%), and urgency (1%). Follow up of the patients was done in Sohag University Hospital, Some patients were contacted by telephone.

Treatment details including surgery, chemotherapy and, radiotherapy are summarized in table 6.

Treatment related toxicities included acute intestinal toxicities observed in most of the patients (49 patients; 79%) and included intestinal colic, diarrhea, constipation and rectal heaviness. Grade 1 toxicities was present in 30 patients (61%), grade 2 in 15

(30%) while grade 3 recorded in 4 patients (9%). No grade 4 toxicities were reported. Chronic intestinal toxicities were observed in 20 patients (32%) and included rectal heaviness, constipation, tenesmus and, bleeding per rectum. Grade 1 was present in 12 patients while, grade 2 was present in 8 ones. No significant association was observed between these toxicities either acute or chronic and studied risk factors including ages of the patients, gender, history of smoking, hypertension, diabetes mellitus, pathological subtype, stage of the tumor or, chemotherapy.

Acute skin toxicities were encountered in 15 patients (24.19%) and included grade 1 and 2 pubic hair loss and erythema. Chronic skin hyper pigmentation was observed in 10 patients with no recorded grade. No significant association was also observed between these toxicities either acute or chronic and studied risk factors including ages of the patients, gender, history of smoking, hypertension, diabetes mellitus, pathological subtype, stage of the tumor or, chemotherapy.

Acute urinary toxicities manifested by increased frequency of micturation and dysuria were recorded in 12 patients (19%) while chronic toxicities were observed in 8 ones (12.9%) including chronic increased frequency of micturition and hematuria were observed in 7 and 5 patients respectively. No reported grade was found. As in other toxicities mentioned above, no significant association was observed between these toxicities either acute or chronic and studied risk factors including ages of the patients, gender, history of smoking, hypertension, diabetes mellitus, pathological subtype, stage of the tumor or, chemotherapy. Table 7 summarizes incidence of treatment related side effects.

Outcomes of treatment at the end of the study are mentioned in table 8. Eight patients developed loco nodal recurrences after a mean time at 9 m (range: 4 – 15 m) all of them developed distant metastasis after a mean time at 10 m (range: 4 – 17 m).

The 2, 3 and 5yr OS of the whole cohort of patients are 66%, 64% and 53.5% respectively. On analyzing the impact of different clinico-pathologic factors on OS as shown in table 9 we found that, age older than 65 yr (figure 1), and SCC histology (figure 2) were significantly associated with poorer OS with ρ value at 0.001and 0.04 respectively .

The 2, 3 and 5yr DFFS of whole cohort of patients was 90%, 84% are 80.5% respectively, on analyzing impact of different clinico-pathologic factors as shown in table 10, no factor found significantly affected DFFS.

The 2, 3 and 5yr LFFS of whole cohort of patients was the same as DFFS at 90%, 84% and 80.5% respectively. On analyzing impact of different clinico-pathologic factors as shown in table 11, no factor found significantly affected LFFS.

Table 4: 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 (5): disease characteristics of studied populations

Characteristics	Number	Percentage (%)
Pathological type		
SCC	24	38.70
TCC	38	61.29
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
N stage		
N0	41	66.13
Nx	21	33.87

Table (6): treatment characteristics

Treatment given	Number	Percentage (%)
Surgery		
Anterior pelvic exenteration	12	19.35
Radical cystectomy	50	80.65
Diversion type		
RC+Neo bladder	19	30.64
RC+Uretero colic	11	17.75
RC+Uretro cutaneous	32	51.61
ORT 50 CGY /25 fraction /5 weeks	62	100%
Concurrent chemotherapy		
No	30	48.39
Yes	32	51.61
Type of chemotherapy		
Weekly Carboplatin	8	25.00
Weekly cisplatin	24	75.00
Duration of PORT		
≤40 day	35	56.45
>40 day	27	43.55

Table (7): Toxicities in studied populations

Characteristics	Number	Percentage (%)
Acute intestinal toxicity		
No	13	21.00
Yes	49	79.00
Chronic intestinal toxicity		
No	42	68.00
Yes	20	32.00
Acute skin toxicity		
No	47	75.81
Yes	15	24.19
Chronic skin toxicity		
No	52	84.00
Yes	10	16.00
Acute urinary toxicity		
No	50	81.00
Yes	12	19.00
Chronic urinary toxicity		
No	54	87.1
Yes	8	12.9

Table (8): Treatment outcomes in studied population

Outcome	Number	Percentage (%)
Local recurrence		
No	54	87.10
Yes	8	12.90
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 (9): Association between OS and studied risk factors

Risk 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	
Pathological type					
SCC*	24	53.85	48.95	37.30	**0.04**
TCC	38	73.68	73.68	63.77	
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	90.00	90.00	56.52	
T4a	10	55.17	55.17	45.14	
Duration of PORT					
≤40 day	35	62.86	59.86	49.37	0.45
>40 day	27	70.18	70.18	60.15	
Chemotherapy					
Yes	32	61.00	59.00	57.22	0.65
No	30	59.50	57.00	55.08	

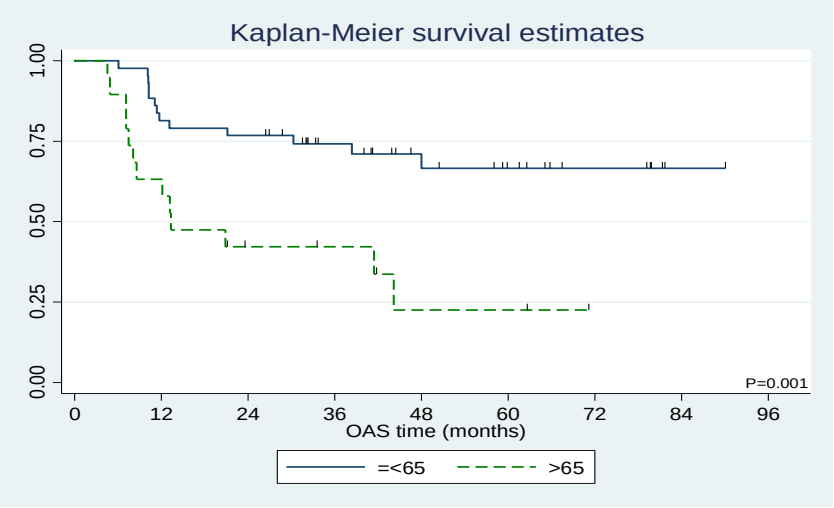

Figure (1): Impact of age on OS

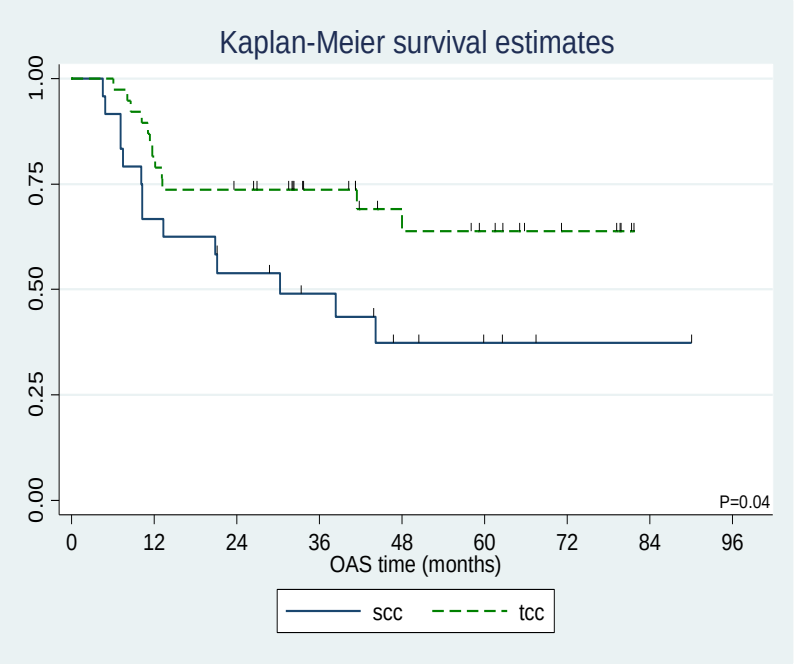

Figure (2): Impact of pathological subtype on OS

Table (10): Association of DFFS and studied risk factors

Risk Factors	Number	Cum survival at 2yrs %	Cum survival at 3yrs %	Cum survival at 5yrs %	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	
Pathological type					
SCC*	24	84.44	70.15	70.15	0.10
TCC	38	93.38	93.38	86.71	
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	
M Stage					
M0	62	89.95	84.44	80.60	
Duration of radiotherapy in days					
≤40 day	35	86.84	78.53	73.62	0.12
>40 day	27	94.44	94.44	94.44	
Chemotherapy					
Yes	32	84.00	79.00	72.60	0.60
No	30	81.40	75.46	70.30	

*** include one case adenocarcinoma**

Table (11): Association between LFFS and studied risk factors

Risk Factors	Number	Cum survival at 2 yrs %	Cum survival at 3 yrs %	Cum survival at 5 yrs %	P-value
Whole group	62	90.00	84.00	80.5	
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	
Pathological type					
SCC*	24	84.44	70.15	70.15	0.10
TCC	38	93.38	93.38	86.71	
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	35	96.00	96.00	96.00	0.96
>40	27	94.74	94.74	94.74	
Chemotherapy					
Yes	32	84.00	79.00	72.60	0.60
No	30	81.40	75.46	70.30	
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	

*** include one case adenocarcinoma**

Discussion

BC is a common malignancy in Egypt representing around 6.94% of all cancers.[33] RC with bilateral pelvic lymphadenectomy remains the standard of care for patients with muscle-invasive BC. However, the high relapse rates following cystectomy alone for patients with muscle-invasive BC have led to the use of neoadjuvant treatment.[34]

Patients who undergo primary surgery, adjuvant treatment may be offered, especially to patients at high risk for recurrence. It is reported that about 25% reduction in the risk of death may be obtained with adjuvant chemotherapy.[29]

Many Egyptian series had reported positive impact of post operative radiotherapy on survival. It led to a remarkable reduction in

the incidence of local recurrence and hence improved the disease-free survival in BC in different stages, grades, and lymph node status.[31] In this small sized study, 62 patients with BC treated by RC with PORT and fulfilled the eligibility criteria were analyzed on the level of different patient, disease and treatment risk factors that might influence the disease control.

It is reported in the literatures that BC is usually diagnosed in older individuals; with a median age at diagnosis around 73 yr with more incidence in males than in females (3:1). The results of the current study show that the mean age at diagnosis is 58.15 yr with male to female ratio at 1.7:1. This shift in the mean age at diagnosis towards younger ages compared to that reported in older studies,[33] could be attributed to the increased awareness among people about cancer especially with easier access of knowledge through the Internet and the widespread installation of cancer treating centers in Egypt in the last decade. All of these factors might altogether contribute to diagnosis of BC at earlier ages.

The reduction in the ratio of BC incidence between males and females that present in the current study (1.7 for males to 1for females) compared to earlier studies while persistence of the same value for females (that is 1) could be attributed to the decline in incidence of bilharzial infestation in men (4.84% in the present study) compared to the past decades.

Also noted in the present study a higher incidence of TCC in contrast to SCC (61.29% versus 38.70%). This rise in incidence towards TCC was also reported in recently published Egyptian studies[32] in contrast to older ones[33]reported on patients treated in the seventies, eighties and nineties of the last century. The last decades have witnessed major changes in environmental and industrial factors that could be implicated in such shift in pathological predilection. More awareness about bilharzial infestation and more effective anti bilharzial treatments become available at the same time more urbani-zation and consumption of tobacco are also present.

The ratio between male to female patients in this study is smaller than in other studies. It is at 1.7 while larger ratios can be observed in larger studies[32]. No significant impact of patient's gender on outcome indices (OS, DFFS, LFFS) was found in the current study, on contrast, conflicting data exist in the literature regarding such point. While some authors reported better OS in male patients[35-38], others reported better OS in females.[32]

Also, no significant association was observed between patient's gender and development of acute or chronic treatment related morbidities. Radiotherapy given to the patients was in accordance to the usual 2 D procedures explained elsewhere in the literatures as regards the dose, schedules, beams energy, beams arrangement and field geometries. No significant correlations between treatments related side effects and studied risk factors as mentioned in the result section.

Concerning the treatment outcome indicators analyzed above, apart from patient's ages > 65 yr and SCC subtype that were significantly associated with inferior OS, no other studied possible risk factors were observed significantly correlated with either OS, DFFS or LFFS. It is understandable and predictable that patients at old age are usually suffering from other co-morbidities like diabetes mellitus, hypertension as well as a long journey with tobacco smoking and all of these factors may contribute to inferior OS. For the significant association between lower OS and SCC subtypes, our results are in accord with other investigators who reported better OS with TCC subtype in contrast to SCC like Balci and colleagues who reported on 460 patients treated with RC. The large size of their study enabled defining some predisposing factors that might lead to that result like advanced stage of SCC, higher incidence of +ve LN and extra vesical extension with SCC than with TCC.[39] We could not find possible predisposing factors to explain the poorer OS with SCC in our study apart from the observation that most of the patients with SCC (18 from 24 patients) were older than 65 yr.

In contrast to these studies, some authors reported different results, Nasr and co workers observed that the OS and DFS for SCC were superior than TCC in a study included 208 patients with BC treated in NCI, Cairo, Egypt between 2007 to 2011 with RC and PORT. Their results were attributed to the higher incidence of +ve LN and higher tumor grades in TCC than in SCC.[32]

Thirty two patients in the current study received radio sensitizer in the form of concomitant chemotherapy either weekly cisplatin at a dose of 30 mg / m^2 or weekly carboplatin at a dose of 1.5 Area Under Concentration Curve (AUC) according to the creatinine clearance and age of the patients. That was a routine practice in our department in patients with relatively good performance status with BC stage ≥ T3, +ve LN and grade 3. Although we have no direct evidence for that practice as RC became less frequently done and most of the practice in the last decade relies on trimodality bladder preservation approach that includes limited surgery in the form of transurethral resection of bladder tumor (TURBT) then definitive radiotherapy concomitant with chemotherapy, it could be extrapolated from the results of many studies with various designs (retrospective and prospective) that adding chemotherapy to radiotherapy gives better rates of local control and OS compared to radiotherapy alone.[40]

The influence of overall treatment time on disease control and survival was addressed by many researchers with different results. Maciejewki and colleagues[41] reported decreased local control rate from 50% to 5% in patients with muscle invasive TCC of the bladder, De Neve and co workers[42] reported similar results with split course irradiation, on the other hand, Moonen et al. reported no influence of time prolongation of radiotherapy on local control of muscle invasive BC . In the present study, the overall treatment time of irradiation (either ≤ 40 days or > 40 days did not affect the treatment outcome in all studied indices (OS, DFFS and, LFFS).

Our study, however found that the 2, 3 and 5 yrs OS were 66%, 64% and, 53.5% with similar figures for DFFS and LFFS at 90%, 84% and 80.5% respectively. Concerning our results on the level of OS, they are not away from those reported by other Egyptian series that studied the efficacy of post operative radiotherapy after RC like Nasr and colleagues[32] who conducted a much more larger study than ours (208 patients) and reported on 3 yrs OS and Disease free survival (DFS) around 60% and 54% respectively with local recurrence rate around 94% at 3 yrs.

Conclusions

In spite of the limitations of the retrospective design of this study, the small study size together with the paucity studies on RC and PORT especially on inter-national level, the results of this study are consistent with other Egyptian ones that supported the practice of PORT after RC. We have recently acquired in our department 3 dimensional radiotherapy facility hoping to further improve the treatment outcomes.

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