Role of Radiotherapy with or without Chemotherapy in Treatment of Cancer Urinary Bladder Surgically Excised: A Retrospective Study

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Abstract:

Background: BC is the 10th most common cancer type worldwide. About 75% of BC is non muscle invasive (NMIBC). However, in MIBC, the standard therapeutic approach consists of neoadjuvant chemotherapy, radical cystectomy (RC), +/- adjuvant chemotherapy. Following RC, in patients with ≥pT3 disease, loco regional recurrence is a significant problem. Adding RTH to CTH in this situation has demonstrated a significant reduction in the rate of loco regional failure.

Purpose of the study: In this retrospective study, we aim to investigate the outcome of treatment of MIBC by RC and post operative RTH +/- CTH.

Patients and methods: This is a retrospective study included patients treated in Sohag University by RC with urinary diversion and pelvic RTH+/- CTH from January 2016 through December 2020.

Results: A cohort of 75 patients identified, Males constituted 91% of them. Two subgroups were identified, tcc and scc representing 69% and 28% respectively. Chemotherapy was documented in 61% of patients. Conventional 2 D RTH technique was implemented in 31 (41%) patients and 3 D RTH technique in 44 (59%) patients. Local, nodal and, distant failures were identified in 9 (12%), 6 (8%) and 7 (9%) patients respectively. Owing to the small number of distinct types of failures and for more meaningful statistical results, all failures were allocated in one group. Only T stage was found significantly affecting the OS in the whole cohort (p=0.05) but not in either one of the two subgroups, TCC and SCC. Both coexistent hypertension and DM significantly reduced the PFS in the whole cohort (p = 0.007 and 0.003 respectively) and in the TCC subgroup only (p = 0.041 and 0.011 respectively). Adding CTH to RTH significantly improved the OS in the TCC subgroup (p = 0.05).

Conclusions: In treatment of MIBC by RC, RTH and CTH, advanced stage, lack of cisplatin based CTH, co existent hypertension and DM adversely affect treatment outcome and further observational studies warranted to elucidate the influence of these comorbidities on treatment outcome.

Key words: Muscle invasive bladder cancer, radical cystectomy, post operative radiotherapy, chemotherapy.

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Introduction:

Urinary bladder carcinoma (BC) is the 10th most common cancer type worldwide [1]. Tobacco smoking is considered the most important risk factor for developing BC and account for about 50% of cases[2], followed by occupational exposure to aromatic amines and ionizing radiation [3]. Painless hematuria is the most common presenting symptom in BC, other common symptoms include dysuria, increased frequency and/or urgency. Abdominopelvic ultrasonography or cross-sectional imaging can identify an intraluminal mass in the bladder, but the final diagnosis is based on cystoscopy and pathological examination of tissues obtained with biopsy or transurethral resection of the bladder tumour (TURBT). Complete resection of all malignant mass should be

achieved. The presence of lamina propria and detrusor muscle in the resected tissue is essential for accurate staging [4].

About 75% of BC is non muscle invasive (NMIBC). The majority of patients with MIBC (pT2a-pT4b) are diagnosed with primary invasive BC and up to 15% of cases have a previous history of NMIBC, almost frequently of high-risk subgroup [3]. In management of NMIBC, as frequent recurrences and risk of progression usually characterize NMIBC, risk-stratified treatment and surveillance protocols are often used in the guidelines of management [5].

However in case of MIBC, the standard therapeutic approach consists of cisplatin-based neoadjuvant chemotherapy (NACTH), followed by radical cystectomy (RC) [6-8]. After RC for pT3-4 and N +ve disease, adjuvant chemotherapy (ACTH) in patients without clinically detectable metastases is currently recommended in the urologic guidelines. After RC In patients with ≥pT3 disease, loco regional recurrence is a significant problem. CTH did not reduce the risk of local-regional recurrences in randomized prospective trials. Adding RTH to CTH in this situation based on an Egyptian NCI study and an Italian one has demonstrated significant reduction in the rate of loco regional failure [9,10]. Due to the negative impact of RC on the quality of life, bladder preserving tri modality therapy (TMT) approach composed of TURBT followed by curative radiotherapy (RTH) with CTH either NACTH and / or ACTH has recently emerged as an alternative to RC [11].

In this retrospective study, we aim to investigate the outcome of treatment of MIBC by RC and post operative RTH +/- CTH in patients treated in the Clinical Oncology and Urology departments in Sohag University Hospital from January 2016 to December 2020 by analyzing the various risk factors that can affect the progression free survival (PFS) and overall survival (OS) as primary end points and treatment related side effects as secondary end point.

Patients and Methods:

In this retrospective study, the included patients should have been treated in the Clinical Oncology and Urology departments in Sohag University Hospital by RC with urinary diversion and pelvic RTH+/- CTH from January 2016 to December 2020. Those patients represent a subgroup taken from a larger retrospective study conducted in the department of Clinical Oncology, Sohag University Hospital and presented in 2022. Eligible patients for enrolment included those between 18 and 75 yrs either males or females with no prior history of cancers and no prior history of pelvic irradiation. The larger study has received an ethical approval from the Ethical Committee in the Faculty of Medicine, Sohag University. All patients in this subgroup had undergone routine physical examination, lab and metastatic work up by CT chest, abdomen and pelvis prior to RTH and CTH. Tumors were staged according to the AJCC / TNM system 2017. RTH technique included the conventional 2-dimensional (2D RTH) and the conformal 3 dimensional technique (3D CRTH).

In case of the 2D RTH, patients were planned in supine position with knee support and both hands on the chest. Using the conventional 2D Simulator machine, three iso centeric irradiation fields were always used, one anterior and 2 lateral wedged fields. The anterior field was extending from the L5/S1 vertebral junction down to the inferior boundary of the obturator foramens and laterally 1.5 cm outside the pelvic brim while, the lateral wedged fields were extending from S1/S2 junction posteriorly to just in front of the symphysis pubis anteriorly with the same upper and lower boundaries as in the anterior fields. In case of 3D CRTH a planning CT scans with slices at 3-5 mm were taken in treatment position with knee support and both hands on the chest. The clinical target volume (CTV) included the operative bed, the common, internal, external iliac, presacral, hypogastric and obturator lymph nodes. The organs at risk (OAR) are the rectum, small bowel and femoral heads. The dose to OAR is assessed by DVHs. The planning treatment volume (PTV) is defined with a 3D margin around the CTV usually a 10 mm isotropic margin was used from the CTV to create the PTV. Irradiation was carried on using a 6 MeV Linear Accelerator machine. For CTH, routine lab was done before each cycle. Patients consent was taken before RTH and CTH as well. During follow up, treatment related side effects were scored according to the Common Terminology Criteria for Adverse Events, CTCAE, version 3.

Data was analyzed using SPSS version 22. 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. P value was considered significant if less than 0.05.

OS was defined as the time between date of diagnosis and date of death or last follow up and PFS was calculated as the time between date of surgery and date of progression or last follow up, both in month.

Ethical approval

The study has been done in accordance to the Medical Research Ethics Committee - Faculty of Medicine – Sohag University and received an ethical approval registration number: Soh-Med-23-10-10PD**.**

Results:

In this retrospective study, a cohort of 75 patients was identified. Age of the patients ranged from 38 to 73 with a median at 59 yr. Mean follow up period was at 11 m (range from 1 to 65 m). Males (68 patients) constituted 91% of the whole cohort while females (7 cases) constituted 8% of cases. History of co-morbid diseases such as hypertension, diabetes mellitus (DM) was identified in 11 (15%) and 7 (9%) patients respectively. History of potential risk factors such as smoking and bilharziasis was present in 39 (52%) and 16 (21%) patients respectively. History of dysuria,

hematuria, increased frequency of micturition, urine retention, urgency and interrupted stream was present in 53 (71%), 41 (55%), 4 (5%), 4(5%), 2(2.6 %) and 2(2.6%) patients respectively.

All patients had been diagnosed by means of cystoscopy and biopsy. Both transitional cell carcinoma (TCC) and squamous cell carcinoma (SCC) represented the largest subgroups and identified in 52 (69%), 21 (28%) patients respectively (total; 97%) while adenocarcinoma was identified in only 2 patients (3%). Staging work up had been done with computerized tomography of the abdomen, pelvis and chest for all patients and no metastasis were documented at presentation.

Maximum tumor dimension ranged between 20 and 120 mm with a median at 45 mm. Tumors with maximum dimension ≤ 45 mm were found in 39 (52%) while those with maximum dimension > 45 mm were present in 32 (43%) of patients respectively. Hydronephrosis reported as moderate/severe was identified in 18 (24%) patients. Fifty patients (67%) had presented with advanced T stage (T3/4) while 22 (29%) presented with earlier stage (T1/2) disease. The majority of patients had no lymph node enlargement at presentation. Post operative pathological examination had revealed N1 and N2 diseases in 10 (13%) and 9 (12%) patients respectively. All patients were treated with postoperative RTH to pelvic lymph nodes at 50.4 Gy / 28 sessions / 5 3.5 wks from Sunday to Thursday each week apart from the governmental holidays and periods of machine work out. Twelve patients had finished RTH sessions in 5 to 6 wk, 15 patients along > 6 wks and 8 ones did not complete the RTH course. RTH was implemented in conventional 2 D technique in 31 (41%) patients during 2016 and 2017 while those treated with 3 D technique constituted 44 (59%) patients and presented to our department in 2018 through 2020.

Eighty percent of patients reported treatment related acute intestinal toxicities in the form of mild/moderate intestinal colic, constipation, diarrhea and rectal heaviness. Thirty percent of patients had reported chronic intestinal symptoms in the form of rectal bleeding and heaviness. No significant association was observed between these toxicities and potential risk factors including age, gender, history of smoking, hypertension, DM, pathological subtype, CTH or RTH technique. Forty six (61%) patients had received CTH in their treatment either neoadjuvant, adjuvant. Gemcitabine/carboplatin or cisplatin represented the main regimen and were given to 33 (41%) and 5 (7%) patients respectively. All treatment failures was identified in 12 (16%) of patients during the follow up period. Local, nodal and, distant failures were identified in 9 (12%), 6 (8%) and 7 (9%) patients respectively. Owing to the small number of distinct types of failures and for more meaningful statistical results, all failures were allocated in one group with more detailing of statistical tests in significant results. Death had been reported in 59 (79%) patients.

The clinico pathologic characteristics in the two largest subgroups TCC and SCC are given in table 1. No significant differences were noticed between both subgroups in the clinico pathologic features studied but, there was a significant association between treatment with CTH and the histopathology, as noticed in table 1, TCC was more associated with CTH than SCC, (p=0.024).

As regards the outcome of management, as seen in table 2 and figure 1, OS in the whole cohort was significantly reduced with advanced T stage (T3/4) compared with earlier stage (T1/2) with p value at 0.05. No other one of the studied potential risk factors has been found significantly impacted the OS in the whole cohort.

Concerning the PFS in the whole cohort, in univariate analysis, only history of hypertension and DM was significantly associated with PFS. Patients with preexisting arterial hypertension and DM have significantly reduced PFS compared to those without (p = 0.007 and 0.003 respectively) as seen in table 2 and figures 2 and 3 respectively. In multivariate analysis, only hypertension was significantly associated with PFS that is patients with no hypertension showed significant decrease in hazard of progression compared to those with hypertension (hazard ratio at 0.248; 95% CI : 0.068 – 0.903 ; p = 0.034).In case of DM, patients with no co existent DM have shown a remarkable but not significant decrease in hazard of progression compared with those with DM (hazard ratio at 0.622; 95% CI : 0.113 – 3.436 ; p = 0.586).

Other studied patient factors e.g; age, sex, history of smoking or bilharziasis, tumor related factors e,g; pathological subtype, tumor size, hydronephrosis, lymph node status and treatment related factors, e.g. CTH, technique of RTH, overall period of RTH and treatment years either 2019/2020 (era of Corona Epidemic) or other years, all these factors were not significantly associated with PFS as seen in table 2.

On dividing the whole cohort into 2 subgroups as seen in table 3, it appears that the same two risk factors, hypertension (figure 4) and DM (figure 5) have a significant influence on PFS but in univariate analysis only (p = 0.041 and 0.011 respectively). However, in multivariate analysis, although there is an evident reduction in hazard of progression in absence of hypertension and DM compared with their co existence, the association is not significant for either any of them (HR 0.321; 95% CI ,082 – 1,260, p = 0.103 for hypertension and for DM, HR 0.602, 95% CI, 0.109 – 3.338; p = 0561).

Another positive finding in our analysis of the studied subgroups is the significant influence of addition of CTH to postoperative RTH on the OS (figure 6). Patients received platinum based CTH showed significantly longer OS compared with those received no CTH or received non platinum based CTH (p = 0.05). The other potential risk factors mentioned above with analysis of the whole cohort were not significantly affecting neither the OS nor the PFS in both TCC subgroup and the SCC one as shown in table 3.

Discussion:

BC is a common disease and for MIBC, treatment modalities include RC, peri operative CTH and post operative RTH or the more recent approach that is bladder preservation TMT.

Although this later treatment approach is more common in developed countries, it is still less popular in developing areas like our locality in the south of Egypt.

In spite of the gap between the two treatment approaches, the retrospective design of our study and the relatively short follow up period due to the impact of Corona epidemic, we could reach some positive findings that are in concordance with many other studies.

Analysis of the whole cohort revealed that advanced T stage was a significant predictor of poor OS (p = 0.05) as seen in table 2 and figure 1. Such a finding is in agreement with several other studies.

Volkmer and colleagues in their study on series of 900 patients to evaluate the stage dependent effect of on survival, reported that locoregional recurrence occurred in 5.7% of patients with p T 1 – 4 while none occurred in pT0 group [12]. In Cheng et al "series of 218 patients, the 10 yr loco regional recurrence free survival were 49% for pT4 while was between 73% - 76% with earlier stages (p = 0.03). [13]. Many other researchers have reported similar results [14 – 21].

The second positive finding in our study is the significant impact of co existent comorbidities namely arterial hypertension and DM on the PFS in the whole cohort and in the subgroup of TCC. Concerning hypertension, a history of co existent hypertension was found in 11 out of 75 patients, the majority of them were at age > 58 y versus at age ≤ 58 yr (80% vs 20%, p = 0.044). These older patients received significantly less ACTH (Among 27 patients did not receive ACTH, 18 were at age > 58 yr, p = 0.029).

As seen in table 2 and figure 2, in the whole cohort, patients with positive history of hypertension showed a significantly shorter PFS compared with no hypertension (p = 0.007). Hypertension is a common morbidity in people older than 60 yr [22] and is a known risk factor for cardiovascular diseases that increase the overall mortality such as angina, myocardial infarction, heart failure, ischemic stroke, and peripheral arterial disease[23]. A large meta analysis on hypertension and cancer survival and relapse conducted by Fausto P and colleagues and included 66 studies on various types of cancer. They found that pre existing hypertension was associated with cancer specific mortality in renal cell carcinoma and urothelial carcinoma [24]. Our results show concordance with these ones. The impact of hypertension on PFS in the whole cohort is significant in univariate analysis (p = 0.007) and in multivariate analysis as well (HR: 0.248; 95% CI: 0.068 – 0.903; p = 0.034).

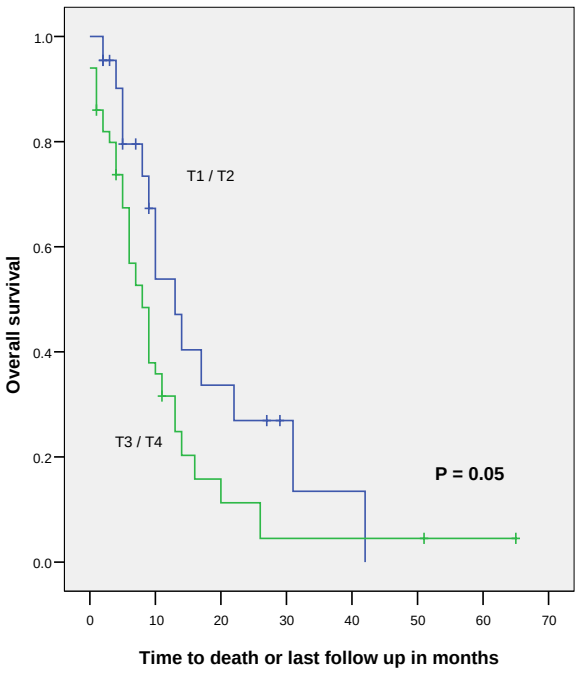

Figure 1. Advanced T stage significantly reduced the OS in the whole cohort

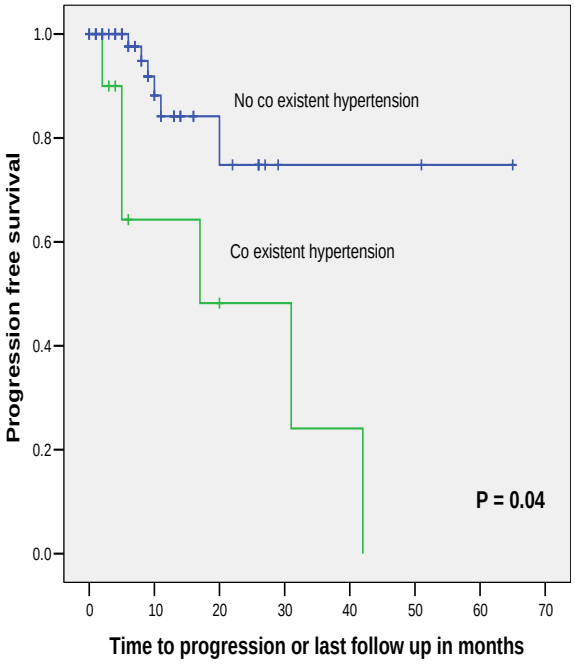

Figure 2. Co existent hypertension significantly reduced the PFS in the whole cohort

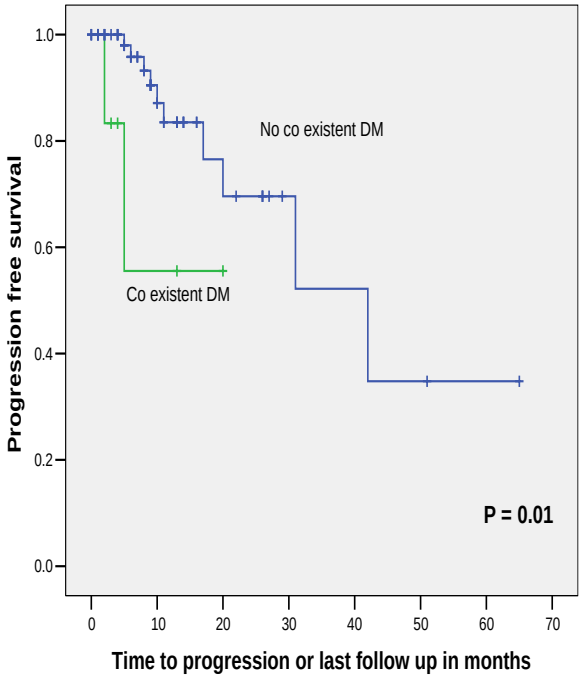

Figure 3. Co existent DM significantly reduced the PFS in the whole cohort

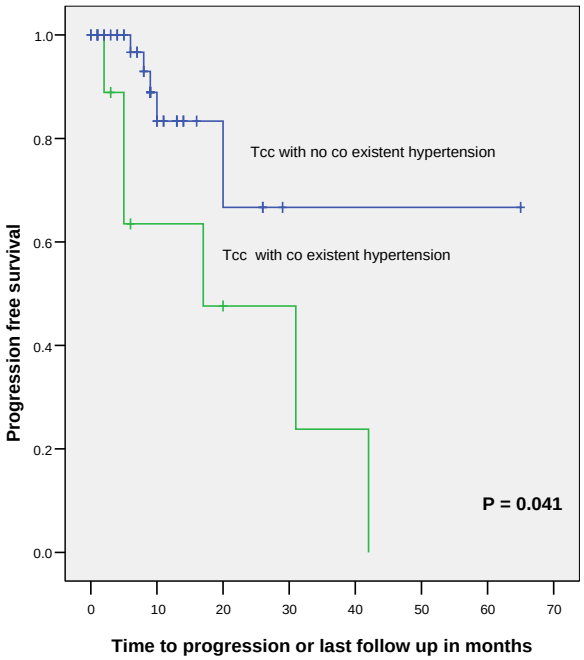

Figure 4. History of hypertension significantly reduced the PFS in the TCC subgroup

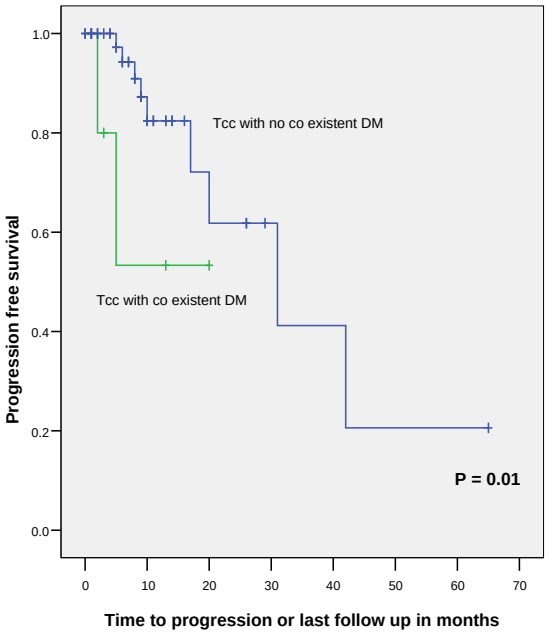

Figure 5. History of DM significantly reduced the PFS in the TCC subgroup

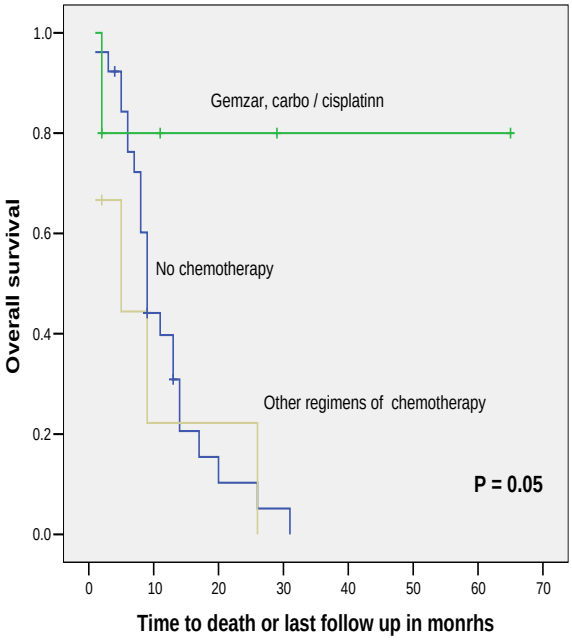

Figure 6. Non platinum based CTH and no CTH significantly reduced the OS in the TCC subgroup

Table 1. The clinico-pathologic features of the patients in both subgroups

Variable	**TCC (52 pt)**	**SCC (21 pt)**	**Total**	**p**
Mean age	59 y	57 y		0.380
Gender :				
Male	47 (71.2%)	19 (28.8%)	66	0.679
Female	5 (71.4%)	2 (28.6%)	7	
History of smoking :				
No	24 (70%)	10 (30%)	34	0.557
Yes	28 (72%)	11 (28%)	39	
History of bilharziaziz :				
No	42 (74%)	15 (26%)	57	0.282
Yes	10 (62.5%)	6 (37.5%)	16	
History of hypertension :				
No	43 (69%)	19 (31%)	62	0.327
Yes	9 (82%)	2 (18%)	11	
History of Diabetes :				
No	47 (71%)	19 (29%)	66	0.679
Yes	5 (71%)	2 (29%)	7	
Maximum size :				
≤ 45 mm	28 (72%)	11 (28%)	39	0.491
> 45 mm	22 (69%)	10 (31%)	32	
Hydronephrosis :				
No / mild	31 (67%)	15 (33%)	46	0.477
Moderate / severe	13 (72%)	5 (28%)	18	
T stage :				
T1/2	17 (77%)	5 (23%)	22	0.308
T3/4	34 (68%)	16 (32%)	50	
Lymph node status :				
No	30 (67%)	15 (33%)	45	0.232
N +ve	21 (78%)	6 (22%)	27	
Chemotherapy :				
No	15 (56%)	12 (44%)	27	**0.024**
yes	37 (80%)	9 (20%)	46	
All recurrences :				
No	41 (67%)	20 (33%)	61	0.080
Yes	11 (92%)	1 (8%)	12	
Radiotherapy technique :				
2D	18 (35%)	13 (62%)	31	0.071
3D	34 (65%)	8 (38%)	42	

Table 2. The association between various clinico-pathologic variables and OS and PFS in the whole cohort

Variable	**OS**	**P value**	**PFS**	**P value**
Age :				
≤ 58 y	13 m		Not reached	0.397
> 58 y	9 m	0.124	42 m	
Gender :				
Male	9 m		Not reached	0.980
Female	16 m	0.227	40 m	
History of smoking :				
No	9 m		43 m	0.686
Yes	9 m	0.639	Not reached	
History of bilharziaziz:				
No	8 m		31 m	0.200
Yes	16 m	0.089	42 m	
History of hypertension :				
No	9 m		Not reached	**0.007**
Yes	6 m	0.543	16 m	
History of Diabetes:				
No	9 m		42 m	**0.003**
Yes	5 m	0.800	Not reached	
Pathological subtype :				
TCC	9 m		30 m	0.144
SCC	7 m	0.897	Not reached	
Maximum size :				
≤ 45 mm	9 m		30 m	0.864
> 45 mm	8 m	0.916	43 m	
Hydronephrosis :				
No / mild	10 m		Not reached	0.693
Moderate / severe	9 m	0.411	42 m	
T stage :				
T1/2	14 m		31 m	0.326
T3/4	8 m	**0.05**	Not reached	
Lymph Node status				
No	10 m		Not reached	0.607
N +ve	9 m	0.370	30 m	
Chemotherapy :				
No	9 m		42 m	0.231
yes	10 m	0.759	31 m	
Treatment year :				
2019/2020	9 m		31 m	0.257
Other years	10 m	0.151	42 m	
Radiotherapy duration :				
= 35 day	11 m		Not reached	0.407
> 35 day	8 m	0.551	Not reached	
Radiotherapy technique :				
2D	10 m		Not reached	0.301
3D	9 m	0.338	31 m	

Table 3 The association between various clinico-pathologic variables and OS and PFS in patients subgroups

Variable	TCC				SCC			
	Median OS	P value	Median PFS	P value	Median oS	P value	Median PFS	P value
Age :								
≤ 58 y	14 m		NR		7 m		NR	0.439
> 58 y	9 m	0.088	17 m	0.49	5 m	0.761	NR	
Gender :								
Male	9 m		NR		6 m		NA	NA
Female	16 m	0.208	21 m	0.627	NA	0.814	NA	
Smoking history:								
No	10 m		40 m		5 m		NR	0.564
Yes	9 m	0.486	NR	0.797	11 m	0.958	NR	
Bilharziasis history:								
No	9 m		31 m		5 m		NR	0.439
Yes	17 m	0.127	43 m	0.144	14 m	**0.083**	NR	
Hypertension :								
No	9 m		NR		7 m		NA	NA
Yes	16 m	0.322	17 m	**0.041**	4 m	0.261	NA	
Diabetes mellitus :								
No	9 m		31 m		7 m		NA	NA
Yes	14 m	0.862	NR	**0.011**	4 m	0.261	NA	
Maximum size :								
≤ 45 mm	9 m		31 m		4 m		NR	0.197
> 45 mm	7 m	0.303	42 m	0.481	13 m	0.229	NR	
Hydronephrosis:								
No / mild	9 m		NR		5 m		NR	0.386
Moderate / severe	8 m	0.157	42 m	0.913	13 m	0.458	NR	
T stage :								
T1/2	15 m		31 m		5 m		NR	0.564
T3/4	9 m	0.07	31 m	0.324	7 m	0.375	NR	
Chemotherapy :								
No	9 m		20 m		2 m		NA	NA
Gemzar/Carbo/Cisplatin	Not reached		NR		7 m		NA	
Other Regimens	5 m	**0.05**	NR	0.768	5 m	0.222	NA	
Treatment year:								
2019/2020	9 m		31 m		1 m		NA	NA
Other years	10 m	0.136	42 m	0.530	6 m	0.070	NA	
Radiotherapy duration :								
= 35 day	10 m		NR		13 m		NA	NA
> 35 day	7 m	0.828	NR	0.811	5 m	0.141	NA	
Radiotherapy technique:								
2D	10 m		42 m		6 m		NR	0.564
3D	9 m	0.163	20 m	0.318	7 m	0.678	NR	

The second comorbidity found associated with poor PFS in the whole cohort was DM. It was reported in 7 (9%) of patients and in contrast to hypertension, it was not significantly associated with older age (p = 0.255), but was significantly associated with hypertension (5 out of 7 patients with DM had a co existent hypertension, p = 0.000). In the whole cohort, patients with no history of DM showed a significantly longer PFS compared with those with a history of DM in a univariate analysis (p = 0.011) as seen in table 2 and figure 3. In a multivariate analysis, there is a remarkable but not significant decrease in hazard of progression with no history of DM compared with those with co existent DM (hazard ratio at 0.622; 95% CI: 0.113 – 3.436; p = 0.586).

It is known that DM is linked with substantial comorbidities and mortality [25]. It has been long recognized that it plays an important role in the development of many cancers including liver, breast, colorectal, pancreatic and, bladder cancers. [26]. The mechanism by which DM contributes to the development of BC is unknown[27].However, some earlier studies assumed that chronic exposure to hyperinsulinemia , hyperglycemia and increased insulin like growth factor (IGF-1) expression induce tumor cell proliferation and inhibits apoptosis [28,29].

More recent studies assumed that high glucose level increases the proliferation of bladder cancer cells through an activation of Wnt/ß-catenin signaling pathway [30], and ERK / p38 MAPK pathway that is associated with high expression of cell cycle machinery and anti apoptotic proteins in bladder epithelial cells [31],. In his study on the impact of DM on recurrence and progression of NMIBC that included 251 patients, Eu Chang and colleagues have reported that DM is an independent predictor of recurrence free survival (RFS)and PFS [27].

Although our study has a few number of patients with co existent DM we can attribute our result to finding in our study that hypertension was significantly correlated with DM in our patients and their coexistence altogether could impose a synergistic effect on PFS that is beside the suspected interplay of the above mentioned pathways.

The third and last positive finding in our study is the significant positive impact of CTH either NACTH or ACTH on OS in the TCC subgroup. As seen in table 3 and figure 6, patients received platinum based CTH demonstrated significantly higher OS curve compared with those received non platinum based CTH or no CTH at all. As MIBC is a highly aggressive disease, it is not uncommonly that subclinical micro metastasis are already present at the time of RC, which leads to subsequent clinical progression and cancer specific mortality [32]. Cisplatin-based NACTH is a standard approach to improve treatment outcomes in patients with MIBC undergoing RC [33]. Two meta analysis reported that neo adjuvant CTH based on cisplatin was associated with improvement in OS at 10 years (36% vs 30%, p = 0.037, and in disease free survival (DFS) up to 23% (HR = 0.77; p = 0.001) was reported by Paul S and colleagues [34, 35]. However, ACTH can be an alternative modality with the advantage of more accurate selection of patients[36]. In a large systematic review included 9 studies and 2,444 patients, Laukhtina and colleagues reported that ACTH was significantly associated with lower likelihood of disease progression compared to observation/placebo with odds ratio (OR) at 0.36 and 95% credible interval (CrI) at 0.13–0.92 and even superior than adjuvant immune check point inhibitors[37]. The result of our study concerning this point is in agreement with the above published studies.

Conclusion:

Although our study has some limitations such as its retrospective design, small number of participants, short median follow up period and lack robust data during follow up due to the influence of Corona epidemics, we could state that the outcome of patients with MIBC treated with RC, post operative RTH and perioperative CTH is significantly influenced by the advanced stage, platinum based peri operative CTH and the coexistent comorbidities, both hypertension and diabetes mellitus. Further well organized observational studies are warranted to accurately establish the impact of these comorbidities on outcome at the same time, proper attention to treatment of these comorbidities during oncological management of these tumors seems essential.

Conflict of interest

None to declare.

Authors′ contributions

First Author: Study design, writing and revision
Second author: data collection.
Third author: writing, revision, tables and figures editing.
Fourth author: Study design, writing and revision.
Fifth author: Study design and data collection

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