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Setting the Dilemma of Adjuvant Radiotherapy in Patients with Locally Advanced Bladder TCC

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ABSTRACT

Objectives: *Muscle Invasive Bladder Cancer (MIBC) remains a lethal disease, despite aggressive local and systemic therapies with Radical Cystectomy (RC) ± Neo-Adjuvant Chemotherapy (NACT). The 5-year Overall Survival (OS) in advanced cases was around 32%. So novel treatment modalities are required. Our aim is to study the impact of adding Postoperative Radiotherapy (PORT) to standard chemotherapy on local control, survival outcomes and toxicity pattern.* ***Methods:*** *In this study, 123 MIBC patients' medical records were reviewed and classified into 3 groups according to their treatment modalities; A (RC Chemotherapy), B (RC Radiotherapy), and C (RC Chemo and Radiotherapy).* ***Results:*** *Over a median follow-up of 18.5 months, the 5-year disease free survival (DFS) of group B was significantly higher (80.4%) compared to groups A and C (41.1% & 29.9% respectively; p= 0.0073). Additionally, the 5-year OS was higher in group B (77%) compared to groups A (33.9%) and C (28.5%), (p=0.041). However, the median Local Recurrence Free Survival (LRFS) for the whole group was 69.03 months (95% CI: 69.03 to 69.03), with no significant difference among the 3 groups (p=0.067).* ***Conclusion:*** *Our results suggest that the addition of adjuvant radiotherapy improved the Disease-Free Survival (DFS) and OS in MIBC patients. Although NACT remains the standard of care, incorporation of PORT should be considered in the future management of these cases.*

Keywords: Adjuvant radiotherapy, Muscle invasive bladder cancer, Neo-adjuvant chemotherapy, Disease-free survival

INTRODUCTION

Bladder Cancer (BC) represents ~3.0% of all new cancer diagnosed cases and ~2.1% of all cancer deaths. It is considered one of the top ten common cancers worldwide [1].

Based on the National Cancer Registry Program (NCRP) in Egypt, Bladder cancer was the second most common cancer in males after liver cancer with a crude incidence of 12.6% [2]. The median age was 60.5 years with a male to female ratio of about 5:1 [3].

Urothelial Transitional Cell Carcinoma (TCC) represents about 90% of BC cases, Squamous Cell Carcinoma (SCC) and Primary bladder adenocarcinoma accounts for 3%-7% and less than 2% respectively [4]. However, they are associated with an advanced stage and a higher mortality [5].

The standard surgical therapeutic approach for localized (cT2-T4a, cN0-Nx, M0) Muscle-Invasive Bladder Cancer (MIBC) is Radical Cystectomy (RC) and urinary diversion in conjunction with Pelvic Lymph Node Dissection (PLND) [6]. Systemic therapy added in the neo-adjuvant setting was crucial to avoid dissemination of micro-metastasis that increases risk of recurrence to 50% following surgery [4].

However, the addition of adjuvant therapies either chemo or radiotherapy following radical cystectomy, are yet controversial according to different authors [7,8].

One of the largest phase II studies addressing the tri-modality approach was carried out in Egypt, and the results were encouraging where the addition of adjuvant radiotherapy showed a significant improvement in 2 years loco-regional recurrence free survival (LRFS) compared to chemotherapy alone (96% *vs* 69%), (HR,0.08; 95% CI, 0.02-0.39; p<0.01), with no impact on the OS; 71% *vs* 60% (HR, 0.61; 95% CI, 0.33-1.11; p=0.11) [9,10].

In the NCCN (National Comprehensive Cancer Network) guidelines, level 2 evidence supported the optional addition of adjuvant Radiotherapy (RT) for patients with MIBC who didn't receive Neo-Adjuvant Chemotherapy (NACT) with high risk factors as positive nodes, positive margins, or T3, T4 lesions [11].

Aim of Work

Primary endpoints:

- Loco-Regional Recurrence Free Survival (LRFS): is defined from the date of radical cystectomy till the development of local recurrence or last follow-up.
- Disease Free Survival (DFS) is defined from the date of radical cystectomy till the date of local or systemic recurrence or death from any cause.

Secondary endpoints:

- Toxicity Profile is the toxicity that arise due to radiotherapy (rectal and sexual adverse effects) and/or chemotherapy (haematological and non-haematological adverse effects.
- Overall Survival (OS) is defined from the date of diagnosis till the date of last follow up or death from any cause.

PATIENTS AND METHODS

This is a retrospective study which included all patients with locally advanced bladder cancer who presented to Kasr El-Aini Center of Clinical Oncology & Nuclear Medicine during the period from January 2016 to December 2020.

The patients' data for eligible patient (using ICD-10 diagnosis coding system) were retrieved from our medical records and we analysed their different clinical and pathological criteria; and their treatment details. Finally, we calculated their Loco-Regional Recurrence Free Survival (LRFS) rate, Disease Free Survival (DFS) and Overall Survival (OS) rates together with the toxicity profiles of the different treatment modalities.

Inclusion Criteria

- Pathologically proven locally advanced bladder cancer patients (≥ pT3, or positive nodes).
- Age equal 80 years or younger.
- No other primaries.
- ECOG performance status of 0 to 2.
- No evidence of distant metastases.
- Adequate renal, hepatic and hematologic function.

Exclusion criteria:

- Metastatic/inoperable disease.
- Incomplete patient data.
- Presence of other primary malignancy.

Patients were then divided into 3 arms

Arm A (SC): Patients who underwent Radical Cystectomy (RC) with adjuvant or neo-adjuvant chemotherapy.

Arm B (SR): Patients who underwent RC and received postoperative radiotherapy alone.

Arm C (SCR): Patients who received tri-modality treatment (Chemotherapy-RC-postoperative radiotherapy)

Chemotherapy Regimens and Toxicity Profiles

Chemotherapy regimens were divided into cisplatin based or carboplatin based according to report, Cisplatin ineligibility criteria proposed in 2011 [12,13]. Toxicity pattern was reviewed/graded based on Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.0).

Statistical Analysis

Data were tabulated and studied by descriptive analysis. The information collected was processed, digitized and managed in databases in Excel files (Microsoft Office) and final formal statistical analysis was performed in which descriptive results for categorical variables were presented by rate and odds ratio and for numerical variables by measures of central tendency and dispersion.

Comparative analysis between categorical variables was performed by Chi-square test and for numerical variables by student t-test. Survival analysis was performed by the Kaplan-Meier method.

Comparison between the two groups was done using Equivalent 2-tailed Student t-test. Differences will be considered significant if the p-value is <0.05 [14].

All statistical calculations were performed using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 17.

RESULTS

Bladder carcinoma constituted 547 (4.02%) cases out of the total 13,603 cancer patients presented at our department during the study period. Files of 123 patients were retrieved as they fulfilled our inclusion criteria. The remaining 427 patients were excluded.

Our patients were divided into 3 arms, Arm A (SC arm) included 54 patients who underwent Radical Cystectomy (RC) with adjuvant or neoadjuvant chemotherapy (43.9%), Arm B (SR arm) included 47 patients who underwent RC and postoperative radiotherapy (38.2%) and Arm C (SCR arm) included 22 patients who received trimodality treatment (RC-chemotherapy-postoperative radiotherapy) (17.8%).

Descriptive Analysis

Patients' characteristics: The median age of our patients was 60 years (range: 25 years-79 years). Out of 123 cases, there were 110 males (89.4%) and 13 females (10.56%) with male to female ratio ~ 8:1.

Thirteen patients (10.6%) had Eastern Cooperative Oncology Group (ECOG) 0 on presentation, 73 patients (59.3%) presented with ECOG 1 and 37 patients (30.1%) presented with ECOG 2 (Table 1).

Table 1 Patients' Characteristics in the 3 studied arms

Variable	SC(n=54)	SR (n=47)	SCR (n=22)	p-Value
Age, median, y	60	60	60	0.2
Gender, No. (%)				0.46
Male	50	40	20	
Female	4	7	2	
Tumor histology, No. (%)				0.0004
Urothelial	51	31	20	
SCC / other	3	16	2	
Tumor grade, No. (%)				0.001
1	0	3	0	
2	3	13	1	
3	50	31	21	
Pathologic T stage, No. (%)				0.018
pT2	7	1	2	
p T3	41	30	12	
pT4	6	16	8	
Pathologic nodal disease, No. (%)				0.014
Positive	31	16	14	
Negative	23	31	8	
≥10 Lymph nodes removed, No. (%)				0.51
Yes	21	20	15	
No	33	27	7	
Events, No. (%)				
Local Failure	7 (13%)	0 (0%)	3 (13.6%)	0.067
Distant metastases	15 (28%)	4 (8.5%)	10 (45.5%)	0.0014
Total relapses	20 (37%)	4 (8.5%)	12 (54.5%)	0.007

Among different comorbidities, Bilharzias is was present in 34 patients (27.6% of cases).

Hematuria was the main manifestation where about 91 cases (74%) presented with Hematuria, followed by dysuria in 71 cases (57.7%).

Pathological characteristics: TCC represented 82.9% (102 patients), Squamous cell carcinoma 15.4 % (19 patients) and 2 patients (1.6%) had mixed histology.

Grade I was present in 2.4% (3 patients), grade II represented 13.8% (17 patients), grade III 82.1% (101 patients) and 2 (1.6 %) patients were missing.

The majority of our patients were in stage III (119 patients representing 96.8%), while stage IV included only 2 patients (1.6%) who were both stage IVA. However, two patients had missing staging. Perineural invasion was found in only 4 patients (3.3%) out of 123 patients.

Treatment Results and Patterns of Relapse

Chemotherapy characteristics: Among 123 patients who underwent radical cystectomy, 76 (61.78%) patients received chemotherapy. Unfortunately, most of these patients (51 patients; 67.1%) received it in an adjuvant setting and only 25 patients (32.89%) received neoadjuvant chemotherapy.

Out of these 76 patients, 22 patients were part of the Trimodality arm (SCR Arm) and the remaining 54 patients were included in the Chemotherapy arm (SC Arm). Chemotherapy was platinum-based, composed of either cisplatin/gemcitabine (CIS/GEM) or carboplatin/gemcitabine (CARBO/GEM) according to report, Cisplatin ineligibility criteria 2011 [9,10]. CIS/GEM was administered to 51 patients (67.1%) and CARBO/GEM was administered to 25 patients (32.9%).

The average number of cycles was 3 cycles (range 1 cycle-6 cycles). Interruptions and delays in chemotherapy were present in 27 patients (35.5%) mainly due to associated toxicity; and 49 patients (64.5%) received chemotherapy in their pre-specified dates.

When calculating the Relative Dose Intensity (RDI), it was found that only 4 patients received the maximum RDI of 100% and the least RDI received among the 76 patients was 38.66%. The optimal RDI (>85%) was found only in 21 patients (27.63% of all 76 patients). Further analysis of distribution of RDI is presented in (Table 2).

Table 2 Distribution of RDI in different ranges

RDI Ranges	Number of Patients
RDI: 30 to <50	5
RDI: 50 to <70	27
RDI: 70 to <90	29
RDI: 90 to 100	15
OPTIMAL RDI >85%	21

Radiotherapy characteristics

Total number of patients who received radiotherapy was 69 patients (56%) out of 123 patients. They were part of two arms; the tri-modality arm (SCR) including 22 patients (17.8%) and the radiotherapy alone arm (SR) including 47 patients (38.2%). Radiotherapy was given at a dose of 45 Gy-50 Gy/25 Fractions in an adjuvant setting only.

Patterns of relapse: Local relapse rates were 13% in the SC arm, 0 in the SR arm and 13.6% in the SCR arm with a borderline significant p-value (p=0.0671).

However, all relapses either local or distant, occurred in 37% in the SC arm, 10.6% in SR arm and 59% in the SCR arm with a statistically significant p-value (p=0.0073).

Survival Analysis

At a median follow up period of 18.5 months (95% CI: 14.7 to 26.8), the median Local Recurrence Free Survival (LRFS) for the whole group was 69 months (95% CI: 66.03 to 73.28); while DFS was 36 months (95% CI: 23.33 to 69.03). The median OS for the whole group was 39 months (95% CI: 24.26 to 64.66) (Figure 1).

There was no difference in the median LRFS between the 3 arms (p=0.067) (Figure 1A).

The median DFS was significantly higher in the adjuvant Radiation arm (SR), compared to SC and SCR arms (NR vs 27.4 and 19.96 months respectively), (p=0.0073), (Figure 1B).

The median OS was also significantly higher in the adjuvant Radiation arm (SR) compared to SC and SCR arms (NR vs 30.16 and 35.56 months respectively), (p=0.041), (Figure 1C).

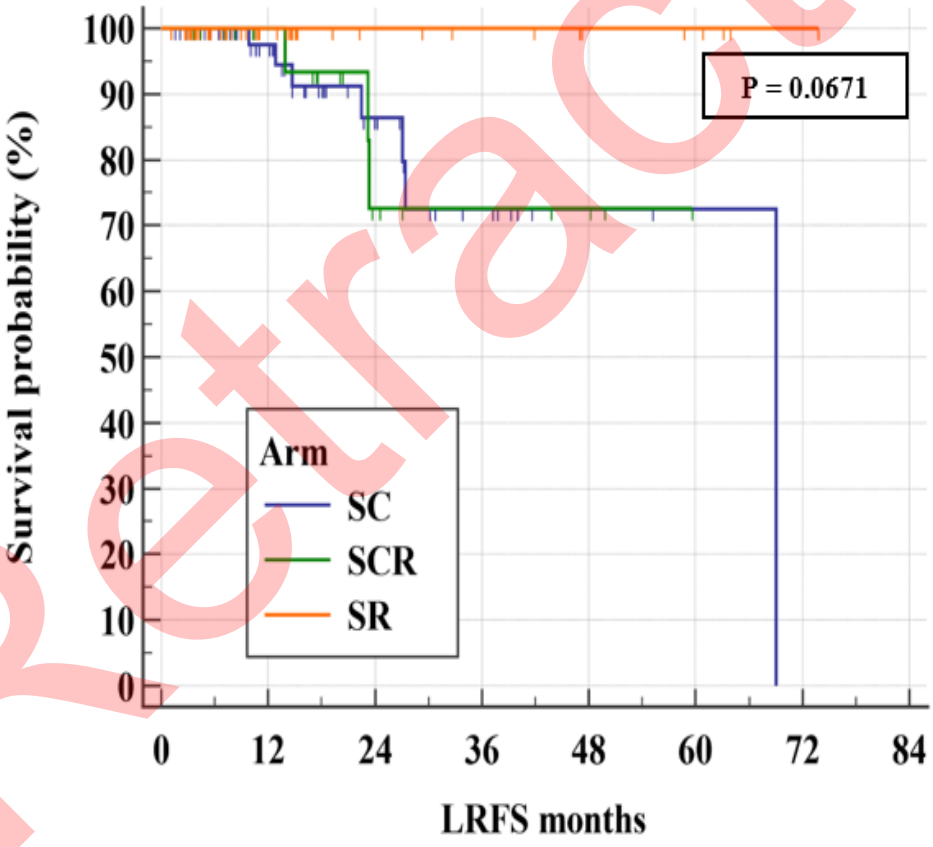

Figure 1A LRFS for the SC *vs* SR *vs* SCR Group

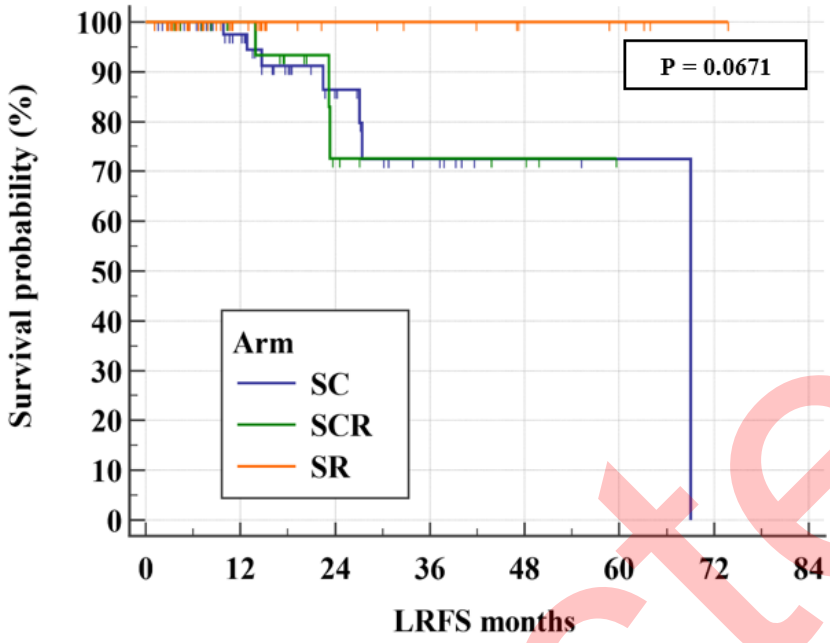

Figure 1B DFS for the SC *vs* SCR *vs* SR Group

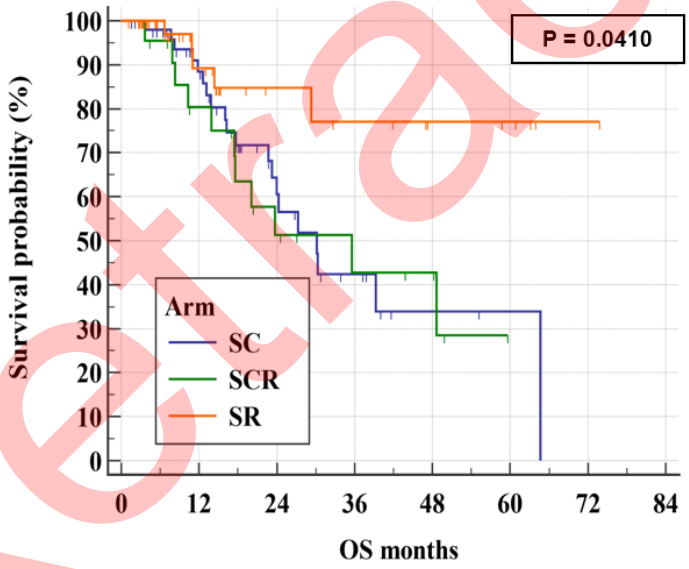

Figure 1C OS for the SC *vs* SCR *vs* SR Group

Kaplan Meier survival curves showing the survival analysis in the 3 arms with p-values

Toxicity Pattern of each ARM

Toxicity pattern was reviewed and graded based on the Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.0).

SC Arm: Among 54 cases who received chemotherapy alone (SC Arm), Grade 3 and 4 haematological toxicity was found in 10 patients (18.5%). While Grade 3 and 4 non-haematological toxicity was found in 11 patients (20.3%).

SR Arm: Grade 3 and 4 Radiotherapy-related toxicity was reported in 8 patients (17%).

SCR Arm: Among 22 patients who received Tri-modality regimen (SCR), Grade 3 and 4 haematological toxicity was reported in 8 patients (36.4%). However, Grade 3 and 4 non-haematological toxicity was reported in 3 patients (13.6%). In addition, Grade 3 and 4 Radiotherapy related toxicity was reported in 4 patients (18.2%).

Prognostic Factors Affecting Survival

By analyzing the impact of different prognostic factors (age, stage, pathology, grade, smoking, bilharzia, perineural invasion) on DFS and OS using Univariate analysis, only the type of therapy received, had an impact on DFS and OS. The rest of the prognostic factors didn't reach statistical significance (Table 3).

Table 3 Represents the Toxicity profiles of the Three Arms (SC, SR, SCR Groups)

	Grade	Haematological			Non-haematological				
		Neutropenia	Anemia	Thrombocytopenia	KFTs	LFTs	GI Toxicities	Sexual Dysfunction	Proclitic
SC Arm	G1	-	-	-	2 (3.7%)	-	28 (51.85%)		
	G2	9 (16.67%)	-	1 (1.85%)	2 (3.7%)	-	7 (12.96%)		
	G3	1(1.85%)	1 (1.85%)	-	2 (3.7%)	1 (1.85 %)	5 (9.26%)		
	G4	4 (7.41%)	1 (1.85%)	3 (5.56%)	-	-	3 (5.56%)		
SCR Arm	G1	-	-	-	1(4.55%)	-	11 (50 %)	-	-
	G2	2 (9.09%)	1 (4.55%)	2 (9.09%)	2 (9.09%)	-	1 (4.55%)	1 (4.5%)	4 (18.2%)
	G3	2 (9.09%)	-	3 (13.64%)	-	-	1 (4.55%)	-	4 (18.2%)
	G4	3 (13.64%)	-	-	-	-	2(9.09%)	-	-
SR Arm	G1							-	3 (6.4%)
	G2							2 (4.3%)	6 (12.8%)
	G3							3 (6.4%)	5 (10.6%)
	G4							-	-

DISCUSSION

Bladder cancers represent about 3.0% of all new cancer cases and ~2.1% of all cancer deaths [1,15]. In Egypt, urinary bladder cancer incidence is among the highest worldwide, and it occupied the second rank for males, after liver cancer [16].

The standard of care in locally advanced MIBC is neo-adjuvant chemotherapy followed by radical cystectomy with 5 year Overall Survival (OS) around 60% [17,18].

The implication of radiotherapy in this setting is yet controversial and depends on the experience of every cancer centre. In the present study, we aimed at analyzing the effect of adjuvant radiotherapy in this group of patients.

The patient's median age is 60 years old (range: 25 years to 79 years) with male to female ratio; 8:1. This was close to a lower median age of 54 years and the male to female ratio was 4:1 [19].

These disparities may be attributed to the differences in the prevalence of tobacco smoking. Tobacco smoking statistics showed a very high prevalence in Egyptian men vs women (38.1% *vs* 0.6% current smokers in 2009) [20].

Regarding the pathology; TCC represented 82.9%, and Squamous cell carcinoma 15.4%, compared to 73% and 27% respectively in 2005. The decrease in the incidence of squamous cell carcinomas, while increase incidence of transitional cell carcinomas in recent years is probably due to a reduction in Schistosoma infection thanks to the national campaign to increase awareness against bilharzia [21,22].

Neoadjuvant and adjuvant therapies have been introduced in many trials in an attempt to improve the results of radical cystectomy.

In our present study, though adjuvant radiotherapy is still controversial, among 123 patients who underwent radical cystectomy, 47 patients (38%) received adjuvant radiotherapy.

Our patients were divided into 3 arms, Arm A (SC) included 54 patients who underwent RC with adjuvant or neoadjuvant chemotherapy (43.9%), Arm B (SR) included 47 patients who underwent RC and postoperative radiotherapy (38.2%) and Arm C (SCR) included 22 patients who received trimodality treatment (RC-chemotherapy-postoperative radiotherapy) (17.8%).

At a median follow up period of 18.5 months (range: 1 months-72 months), the median LRFS for the whole group was 69.03 months; while DFS was 36.33 months. This was further translated into a 5 year LRFS rate of 80.7%, a 5-year DFS rate of 49% and a 5 years OS rate of 44.3%.

Comparing the survival results of the 3 arms in our study showed that the 5 years LRFS rate was 72.5%, 100% and 72.6% in arms A, B and C respectively, with a borderline significance ($p = 0.0671$). However, the 5 years DFS and OS rates were significantly higher in the radiotherapy arm (Arm B), with 5 years DFS 41.1%, 80.4% and 29.9% ($p=0.0073$), and 5 years OS 33.9%, 77% and 28.5% ($p=0.0410$), in arms A, B and C respectively.

In the chemotherapy arm (Arm A), or results showed that the 5 year LRFS rate was 72.5% which is similar to the study conduct in which the adjuvant chemotherapy arm demonstrated a LRFS rate of 69%. These results were comparable since the majority of the patients included in our chemotherapy arm received chemotherapy in the adjuvant setting.

A retrospective study was published in 2018 about the role of adjuvant chemotherapy in locally advanced MIBC, it included 656 patients which were divided into a group receiving AC (Adjuvant Chemotherapy) and the other group receiving NACT (Neoadjuvant Chemotherapy). This study demonstrated superior median DFS for NACT compared to AC (34.6 months *vs* 24.9 months), with a HR: 0.78 (95% CI: 0.63-0.96, $p=0.02$) [23].

Another large meta-analysis of neo-adjuvant chemotherapy for stages II and III TCC including all RCTs conducted between 1984 and 2002, concluded that NACT for provides an absolute overall survival benefit of 6.5% (from 50% to 56.5%), primarily due to a decrease in distant metastases [24].

The 5 year OS rate in Arm A in our study was 33.9%. It is much lower than that reported in the SWOG-8710 trial which studied the impact of neoadjuvant MVAC and resulted in a 5 year OS of 77% [25]. The discrepancy between these results is attributed to the lower percentage of patients receiving NAC in our group (only 35%) of this population. While most of our patients received chemotherapy in the adjuvant setting. In addition to the suboptimal administration of chemotherapy, with an optimal RDI of >85% being given to 27.6% only of our patients.

Another characteristic that was present in Arm A (SC) and Arm C (SCR) was the interruptions and delays. Based on our findings, interruptions and delays in chemotherapy were present in 27 patients (35.5%) mainly due to associated toxicity, however 49 patients (64.5%) received their chemotherapy regimens in their pre-specified dates.

However, regarding DFS in Arm A, the 5 year DFS was 41.1%, quite similar to the study DFS of 47.6% [26]. As Sternberg's study included similar protocols Gem/CIS and administered chemotherapy in the adjuvant setting.

No data could be found on RDI impact on BC patients' survival. However, the JONIE1 Study reported a significant difference in the 5 years OS in breast cancer patients who received NACT with an RDI ≥ 85% (91.2%) *vs* RDI <85% (76.3%) (p=0.015) [27].

In the Adjuvant radiotherapy arm (Arm B), results were in concordance with another Egyptian study that studied the effect of post-operative radiotherapy on locally advanced MIBC patients. The 5 year DFS and LRFS rates were 44% and 93% in the radiotherapy arm [28]. Our results reported a higher 5-year LRFS rate of 100%, and 5 year DFS rate of 80.4%. However, 80% of the patients in study had squamous cell histology and only 20% urothelial neoplasms; in contrary to our study that included 82.9% with urothelial neoplasm and 15.4% with squamous cell carcinoma. This was further clarified by another [28]. Phase II trial in 2018 in which TCC represented nearly half of the patient population, where adjuvant radiotherapy established a 3 year LRFS and DFS of 87% and 63%, respectively.

As regards to OS in the Adjuvant Radiotherapy arm (Arm B), the 5 year OS rate was 77% which was higher than that reported by Monim *et al*. in 2013 who reported a 3 year OS rate of 51.8% with adjuvant radiotherapy [29]. However, in that study as well, TCC represented only 51% of the study population.

Finally, in the trimodality approach (Arm C); the 5 year LRFS rate was 72.6% which is similar to Arm A (72.5%). This was also seen in the 5 year OS rate of 28.5% *vs* 33.9%. These results are in contrary who reported a significant superiority of the trimodality treatment with a 3 year LRFS of 96% (p<0.01) and 5 year DFS of 68% (p=0.07) and OS of 71% (p=0.11) [28].

This controversy could be attributed to different protocols of chemotherapy and radiotherapy administration in our study and trial. In our study, patients received the chemotherapy regimens in neoadjuvant or adjuvant settings and then started the radiotherapy sessions afterwards and this resulted in a delay in radiotherapy administration. However, chemotherapy cycles were sandwiched before and after RT. This allowed early administration of radiotherapy and better compliance to chemotherapy and reduced toxicity. Also in our study, the trimodality arm included 36.4% of the patients with T4 disease, in comparison to 10.7% only in study.

To confirm the effect of radiotherapy, we analyzed the impact of different prognostic factors on DFS and OS. The addition of adjuvant therapy only had a significant impact on the DFS and OS (p=0.0073 and p=0.041 respectively). Other analyzed factors were not statistically significant [29].

The earlier studies in bladder cancer have demonstrated positive impact of adjuvant RT in decreasing pelvic recurrences and improving DFS and OS compared to radical cystectomy alone [30]. However, the enthusiasm towards adjuvant RT waned decades ago mostly because of excessive gastrointestinal toxicity. In the clinical trial conducted at the NCI in Egypt between 1981-1984, the authors reported significant late GI toxicity in 36% of cases. Reisinger *et al*. reported severe late toxicity in 20 of 40 patients (50%) treated with trimodality approach [28].

In these elderly studies, the high reported RT toxicities are likely related to the use of older 2D RT techniques, the larger volume of RT fields including the whole pelvis and the field arrangement by AP/PA beams with inclusion of larger volumes of the bowel [30].

With more precise identification of the Organs At Risk (OARs) as well as using more advanced RT techniques (3D Conformal RT (CRT) or Intensity Modulated RT (IMRT)), we could potentially reduce the bowel dose and improve the therapeutic ratio of adjuvant RT. In our series, we used adjuvant RT by 3D CRT techniques. We reported grade 3-4 GI toxicities of 18.2% in the trimodality approach and 10.6% in the adjuvant radiotherapy arm.

On the contrary, a multicentric phase II trial reported an acute grade 2 Gastrointestinal (GI) toxicity of 61% with the adjuvant radiotherapy which was much higher than that reported in our study (12.8%).

Another Egyptian study reported at ASTRO 2016, the late grade 3^{+} GI toxicity of adjuvant chemo-radiotherapy using 3-D CRT was only 7%. Thus, a critical challenge for adjuvant RT in locally advanced MIBC is the proper selection of patients who will more likely benefit without high toxicity. Multiple clinical trials of post-operative RT are currently ongoing to fulfil this unmet need [NCT02397434]. They are using more advanced RT techniques (IMRT) to lower the GI toxicities and in most of them, the RT volume is designed as per the international consensus guideline [30].

CONCLUSION

Our results suggest that the addition of adjuvant radiotherapy improved the Disease-Free Survival (DFS) and OS in MIBC patients. Although NACT remains the standard of care, incorporation of PORT should be considered in the future management of these cases.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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