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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